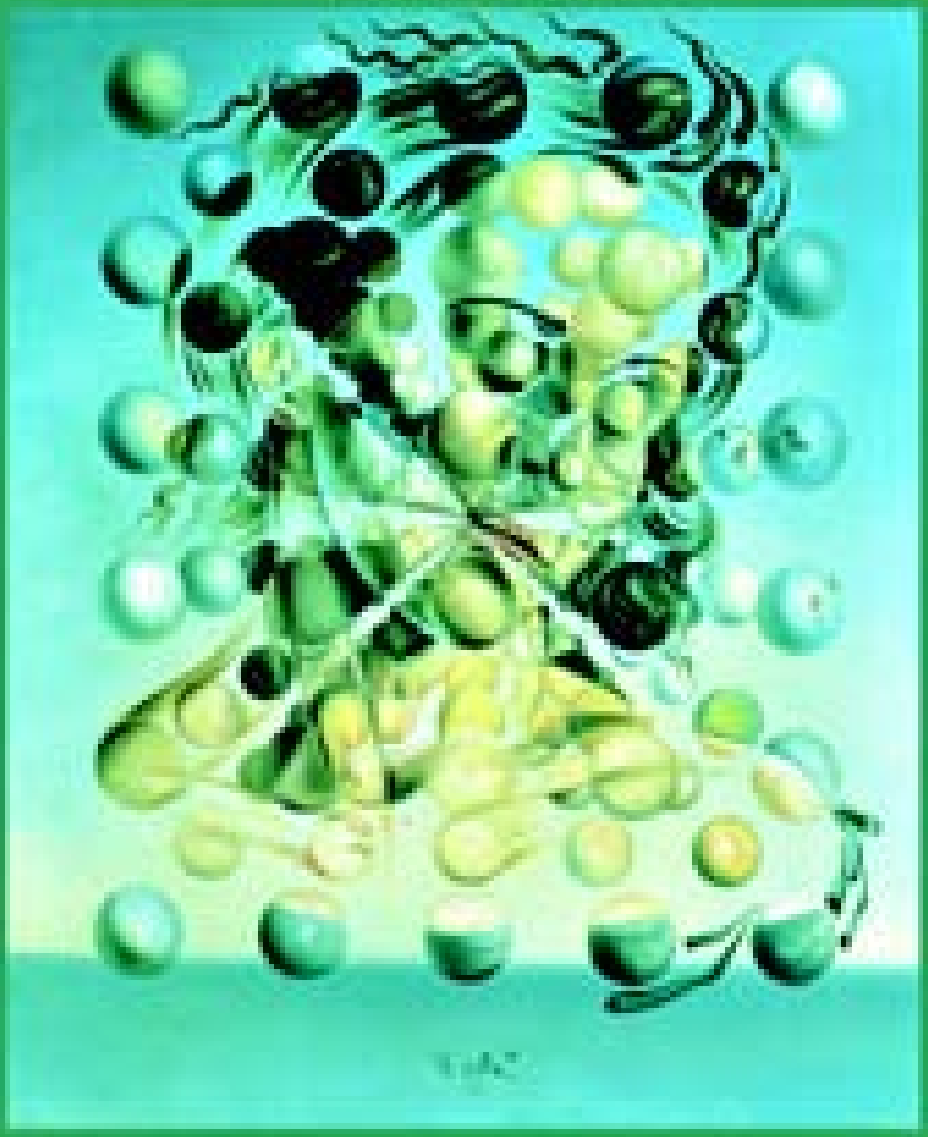

Olfaction and the Brain

Edited by
Warrick Brewer, David Castle
and Christos Pantelis

Foreword by Peter Doherty

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Olfaction and the Brain

Olfaction and its relation to mental health is an area of growing interest, evidenced by the 2004 Nobel Prize in Physiology or Medicine being awarded for discoveries relating to odorant receptors and the organization of the olfactory system. Olfaction is of particular interest to specialists seeking a fuller understanding of schizophrenia. Clear deficits in the sense of smell could predict schizophrenia in apparently unaffected individuals.

In this highly timely book, Warrick Brewer and his team of experts set out our current understanding of olfaction and mental health, relating it to broader principles of neural development and processing as a foundation for understanding psychopathology. The neuropathological, neuropsychological and neuropsychiatric aspects of olfactory function and dysfunction are all covered (drawing on the latest neuroimaging techniques where appropriate), and indications for future research and applications are discussed.
This will be a source of state-of-the art information and inspiration to all mental health professionals.

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with a foreword by Peter Doherty

Peter Doherty jointly won the Nobel Prize in Physiology or Medicine in 1996 for his work in immunology.

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Foreword

While there is still much to be discovered in many areas of biology, perhaps the greatest challenge is to understand the human brain, to illuminate the mind/brain duality. Unlike philosophy and religion, which can sometimes regress into the scholasticism that so limited human advancement and well-being through the dark ages, science is evidence-based and moves forward by exploration, hypothesis and experiment. Science depends on objective measurement. No matter how bright the individual research investigators may be, the conclusions that are reached can only be as good as the underlying observational systems. How do we measure the workings of the brain?

The analysis of brain function has, of course, been enormously enhanced in recent years by technologies like Magnetic Resonance Imaging (MRI) and the capacity to record various electrophysiological outputs. What then becomes important is the source and nature of the input stimuli that induce distinctive neural response patterns. When it comes to such access, the senses of sight, touch and smell provide, of course, primary, natural 'windows' to the brain. At least in the consciousness of medical scientists, smell came to the fore in late 2004 when Richard Axel and Linda Buck were awarded the Nobel Prize for Medicine, for 'their discoveries of odorant receptors and the organization of the olfactory system'.

Though I work with immunity, the other great, complex biological system that mediates specific recognition of (and appropriate responses to) external stimuli, olfaction is an area that has long interested me. A substantial component of my research over the past 30 or more years has focused on the major histocompatibility complex (MHC), the region of the higher vertebrate genome that encodes the strong transplantation antigens, the targets of organ graft rejection. When our own (self) class I MHC molecules are modified by the attachment of a short, 'non-self' peptide (8–10 amino acids) from an infecting virus or some other pathogen, any cell expressing this 'altered-self' complex is seen as 'foreign' by the 'hit men' of the immune system, the cytotoxic T lymphocytes (CTLs) that patrol the body looking for evidence of invasion and damage that must be neutralised in order to maintain good health. Perhaps to avoid any possibility that a virus or bacterium may evolve by mutating to defeat

this immune surveillance mechanism, the class I MHC molecules are enormously diverse (or polymorphic) within any given mammalian species.

What amazed everyone in the transplantation field when the first results were reported in the late 1970s is that animals that rely heavily on the sense of smell, such as mice, rats and police tracker dogs, can readily distinguish between individuals of their own (or different) species on the basis of class I MHC molecular diversity. Experiments using a 'sweaty T shirt test' have shown that the same odorant-based discrimination process works in humans. Furthermore, an 'electronic sniffer nose' developed originally to detect air-borne chemical 'signatures' emitted by the explosives in land mines can also be programmed to tell the difference between various blood and urine samples from people (or mice) of different MHC types. You will be familiar with this technology if your portable computer has ever been 'swabbed' at an airport security checkpoint, though the technician is looking for evidence of a bomb and is not (we hope) trying to classify you by your particular body odour!

The mechanism underlying olfactory MHC 'typing' is still far from clear, though like the electronic nose, it clearly depends on the recognition of various volatile compounds. Even more surprising, recent studies have shown that other areas of the MHC are coding for some of the odorant receptors that determine pheromone recognition. Could the MHC polymorphism that is so important for immunity simply be a reflection of a much older (in evolutionary terms) process based on odorant-determined sexual preference? (See, 'On the Nose: shared themes for the sensory and immune self'. *Nature Immunology* 4:1043–45, 2003)

The present volume is particularly fascinating as it links olfaction with a broad range of insights and observations based on molecular neurobiology, neurology, psychiatry and psychology. As an immunologist who is also intrigued by brain function and by philosophical ideas that incorporate findings from contemporary neuroscience, it seems to me that a big question facing us concerns how we deal with modes of behaviour that are fundamentally determined by genetics and physiological response patterns, especially if these should happen to involve consequences that are considered to be inappropriate or even anti-social. Because the sense of smell can be used to access neural mechanisms in ways that are non-invasive and unlikely to upset those who are threatened by medical procedures, fundamental and clinical research that both probes and utilizes olfaction has the potential to help humanity resolve some of these difficult issues. This widely ranging book provides a useful and informative compendium that allows the general science and informed lay reader to access an important, complex and fascinating field of human enquiry.

Peter C. Doherty

Preface

This book provides a timely and up-to-date overview of how we understand olfaction, its neurobiological basis as well as providing an evolutionary perspective. The neuropathological, neuropsychological and neuropsychiatric aspects of olfactory function and dysfunction are considered, drawing on the latest neuroimaging techniques, where appropriate. A strong focus is on schizophrenia, as this disorder represents compromise of the unique and complex interplay between aspects of the developing 'self' that include biology, psychology and the environment — all of which involve olfaction. The intent is to illustrate the advantages of extending our understanding of this primary sense, which in turn widens our knowledge of broader principles of neural development and processing as a foundation for understanding psychopathology. The overall aim is to elevate the often under-estimated sense of smell to a level of significance that should stimulate readers to consider olfactory models and principles of function as a guide to broader research paradigms, and should also encourage wider use of olfactory assessment in neurological, psychiatric and psychological settings during the process of diagnosis and assessment.

Chapter authors are internationally recognised experts in their respective fields who have also demonstrated their ability not only to understand and enhance our knowledge of olfaction within the perspective of a wide variety of broader clinical and research programs, but to relate their knowledge of complicated neurobiological processes in a readable and accessible manner.

Section I sets the foundation for the rest of the book, with Chapter 1 providing a detailed description of the structure and function of the primary olfactory system (Mackay-Sim and Royet). This chapter encompasses an overview of how the chemical properties of odourants are encoded into neural activity. In addition, these authors describe the regions of neural activity that are involved in the various aspects of olfactory processing. This chapter includes a detailed exploration of the olfactory epithelium and the olfactory bulb and provides the

link between such basic biology and olfactory perception. In Chapter 2, Djordevic and Jones-Gotman evolve this further, with a particular focus on temporal lobe functioning and olfaction. Their work derives from their studies in epilepsy in Montreal, with an emphasis on neuroimaging techniques. Based on their functional imaging work in London, Heining and Phillips (Chapter 3) examine more intricate aspects of the relationship between components of olfaction and olfactory pathways and socio-biological behaviour. They provide an intriguing account of the role of disgust and the amygdala in relation to olfactory stimuli, and discuss the functional implications of compromise of normal reactive emotional responses to aversive stimuli and the relevance to understanding mental illness. Doop, Mohr, Folley, Brewer and Park explore the relationship between the higher cognitive processes and olfaction in Chapter 4. The evocative nature of olfactory memory particularly, and its role in the re-creation of the self, are reflected in this chapter to draw the reader into a deeper appreciation of this most romantic of the senses.

An aim of Section I is to reflect novel methods to explore the hierarchical nature of olfactory stimulus processing from sensory experience in olfactory epithelium through to emotional processing in the limbic system and higher order olfactory information processing in frontal regions, and to understand these processes within a neurodevelopmental framework. Féron, McCurdy, McGrath and Mackay-Sim describe in Chapter 5 how careful exploration of the process of neurogenesis of the olfactory bulb might uncover more general principles that help us understand neurodevelopment generally, and neuropsychiatric disorders more specifically — particularly schizophrenia. Their work is based on a unique Australian research programme that relies upon examination of olfactory neuro-epithelial cultures that are gained from nasal biopsy. Brewer, Wood, de Luca and Pantelis extend this thesis in Chapter 6, and consider the various aspects of olfactory processing in normal individuals and in pathological states within a neurodevelopmental perspective. Based on their work over the last decade, they propose that the nature of olfactory abnormalities and the brain regions involved in disorders in early life need to be understood by considering the brain maturational stage at the time of onset of such disorders. These authors highlight the importance of understanding the maturation of various aspects of olfactory function and of relevant fronto-limbic circuitry, and particularly emphasise the importance of maturation of higher-order olfactory function (implicating orbito-frontal neural systems) in understanding the nature of olfactory disturbances in disorders of adolescence and early adulthood.

In the final Chapter of Section I, Lubman, Yücel and Brewer describe a model of orbito-frontal cortex (OFC) functioning and associated behaviour, and outline how OFC compromise would be expected to result in reduced ability

to regulate affect and in dysfunctional behaviour, such as addiction. While the focus in this chapter is more on disordered behaviour rather than olfaction *per se*, the purpose is to stimulate implementation of less-obvious models of research in domains that might usefully exploit tasks of olfactory ability and their differential timing of maturation over the course of development. Here, the aim is to elucidate the nature and course of those same disorders with an emphasis on early detection.

Section II traces influences on the development of olfaction in humans in the context of evolution, with an emphasis on communication. The roles that genes, gender and pheromones play in the foundation of olfactory function are described. An evolutionary perspective on the adaptive nature of primate olfaction and anatomy by Smith and Rossie (Chapter 8) sets the scene for the ensuing chapters that outline the importance of olfaction as a facilitator of social interaction. Functional implications of skull and nasal structure in primates are described. Evidence of adaptation is drawn from the nervous system, with reference to olfactory progressive diminution from its state in other mammals to that in primates, particularly in the fields of comparative neuroanatomy and neurophysiology. In terms of genetic implications on olfaction, Mesholam-Gately and Seidman describe family and high-risk schizophrenia studies (Chapter 9) to demonstrate how disordered olfactory functioning might provide clues to the genetic foundations of complex neuropsychiatric diseases in general and, in particular, biological markers for schizophrenia. In a similar context, Good and Kopala (Chapter 10) review sex differences in olfactory ability, and reinforce the notion of how important odour cues carry information regarding fertility status or genetic make-up. Implications of genetic influences on olfactory function from the perspective of gender, and associated relevance to psychiatry, are also outlined. How such differences may impact on increasing our understanding of psychopathologies such as schizophrenia is also explored. In further detail, Stoddart (Chapter 11) expands our understanding of the nature of pheromones and chemistry via comparative anatomy. He includes a description of recent controversial findings regarding the vomeronasal organ. This chapter provides a historical perspective on understanding the role of chemical messengers in animals and humans. Returning to implications of these primal aspects of social communication for humans, understanding olfaction in the context of social behaviour is extremely pertinent to the human condition. For most mammals, social hierarchy and territory are recognised by odour, and smell plays a key role in identifying life-enhancing stimuli and enemies and in determining safety from danger. The brain circuitry involved in emotional processing and olfactory function is overlapping and olfactory information is unique in comparison to other sensory modalities because of its direct input

to the prefrontal cortex. Malaspina, Corcoran and Goudsmit (Chapter 12) provide a fascinating review of how this understanding of neural circuitry and the behaviour it mediates facilitates social communication via pheromones.

Finally, Section III focuses on specific assessment and detection of disorders of olfactory function in neuropsychiatric disorders. Doty (Chapter 13) describes the utility of standardised assessment of olfactory function, with particular emphasis on sensitivity and specificity across a range of disorders that manifest reduced olfaction. Specific reference to available bedside tests is included. Pantelis and Brewer (Chapter 14) provide an account of olfactory compromise of neuropsychiatric disorders, including early neurodevelopmental disorders and late neurodegenerative conditions, while Hawkes (Chapter 15) provides a more detailed account of the nature and extent of olfactory deficits in disorders of the striatum, particularly neurodegenerative disorders. The emergence of olfactory deficits at various stages of each illness and their neurobiological and clinical implications is discussed in these two chapters. In Chapter 16, Moberg and Turetsky review olfactory disorders in schizophrenia. The focus on olfactory function in neuropsychiatric disorders is continued by Velakoulis (Chapter 17), where structural and functional imaging research concerning olfactory hallucinations is explored, with particular focus on pathological conditions of the temporal lobe. This includes a historical analysis of the epilepsy and psychosis literature that is associated with olfactory hallucinations. In the closing chapter, Phillips, Gunderson, Gruber and Castle (Chapter 18) review the literature on the Olfactory Reference Syndrome (ORS) — an under-recognised type of delusional disorder that has been described for more than a century. It consists of a false belief that one emits an offensive body odour and is often accompanied by prominent delusions of reference and repetitive behaviours aimed at checking or reducing the perceived odour. This chapter discusses this syndrome's history, clinical features, prevalence, treatment response, possible pathogenesis and nosological status.

It is hoped that this book will stimulate clinicians and researchers across the neuroscientific disciplines to consider the unique role and functional implications of olfaction. We are only at the beginning of unlocking the mysteries of our most primal sense, and we trust that our authors trigger interest in further exploration. We fully expect that such interest will expand our appreciation of this fascinating window to the mind.

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Section I

Neurology, neurophysiology and neuropsychology: olfactory clues to brain development and disorder

1

Structure and function of the olfactory system

Alan Mackay-Sim and Jean-Pierre Royet

Introduction

The olfactory system comprises a sensory organ (the olfactory epithelium) and specific olfactory brain regions, the first of which is the olfactory bulb. The perception of odours poses interesting and different problems for the nervous system — problems unique to the odorous world. The first of these is that there is no single dimension that relates stimulus to sensation. Vision and hearing are stimulated by predictable variations in frequencies of light and sound; touch by variations in frequencies of pressure on the skin. Odorant molecules have no obvious connections with each other except that they are odorous — that is, they evoke sensations in the olfactory system. The second unique attribute of the olfactory system is that there seems to be no limit to the number of odorous molecules that can be detected and described. Vision, hearing and touch all operate within limited spectra of light, sound and pressure, predictable spectra to which the systems have evolved. Odorous molecules are mainly limited to molecules of 200 to 400 mW but within that range, there are essentially an infinite number of odorous molecules. The molecular structures are highly variable and no individual or group of individuals has been exposed to all of the range, or possibly even the majority of the range.

How, then, could a system evolve to detect and respond to such an open ended set of stimuli? The immune system has a similar task and has solved it by using a variable rearrangement of its genetic code to generate protein receptors of huge range. The olfactory system has solved this problem by generating a huge number of individual receptor genes. Of the approximately 30,000 genes in

the mouse genome, more than 1000 are for olfactory receptors (Buck & Axel, 1991). It is a source of wonder that one-thirtieth of the genome is devoted to detecting odours. Interestingly, humans have about 900 olfactory receptor gene sequences but 63% are interrupted with sequences so as to render them non-coding, so-called 'pseudogenes' (Glusman *et al.*, 2001); although even humans, with their reduced dependence on smell, have about 300 active olfactory receptor genes (Glusman *et al.*, 2001). This begs the question; what is it about the stimulus that requires such a huge investment of genes? The visual system needs only three genes to detect the colour spectrum. The auditory system just requires a specialised physical structure – the cochlea, which is constructed via genes used for multiple other roles in development. The olfactory system requires one-thirtieth of the genome. An intriguing aspect of the olfactory system is that these odorant receptor genes are involved both in odorant detection as well as in establishing the basic anatomy of the olfactory system that allows that detection.

The first part of this chapter provides an overview of the anatomy of the primary olfactory system, the olfactory mucosa and olfactory bulb, and how this contributes to our current understandings of how the chemical properties of odorant molecules are encoded into neural activity. The second part of this review covers the consequences of this neural activity and how it defines the regions of the human brain involved in olfactory perception.

The olfactory epithelium

The olfactory mucosa is the region of the nasal cavity that is specialised for the detection of odorants. It comprises the olfactory epithelium and its underlying lamina propria. The olfactory mucosa is nominally located in the superior and posterior part of the nasal cavity, close to the cribriform plate through which the olfactory nerves project to find the olfactory bulb – the initial olfactory region of the central nervous system (Figure 1.1). In adult humans the olfactory mucosa is not always contiguous and can be found more anteriorly and inferiorly on the nasal septum and lateral wall (Féron *et al.*, 1998; Leopold *et al.*, 2000). Unusually, the olfactory epithelium undergoes a continual process of neurogenesis in which new neurons are continually generated throughout adult life, and this may explain the discontinuity and spread of the olfactory mucosa (Féron *et al.*, 1998). The advantages of utilising this process for mapping neural development more generally are expanded in Chapter 5.

The axons of the sensory neurons leave the olfactory epithelium and gather in bundles within the lamina propria to course superiorly and posteriorly.

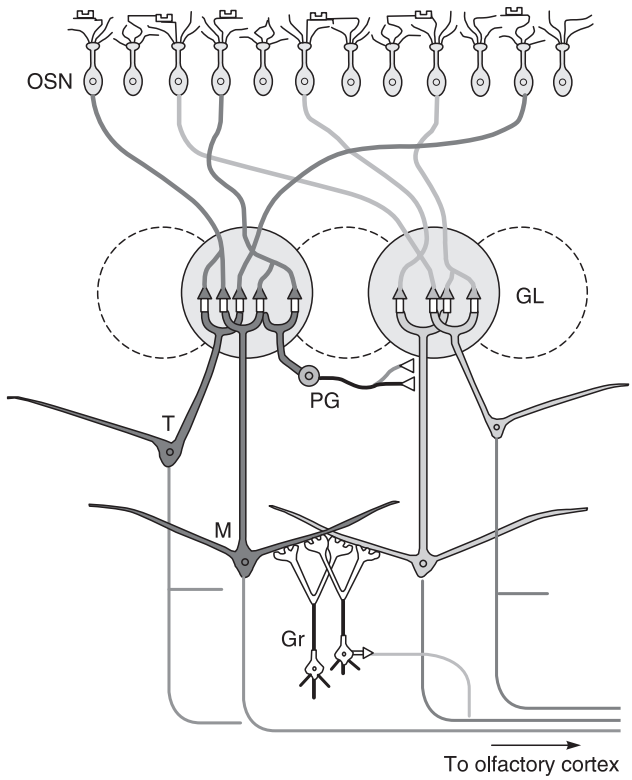

Figure 1.1 Each olfactory sensory neuron in the nose (OSN) projects its axon to a single glomerulus (GL) in the olfactory bulb where it synapses with a mitral cell (M) and perhaps a tufted cell (T), both of which provide the output to the olfactory cortex. Sensory information is modulated by periglomerular interneurons (PG) and the inhibitory granule cells (G). Each glomerulus receives input from hundreds of olfactory sensory neurons. Each mitral and tufted cell receives input from a single glomerulus. Modified from Mori *et al*. 1999.

As they do, they gather into larger fascicles that form the fila olfactoria that traverse the skull base through the many openings of the cribriform plate to enter the olfactory bulb. In the olfactory bulb, the axons defasciculate and enter specialised structures, glomeruli, within which the sensory axons synapse with the mitral cells of the olfactory bulb.

Within the olfactory epithelium, the olfactory sensory neurons express just one of the many odorant receptor genes (Buck & Axel, 1991). Cells expressing each gene are distributed seemingly 'randomly' within the olfactory epithelium, subject only to subgroups of these cells being confined to several broad regions within the nasal cavity (Ressler *et al*., 1993). Surprisingly, when these sensory

neurons send their axons to the olfactory bulbs, the glomeruli to which they are restricted are confined to a single glomerulus on either side of the olfactory bulb (Mombaerts *et al.*, 1996). Thus in mice there are approximately 1800 glomeruli (Royet *et al.*, 1988) and approximately 1000 receptor genes (Buck & Axel, 1991). Recent experiments indicate that each glomerulus is innervated by sensory neurons expressing only one receptor gene (Mombaerts *et al.*, 1996). The identity of the receptor gene borne by each sensory neuron is involved in targeting its axon to a specific glomerulus, although the receptor gene is necessary but not sufficient to address the axon to a particular glomerulus.

Olfactory sensory neurons each respond to many different odorants (Duchamp-Viret *et al.*, 1999) even though each is thought to express only a single odorant receptor gene. Thus each odorant receptor protein can apparently detect some aspects of a variety of different odorant molecules and each odorant can interact with multiple receptors (Araneda *et al.*, 2004). This heterogeneity of response continues to provide a conundrum for understanding the relation between odorant molecular properties and the odorant-binding domain within the receptor molecule.

The olfactory bulb

The cellular structure of the olfactory bulb is well established (Mori, 1987). Incoming sensory information passes to the mitral and tufted cells that provide the output to the higher olfactory centres (Figure 1.1). This output is heavily modulated by the interneurons present at several anatomical and processing levels within the olfactory bulb. Around the glomeruli are several types of interneurons, many of which are dopaminergic, whose axons and dendrites form part of the complex neuropil within the glomeruli. Deep in the olfactory bulb are the granule cells, which are without axons, but whose dendrites connect with mitral cell dendrites in more superficial layers, modulating their activity via complementary pairs of synapses from granule cell dendrites to mitral and tufted cells, and in the reverse direction, the so-called 'dendrodendritic synapses'.

The physiology of the olfactory bulb is dominated by the spatial nature of the input. Specifically, because of the spatial patterning of the sensory axons expressing different odorant receptor genes, odorants presented in the nose stimulate different patches of glomeruli on the surface of the olfactory bulbs (Figure 1.2). Because each mitral cell has a dendrite in only a single glomerulus, the activity of the mitral cells is spatially distributed such that odorants are represented in the olfactory bulb by a distributed pattern of mitral cell activity (Leon & Johnson, 2003; Lowe, 2003; Mori *et al.*, 1999). The nature of

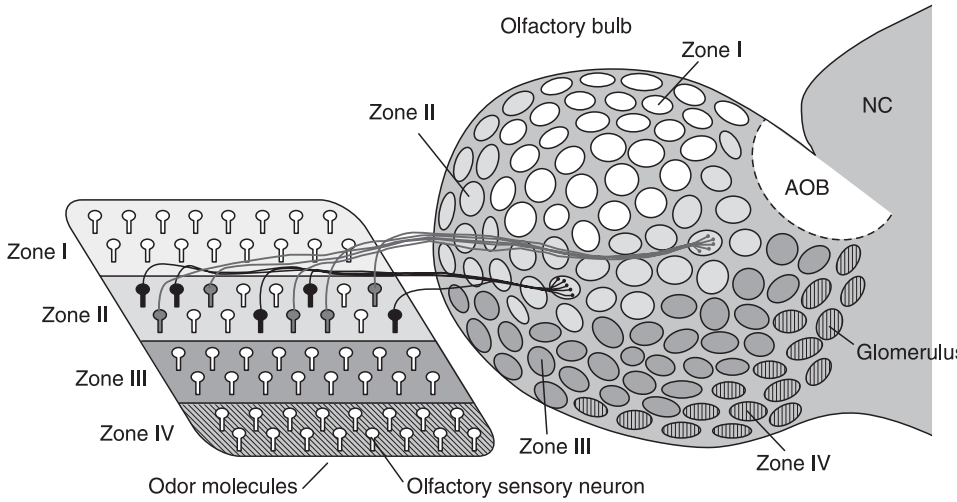

Figure 1.2 The inputs to the olfactory bulb preserve, in a broad way, spatial relationships between olfactory sensory neurons. The olfactory epithelium can be divided into four 'zones', characterised by the subfamilies of the olfactory receptor genes expressed by the sensory neurons in those zones. These four epithelial zones are represented by four zones of projection of the sensory axons to glomeruli on the surface of the olfactory bulb. Within each epithelial zone, each sensory neuron expresses a single olfactory receptor gene. Within the bulbar zone, each glomerulus receives axons from sensory neurons expressing a single olfactory receptor gene. Each olfactory receptor gene is represented by two glomeruli, one on the lateral surface and one on the medial surface of the olfactory bulb. Modified from (Mori *et al.*, 1999).

interneuron connectivity then leads to a sharpening of the response of the mitral cell both in time and space, with the effect of narrowing the responses of the mitral cells to a smaller number of odorant molecules compared to the sensory neurons (Lowe, 2003; Mori *et al.*, 1999). Similarly the mitral cell response is narrow in time as well (Lowe, 2003; Mori *et al.*, 1999).

A notable feature of olfactory bulb anatomy is the convergence of feedback from higher centres whose axons project onto the interneurons at the granule and periglomerular levels. Combined with the observation that cellular models of memory are evident in the activity of olfactory bulb neurons (Wilson *et al.*, 2004), these features suggest that the olfactory bulb is not merely a passive conduit for sensory information, modulated and sharpened as it is by interneuron activity. There is ample evidence that the olfactory bulb physiology is modulated by prior exposure and experience with odorants (McLean *et al.*, 1999) and evidence for feedback superimposed on the olfactory bulb (McLean & Harley, 2004). It is thus possible that the olfactory bulb acts as a filter of some

sort that matches expected patterns of activity associated with food, mates or predators, for example, with the pattern of sensory nerve activity.

What the nose tells the brain

Any hypothesis about the encoding of odorant molecules must reconcile several aspects of human perception. The first is that 'odour' does not refer to any obvious specific molecular feature of the odorant. For example, all odorants containing sulphur smell are 'sulphurous' but they do not smell the same. This illustrates the second aspect, namely that there seems to be a huge variety of perceptual experiences of 'odour' as there are a huge number of odorants. The third aspect is that 'odour' is a holistic experience, such that complex mixtures such as coffee have a single percept, as do single odorant molecules. Humans are relatively poor at discriminating the components of mixtures and cannot distinguish more than three or four separate components (Laing & Francis, 1989). A fourth aspect is that, for most odorants, their identification does not change with concentration: there is perceptual constancy with increasing concentration.

The first evidence proposed for a mechanism of encoding odorants was that different odorants were encoded in spatial patterns of activity in the olfactory bulb (Kauer & White, 2001; Leon & Johnson, 2003). This hypothesis has proved to be prescient, although it has taken many years and the advent of new technologies to provide a satisfactory mechanism to explain these observations. Initial experiments emphasised the spatial differences in activity in the olfactory epithelium, but the apparent complexity in the connectivity between the epithelium and the bulb remained an obstacle to understanding. When the true nature of the connectivity was revealed in the expression of olfactory receptor genes, the focus turned to the glomeruli of the olfactory bulb as the originators of a 'spatial code' (Mombaerts *et al.*, 1996; Mori *et al.*, 1999; Ressler *et al.*, 1993).

There are many ways to examine the spatial nature of responses in the olfactory glomeruli. The one that has allowed the most extensive and thorough examination is the method of uptake of 2-deoxyglucose, a molecule accumulated by active neurons that can be revealed by autoradiography in histological sections. After a thorough series of investigations in which the mapping of active glomeruli was correlated with systematic variation in odorant stimuli, several features of a 'spatial code for odour' were discerned (reviewed in Leon & Johnson (2003)). It is apparent that the surface of the olfactory bulb is composed of groups of glomeruli, called 'modules', that appear to encode molecular functional groups (Figure 1.3). Thus, for example, all ketones would activate

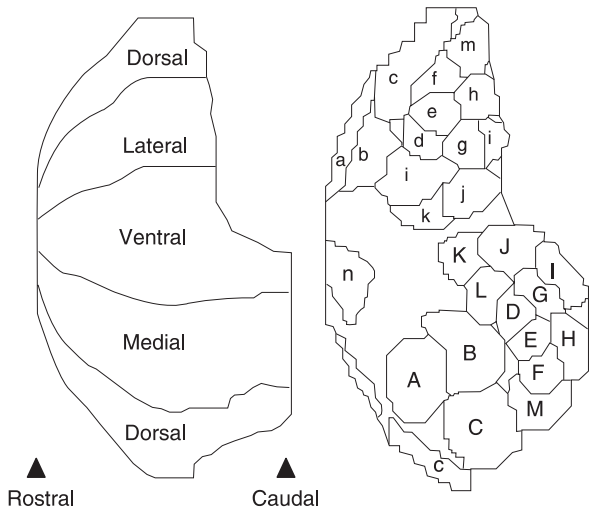

Figure 1.3 Odorants stimulation in the nose is represented as a spatial pattern of activity within the olfactory bulb. Odorant-induced activity is measured by the uptake of 2-deoxy-glucose and the positions of the active glomeruli are noted on a standardised 'map' of the surface of the olfactory bulb. On the left is an example of a such a map in which the bulbar surface is represented as a flat surface with the regions indicated. On the right the map is subdivided into subregions or 'modules' which are defined by odorant-induced activity within the glomeruli. These modules represent regions of active glomeruli, each of which was active during stimulation by at least 3 out of 54 odorants tested. For most odorants a module on the medial aspect corresponded to a module on the lateral aspect shown by upper and lower case letters. Each odorant activated a different combination of modules, giving a unique pattern of activity for each odorant. Modified from (Leon & Johnson, 2003).

glomeruli in the same modules, which would be spatially separate from the module activated by acids or alcohols (Leon & Johnson, 2003). Molecules of similar structure, such as organic acids with increasing carbon chain lengths, would activate neighbouring glomeruli, with the focus of activity moving systematically across the surface of the olfactory bulb. These observations suggest that olfactory bulb activity is 'chemotopically' organised, its role being to parse the odorant signal into a set of activities representing functional groups, carbon chain length and other structural features (Leon & Johnson, 2003).

These observations at the level of the glomerulus are reinforced by observations of the responses of mitral cells after systematic analyses of their responses to odorants within molecular series reviewed by Mori *et al.* [1999]. Each mitral cell is connected to a single glomerulus and so its responses must be dominated by the activity in that glomerulus and, by inference, by the activity of the single odorant receptor present in the sensory neurons projecting to that

glomerulus (Johnson *et al.*, 1998). Mitral cells adjacent to each other project to the same or neighbouring glomerulus. Careful investigation of neighbouring mitral cells indicates that they have similar responses and that they tend to be activated by odorants of a similar molecular class, such as acids or ketones, or those containing a benzene ring (Mori *et al.*, 1999). Mitral cells separated spatially are activated by odorants carrying different functional groups (Mori *et al.*, 1999), an observation that would be predicted by the spatial differences in activity across the glomeruli (Johnson *et al.*, 1998). Thus, the mitral cells appear to function as 'molecular feature detectors', a property brought about by the spatial segregation of inputs into the olfactory bulb by way of the singular expression of odorant receptors in individual sensory neurons and their targeting to distinct points in a spatial 'map' on the surface of the olfactory bulb.

An understanding of this spatial map is now such that the neural map can be predicted from the structure of the molecule (Leon & Johnson, 2003). But is this information used by the animal? Evidence that it is comes from a study of the ability of rats to discriminate optical isomers (enantiomers), molecules that differ in structure as mirror images. Enantiomers that humans can identify as different (*l*- and *d*-carvone) activated different spatial maps of glomerular activity and were discriminated by rats (Leon & Johnson, 2003). Enantiomers that humans do not distinguish (*l*- and *d*-limonene, *l*- and *d*-terpinen-4-ol) activated similar spatial maps of glomerular activity and were not discriminated by rats in non-reinforced behavioural testing (Linster *et al.*, 2002). It is notable that the variation of glomerular activity within the larger modules allows rats to discriminate otherwise similar enantiomers, if the learning is reinforced (Linster *et al.*, 2001), and that glomerular activity is enhanced by such reinforcement (Coopersmith & Leon, 1984). This ability to learn to make use of small differences in glomerular activity may explain the remarkable ability of rats to learn to discriminate odorants even after large lesions of the olfactory bulb (Bisulco & Slotnick, 2003).

In summary, the functional anatomy of the primary olfactory pathway appears to impose a spatial component to the activity of cells within the olfactory bulb such that a 'topographic map' of activity across the surface of the olfactory bulb is converted into a 'chemotopic map' of molecular features extracted from the odorant stimulus. Our present level of understanding suggests that these molecular features are then reassembled into more complex representations of the stimuli, at least in the piriform cortex. In concept at least, this aspect of olfactory processing resembles that which occurs in the visual cortex whereby the visual image is initially decomposed into salient features in the responses of primary cortical neurons (features such as orientation, velocity and direction of movement, colour) before being reassembled into more complex representations of faces, hands or movement.

Other chemosensory systems in the nose

It is commonly known that 'smelling' an odour is a function of the nose and that the 'olfactory system' is responsible for this sensation, starting with the sensory organ, the olfactory mucosa, in the dorso-posterior part of the nasal cavity. Less well known is the contribution of the trigeminal nerve in odour sensation, especially in perceptions of odour 'strength' and pungency.

The trigeminal nerve innervates the face, including the oral and nasal cavities, and the cornea and conjunctiva of the eye (Silver & Finger, 1991). In animal experiments, it is shown that the trigeminal nerve responds to many chemical compounds that are 'odorous' to humans (Silver & Finger, 1991) and humans judged to have no functional olfactory system can detect a large range of odorants presented to the nose, presumably via the trigeminal nerve (Doty *et al.*, 1978). Therefore, any consideration of olfactory anatomy and function must acknowledge the contribution of sensations via this 'somatosensory' input.

Olfactory-guided behaviour, most notably food selection and eating, also involves the gustatory system as well as the olfactory and trigeminal systems. The gustatory system provides perceptions of sweet, sour, salty and bitter as well as umami, the taste of monosodium glutamate (Gilbertson *et al.*, 2000). The trigeminal nerve in the mouth provides touch, temperature and 'hot spicy' sensations, and the three sensory systems contribute to the perception of flavour, the 'taste' of food. Commonly, persons reporting loss of 'taste' of food actually have olfactory deficits (Doty *et al.*, 1991). This is evident in human cerebral imaging experiments where the orbitofrontal cortex and insular cortex are activated by olfactory, gustatory and trigeminal stimuli.

The higher olfactory (and CHEMOSENSORY) centres

Anatomy

The olfactory system is characterised by relatively direct connections (that is, few synapses) to brain structures implicated in memory and emotion such as the hippocampus, thalamus, and frontal cortex. It thus gives the impression of a phylogenetically ancient sensory integration system isolated from the more recent neocortex.

The primary olfactory cortex

The olfactory tract carries the axons leaving the olfactory bulb and these project to the structures collectively termed the primary olfactory cortex. This comprises the anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, the periamygdaloid cortex (that overlies the amygdaloid complex), the lateral

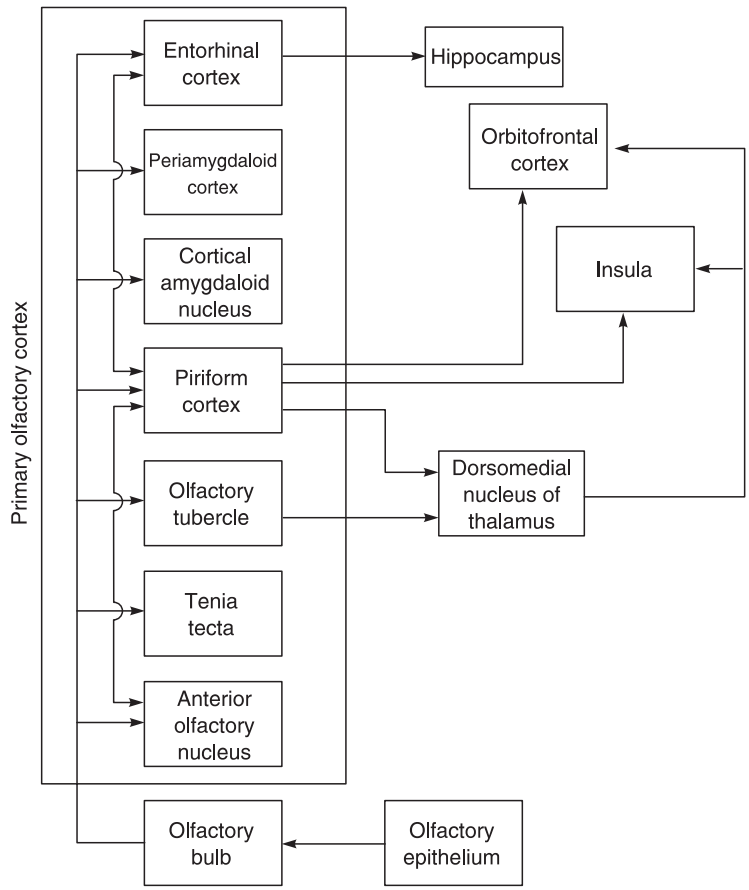

Figure 1.4 Major efferent connections of the olfactory system.

entorhinal cortex, the cortical amygdaloid nuclei, the ventral tenia tecta, and the nucleus of the lateral olfactory tract (Figure 1.4) (Allison, 1954; Carmichael *et al.*, 1994).

Caudomedially, the entorhinal cortex gives way to the parasubiculum, presubiculum and subiculum; the latter blends with field CA1 of Ammon's horn of the hippocampus. This continuous expanse of gradually changing cortical architecture from the olfactory bulb to the CA fields of the hippocampus was one reason why early anatomists referred to this region as the *rhinencephalon* (from the Greek 'rhines' – a nose), believing that it constituted the 'smell brain'. It is still recognised that the olfactory system is the sensory system with the most direct access to the hippocampus.

Though historically referred to as a 'nucleus', the anterior olfactory nucleus is now considered a cortical structure. In the monkey, this consists of a single,

loosely arranged layer of cell bodies deep to a thin plexiform layer (Price, 1990). In humans, this structure is less distinct, delimited from the adjacent orbital neocortex only by slight differences in cell size and packing density (Price, 1990). The axons of the anterior olfactory nucleus project either rostrally to the ipsilateral olfactory bulb, or caudally, joining the anterior commissure to cross the midline and terminate in the contralateral anterior olfactory nucleus and/or olfactory bulb. From a functional point of view, the major interbulbar connections of the anterior olfactory nucleus implicate this structure in the interhemispheric processing of olfactory information (Shipley & Reyes, 1991), particularly olfactory memories (Kucharski & Hall, 1987). There is evidence that bi-nasal mechanisms operate in the spatial localisation of odours (Bennett, 1968) and that the anterior olfactory nucleus system may play a significant role in such mechanisms.

In the rat and the monkey, the piriform cortex is the largest of the olfactory areas and occupies a central position in the primary olfactory cortex (Carmichael *et al.*, 1994). Rostrally, it is situated on the posterior orbital surface, caudal to the anterior olfactory nucleus and lateral to the lateral olfactory tract. At the limen insula, it continues caudally and ventrally onto the dorsomedial edge of the temporal lobe (Carmichael *et al.*, 1994). In man, the piriform cortex is found in two parts which face each other around the choroidal fissure, forming the superior and inferior lips of the rostral part of this fissure and which are continuous in the fundus of the fissure (Allison, 1954; Eslinger *et al.*, 1982; Poellinger *et al.*, 2001). The superior lip is the frontal piriform region whose laminar organisation consists of two cell layers — olfactory tract fibres terminating mainly in the outer plexiform layer. The inferior lip is the temporal prepiriform cortex that is of similar laminar organisation to the frontal region.

The olfactory tubercle in rodents and rabbits is a prominent bulge on the base of the hemisphere just caudal to the olfactory peduncle (Shipley & Reyes, 1991). Like the anterior olfactory nucleus and piriform cortex, the olfactory tubercle has a superficial plexiform layer, but the deeper cellular architecture of the tubercle is intermediate between a cortical and a striated structure (Heimer *et al.*, 1987). Unlike the piriform cortex, the tubercle does not send a reciprocal projection to the olfactory bulb (Shipley & Reyes, 1991). In the monkey, the olfactory tubercle is subdivided into several parts (Turner *et al.*, 1978), but in humans it is poorly developed and difficult to distinguish (Price, 1990).

In man, the entorhinal cortex is located in the ventromedial surface of the temporal lobe. This area is comparatively large in humans. It constitutes an essential component of the hippocampal formation and the route through which the neocortex interacts with the hippocampus. Ramon y Cajal (Cajal, 1901–1902) identified it in humans and then differentiated seven layers.

Brodmann (Brodmann, 1909) called this region area 28, and depicted a medial area that he called area 34. Subsequent studies increased the number of divisions to as many as 23 different fields (Insausti *et al.*, 1995). In short, the entorhinal cortex of man is heterogeneous and complex. Knowledge about its connections derives largely from data in nonhuman primates. In the monkey, the olfactory input to the entorhinal cortex is about 12.5% of the total entorhinal surface area (Amaral *et al.*, 1987) whereas in the rat, at least half receives fibres from the olfactory bulb (Carmichael *et al.*, 1994). Such a diminution of the olfactory influence over the entorhinal cortex, and hence over the hippocampal formation, presumably reflects the greater prominence of the visual system in primates (Carmichael *et al.*, 1994). The entorhinal cortex in humans is probably involved in memory processing (Van Hoesen *et al.*, 1991).

Reciprocal connections of the olfactory system

One feature of the olfactory system that distinguishes it from other sensory systems is a tremendously rich supply of centrifugal fibres (Doty *et al.*, 1997). The most prominent projections to the olfactory bulb come from the pyramidal cells of the anterior olfactory nucleus, the piriform cortex, the lateral entorhinal cortex, the amygdaloid areas, the nucleus of the lateral olfactory tract, the diagonal band of Broca, the raphe nuclei, the locus coeruleus, and the hypothalamus (McLean & Shipley, 1987; Price & Powell, 1970; Shipley & Adamek, 1984). These centrifugal projections may play a substantial role in the modulation of behaviour (Pager *et al.*, 1972; Royet & Pager, 1980; 1981).

The secondary olfactory areas

The major projections of the piriform cortex are to the amygdala, entorhinal cortex, dorsomedial nucleus of thalamus, hypothalamus, ventral putamen, orbitofrontal cortex, and insular cortex (Benjamin & Jackson, 1974; Krettek & Price, 1978; Powell *et al.*, 1965; Price & Slotnick, 1983; Scott & Leonard, 1971). Direct input to the prefrontal cortex from the olfactory bulb and piriform cortex are also reported (Cinelli *et al.*, 1987; Gerfen & Clavier, 1979). The dorsomedial nucleus of the thalamus has connections with a wide expanse of orbitofrontal cortex (Potter & Nauta, 1979; Von Bonin & Green, 1949; Walker, 1940).

The orbitofrontal cortex is under-developed in rodents compared with its significant representation in primates (Critchley & Rolls, 1996). In the macaque, the orbital and medial parts of the prefrontal cortex constitute just over half of the pre-frontal cortical surface area and approximately 6% of the total cortical surface (Carmichael *et al.*, 1994). Analysing the architectonic structure of the orbital and medial parts of the prefrontal cortex, these authors reveal a mosaic of 22 distinct areas in the orbital and medial prefrontal cortex (Figure 1.5).

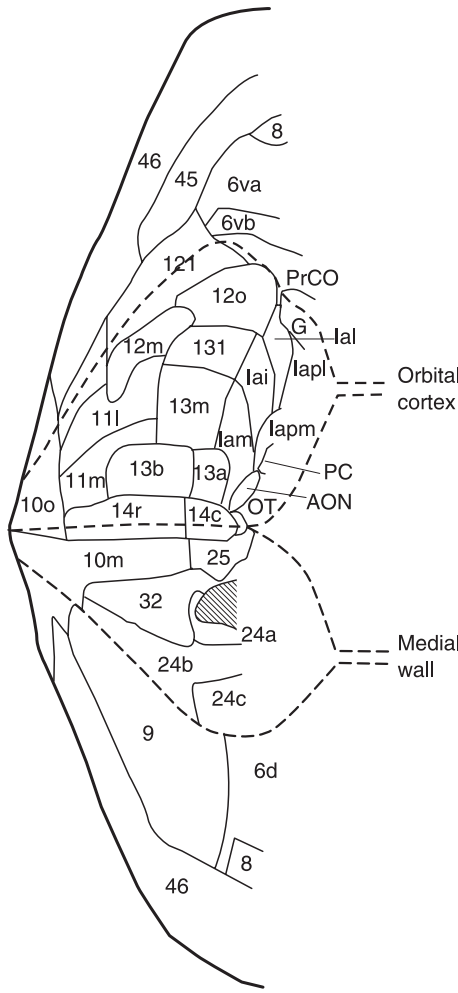

Figure 1.5 Unfolded map of prefrontal cortex showing the area boundaries. The top and bottom of the map represents the depths of the principle sulcus, and the orbital and medial wall cortices lie in the centre. AON, anterior olfactory nucleus; G, gustatory cortex; Iai, Ial, Iam, Iapl and Iapm, intermediate, lateral, medial, posterolateral and posteromedial agranular insular area; OT, olfactory tubercle; PC, piriform cortex; PrOC, precentral opercular cortex. (From Carmichael *et al.*, 1994.)

Most of these are subdivided from seven larger areas originally defined by Walker (Walker, 1940). Of the 22 areas, nine receive a direct projection from the primary olfactory cortex (Carmichael *et al.*, 1994) without an intervening synapse in the dorsomedial thalamus in contrast to other sensory modalities. In the rat, the orbitofrontal cortex plays a role in the organisation of odour-guided

behaviour and in cross-modality integration (Eichenbaum *et al.*, 1980). In the monkey, it is involved in associational learning (Rolls, 2004).

Function

Until recent developments in human brain imaging, understanding of the neural correlates of human olfaction was obtained from human lesion studies (Abraham & Mathai, 1983; Eichenbaum *et al.*, 1983; Eskenazi *et al.*, 1988; Gazzaniga *et al.*, 1975; Gordon & Sperry, 1969; Mair & Engen, 1976; Zatorre & Jones-Gotman, 1991). With the development of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), it was possible to reveal large-scale activation patterns associated with particular cognitive processes, allowing the identification of the neural networks specifically activated by chemosensory stimuli (Royet & Plailly, 2004; Zald & Pardo, 2000; Zatorre & Jones-Gotman, 2000). These emerging data are providing an exciting new understanding of brain function and are leading to specific and exceptional insights, as discussed below.

When odorants are passively delivered to subjects, the right orbitofrontal cortex is activated and sometimes the piriform cortex (Francis *et al.*, 1999; Levy *et al.*, 1997; O'Doherty *et al.*, 2000; Savic *et al.*, 2000; Small *et al.*, 1997; Sobel *et al.*, 1997; 1998; 2000; Yousem *et al.*, 1997; Zatorre *et al.*, 1992). The right orbitofrontal cortex is always activated, independently of which side of the nose is stimulated, although the right nostril stimulation is a more effective stimulus (Savic & Gulyas, 2000; Zatorre & Jones-Gotman, 2000). Asymmetry is also observed in the perception of complex stimuli by other sensory modalities (Bryden & Bulman-Fleming, 1994). The relative lack of activation of the piriform cortex is consistent with rapid habituation after an initial rapid activation (Poellinger *et al.*, 2001; Sobel *et al.*, 2000) as observed in rat piriform cortex (Litaudon *et al.*, 1997). The odorant-activated region of the orbitofrontal cortex (within Brodmann Area 11) is more posterior than that identified in human lesion studies (Brodmann Area 13) (Abraham & Mathai, 1983; Jones-Gotman & Zatorre, 1993; Rausch *et al.*, 1977; Zatorre & Jones-Gotman, 1991; Zucco & Tressoldi, 1988). This odorant-activated region is strongly connected with the piriform cortex and amygdala (Zald & Pardo, 2000; Zatorre & Jones-Gotman, 2000), is structurally homologous to Walker's area 13 in the monkey (Walker, 1940) and has been identified previously as an olfactory area in humans (Petrides & Pandya, 1994).

When odorants are delivered to subjects involved in specific olfactory tasks, it is possible to reveal more detailed information regarding successive

steps of odour processing. These tasks currently used in olfaction research (detection, discrimination, recognition memory, identification) (Dade *et al.*, 2002; Kareken *et al.*, 2001; Savic *et al.*, 2000; Zatorre & Jones-Gotman, 2000), or inferred from recent concepts of cognitive psychology (intensity, pleasantness, familiarity and edibility judgements) (Royet *et al.*, 1999) reflect different levels of olfactory processing, ranging from simple sensory analysis to deep or semantic analysis. They have revealed specific activation in a neural network including many brain regions (orbitofrontal, piriform, entorhinal, and inferior frontal cortices, amygdala, hypothalamus, cingulate gyrus, thalamus, insula, cerebellum, visual areas). Overall, olfactory functions seem to be organised in both *a parallel and hierarchical manner*, depending on the character and complexity of the task (Royet *et al.*, 1999; 2001; Savic *et al.*, 2000).

Odour familiarity and memory

The piriform cortex in humans appears to be involved in odour recognition memory, as indicated by strong bilateral PET activity in long-term, rather than short-term, recognition tasks (Dade *et al.*, 2002). In the rat, the piriform cortex is involved in associative learning and memory (Haberly & Bower, 1989; Hasselmo & Barkai, 1995; Jung *et al.*, 1990; Litaudon *et al.*, 1997). Consistent with this, the human piriform cortex is active during odour familiarity judgments (Plailly *et al.*, 2003), in addition to the right orbitofrontal cortex (Royet *et al.*, 1999; 2001). Other structures of the medial temporal lobe such as the hippocampus and the perirhinal and parahippocampal regions are currently of interest in several aspects of memory such as associative versus non-associative memory, episodic versus semantic memory and recollection vs. familiarity (Squire *et al.*, 2004). Accordingly, it is not surprising that these areas are activated during odour discrimination (Kareken *et al.*, 2003; Savic *et al.*, 2000), familiarity judgements (Plailly *et al.*, 2003) and during familiar odour stimulation (Savic & Berglund, 2004). Further studies are needed to clarify the specific roles of these different areas in olfactory memory.

'Working memory' refers to the short-term maintenance and active manipulation of information while performing complex cognitive tasks (Baddeley, 1996). There is much evidence that the prefrontal cortex is involved in working memory (Goldman-Rakic, 1995). Both olfactory and face working memory engage the dorsolateral, ventrolateral and frontal polar cortices, leading to the conclusion that working memory engages frontal cortical areas independently of the sensory modality, although modality-specific populations of neurons within these regions cannot be excluded (Dade *et al.*, 2001).

Odour identification

The left inferior temporal gyrus (BA 47) is activated in making edibility judgements about odours, a task thought to involve the activation of semantic odour representations (Royet *et al.*, 1999). We demonstrated that activation of this area was related to naming odours, an interpretation corroborated by more recent studies showing its activation during odour identification (Kareken *et al.*, 2003). Activation of this region during a familiarity judgement task is also reported, reflecting the fact that odour familiarity is a strong predictor of odour naming (Royet *et al.*, 1999; Savic & Berglund, 2004). Edibility judgments about odours also activate visual areas (Qureshy *et al.*, 2000; Royet *et al.*, 1999; 2001). Visual areas may be important for evoking the object evoked by the odour, participating in the semantic processing of odours, and hence assisting in judgements about edibility.

Odour pleasantness and hedonic judgement

It is well known that the most salient characteristic of an odour is pleasantness (Engen & McBurney, 1964), but involvement of orbitofrontal cortex and amygdala in this perception was shown only recently. Highly aversive odorants activate the left orbitofrontal cortex and the amygdala bilaterally, while less aversive odorants activate only the left orbitofrontal cortex (Zald & Pardo, 1997). The left orbitofrontal cortex and amygdala further operate in unison when exposed to an unpleasant odorant but not during a task involving only odorant detection (Zald *et al.*, 1998). The left orbitofrontal cortex, temporal pole, and superior frontal gyrus are activated in PET scans when subjects are presented with emotionally valenced olfactory, visual and auditory stimuli (Royet *et al.*, 2000). This suggests that pleasant and unpleasant emotional judgments call upon the same core network in the left hemisphere regardless of the sensory modality. In contrast, the left amygdala is more easily activated by emotionally valenced olfactory stimuli than by other sensory stimuli (Royet *et al.*, 2000). This is consistent with the idea that odours are more emotional and more potent activators of the amygdala than visual and auditory stimuli.

Odour and taste intensity are shown to be associated with activation of the amygdala and piriform cortex (Anderson *et al.*, 2003; Rolls *et al.*, 2003; Small *et al.*, 2003). However, activity within the left amygdala and piriform cortex is also found to be significantly correlated with subjective ratings of perceived aversiveness, but not with perceived intensity (Royet *et al.*, 2003; Zald & Pardo, 1997). These apparent discrepancies are explained by the fact that unpleasant odours can induce intense negative emotional reactions (e.g. disgust; see Chapter 3) whereas pleasant odours rarely induce intense emotional reactions

(e.g. euphoria). Thus, the greater activation by unpleasant odours reflects the strength of the emotional response rather than sensory intensity. This is consistent with the hypothesis that the amygdala mediates both negative and positive emotions, and that differences in activity of this area stem from the intensity of the induced emotion (Rolls, 1999). Accordingly, the activation of the amygdala by negative stimuli (Gottfried *et al.*, 2002; Royet *et al.*, 2003; Zald & Pardo, 1997) can be explained by the level of arousal that these stimuli induce (Zald, 2003). For a more detailed analysis of the contribution of the amygdaloid complex to olfactory function, see Chapter 3.

In contrast to the amygdala, the left orbitofrontal cortex is activated when subjects are specifically asked to judge whether an odour is pleasant or unpleasant compared to passively smelling these same odorants (Royet *et al.*, 2003). This finding suggests that the left orbitofrontal cortex is involved in the conscious assessment of the emotional quality of odours. Hence, orbitofrontal cortex activation during passive detection of mildly pleasant and unpleasant odorants (Zald & Pardo, 1997) is probably evoked by spontaneous hedonic judgements.

The insular cortex is activated by both olfactory and gustatory stimulation (Cerf-Ducastel & Murphy, 2001; Faurion *et al.*, 1999; Kareken *et al.*, 2003; Savic *et al.*, 2000; Small *et al.*, 1997; 1999; Zatorre *et al.*, 1992), especially when stimuli are unpleasant (Royet *et al.*, 2003; Zald *et al.*, 1998). 'Pure' olfactory stimuli such as vanillin activate only the primary olfactory areas, while irritating stimuli such as acetone activate the anterior and central insula and claustrum (Savic *et al.*, 2002). The activations with acetone are reported to resemble those observed with various painful stimuli (Casey *et al.*, 1996; Rainville *et al.*, 1999), and are therefore attributed to trigeminal stimulation by acetone. Insular activation is also observed after tactile, electrical, vibratory and thermal stimulations, as well as swallowing, urinary retention/micturation and visceral stimulation (Peyron *et al.*, 2000). Insula activation is also found during biological urges, such as dyspneoa, hunger, thirst and nausea (Banzett *et al.*, 2000; Peiffer *et al.*, 2001; Tataranni *et al.*, 1999), as well as during a variety of emotional conditions such as exposure to frightening faces, sadness, anguish, fear, happiness, sexual excitation, phobia and obsessive-compulsive urges (Damasio *et al.*, 2000; Morris *et al.*, 1998; Rauch *et al.*, 1995). It is thought that the anterior insula may therefore serve as an internal alarm centre alerting the individual to potentially distressing interoceptive sensory stimuli, and imbuing them with negative emotional significance (Reiman, 1997). Consistent with this interpretation, we recently showed that the anterior insula is activated when subjects inhale a disgusting odour as well as when they observe faces showing expressions of disgust (Wicker *et al.*, 2003).

Summary and conclusions

The last decade has witnessed tremendous advances in the understanding of the olfactory system. Advances in genetics and molecular biology have provided an understanding of the sensory transduction in the olfactory epithelium and have elucidated the spatial mechanisms underlying the encoding of odorant properties in the olfactory bulb. Advances in brain imaging are confirming the neuroanatomy of olfactory regions in the human brain and allowing, for the first time, analyses of the neural correlates of complex olfactory functions in human cognition. For example, insights into brain lateralisation can be gained from the common finding of the PET and fMRI studies described above, that the right hemisphere is more involved in recognition memory, whereas the left hemisphere is more involved in the emotional processing of odours. These basic perceptual processes appear to be lateralised in the orbitofrontal cortex and primary olfactory areas (for review, Royet & Plailly, 2004).

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2

Olfaction and the temporal lobes

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Introduction

There was a time in the history of anatomy and medicine when the temporal lobes were considered to be *the* olfactory brain. In an early paper describing a patient with a brain tumor and olfactory auras, Jackson and Beevor (1889a) refer to the 'anterior tip of the temporo-sphenoidal lobe' as the 'pyriform or hippocampal lobule' (p. 350). They also mention that Broca had described this part of the brain as being well developed in animals with a keen sense of smell, and as being rudimentary in animals with poorer smelling. Since then, our understanding of temporal-lobe function has evolved greatly. We know that the temporal lobes are heterogeneous structures consisting of several subregions, and that this complex set of structures participates in a wide variety of cognitive and emotional functions and behaviors. However, the old wisdom that the temporal lobes have a great importance in olfaction is still valid, and in this chapter, we review the main findings elucidating this relationship.

A brief overview: anatomy and uniqueness of the olfactory system

In most senses, the primary sensory area consists of one region, and adjacent areas usually constitute the secondary sensory regions. In olfaction, however, a whole *series* of structures constitutes the primary olfactory cortex (POC), and interestingly, some of these structures are not cortical. Carmichael *et al.* (1994) listed eight principal structures that constitute the POC in the macaque monkey, and a similar composition can be assumed in humans: the anterior olfactory nucleus, the ventral tenia tecta, the piriform cortex, the olfactory tubercle,

the periamygdaloid cortex, the nucleus of the lateral olfactory tract of the amygdala, the anterior cortical nucleus of the amygdala and the rostral entorhinal cortex. In addition, dense clusters of small cells that constitute the islands of Calleja are found inserted within the POC structures (Price, 1990) and the most ventral portions of the claustrum join this complex. Furthermore, the nucleus of the diagonal band, even though not a cortical structure, receives fibres from, and sends them to the olfactory bulb (Carmichael *et al.*, 1994). Besides the fact that a number of structures jointly form the POC, these are interconnected via an elaborate and dense associational fibre system demonstrated in the rat (Price, 1990) and monkey (Carmichael *et al.*, 1994), and assumed in humans (Price, 1990).

The piriform cortex is only one portion of the POC located at the inferior fronto-temporal junction; its larger part, often referred to as the posterior piriform cortex, falls within the borders of the temporal lobe, whereas its smaller part, referred to as the anterior piriform cortex, falls within the most caudal portion of the orbitofrontal region of the frontal lobe. The piriform cortex receives the largest conglomeration of direct inputs from the olfactory bulbs, which is why it has traditionally been considered *the* primary olfactory cortex, and the fact that the POC contains a series of other structures has often been ignored. To make things more complicated, some authors who study the piriform cortex have proposed that this structure corresponds functionally more to a 'higher-order' or 'association' than a primary sensory area (Haberly, 2001; Johnson *et al.*, 2000), and refer to all POC structures including the piriform cortex as 'secondary olfactory structures' (Cleland & Linster, 2003). According to this view, the first central olfactory relay is in the olfactory bulbs, which extract specific stimulus features – a function characteristic of the primary sensory areas in the brain (Haberly, 2001; Johnson *et al.*, 2000).

Another series of structures constitutes the secondary olfactory cortex (SOC): these include the posterior orbitofrontal cortex (OFC), and probably the medial and subcallosal prefrontal cortex and the agranular insular cortex (Carmichael *et al.*, 1994; Price, 1990). The primary olfactory structures project to the SOC and to a series of subcortical regions including the thalamus, hypothalamus and ventral striatum (Price, 1990).

Besides anatomical complexity, there is an important cytoarchitectonic difference between the olfactory regions and the cortical areas belonging to other senses. The visual, auditory and somatosensory primary and secondary areas are neocortical (i.e. they have six cortical layers), but this is not the case in the olfactory system. Basically, the POC is a collection of structures belonging to allocortex (paleocortex) – the old (or 'primitive') cortex that is thinner and structurally less complex (having three cortical layers) than the neocortex

(Carmichael *et al.*, 1994; Mai *et al.*, 1997; Price, 1990). Further, the SOC (such as posterior OFC and rostral insula) belongs to agranular/dysgranular cortex without, or with poorly developed, layer IV (Carmichael & Price, 1994), which is not the case with other sensory systems. In other potential components of the SOC, layer IV is also poorly developed (gyrus rectus or area 14) or absent (the subcallosal gyrus or area 25) (Petrides & Pandya, 1994). Overall, both primary and secondary cortical areas in other senses (except gustation) belong to neocortex, whereas the first cortical processing in olfaction happens within the paleocortex and the second within agranular/dysgranular cortex. Only after that does olfactory information reach the fully developed six-layered neocortex.

Another feature of the olfactory system is that its link with the limbic system is more intimate than that of other sensory systems. First, the POC includes several superficial parts of the amygdala: the anterior cortical nucleus, nucleus of the lateral olfactory tract, and the periamygdaloid cortex. The periamygdaloid cortex in both the rat and monkey projects to deeper nuclei of the amygdala (Price, 1987). Second, the periamygdaloid cortex projects to the subiculum, and entorhinal cortex projects to the rostral hippocampus. Therefore, in olfaction, the link between the periphery and amygdala and hippocampus is di-synaptic, whereas in the other senses, limbic projections go through a series of cortical relays (Carmichael *et al.*, 1994). The hypothalamic area is also closely connected to, and can be considered part of, the olfactory system, as several POC structures send projections to the hypothalamus in the rat, and odorant stimulation elicits electrophysiological responses in the lateral hypothalamic area in the monkey (Price, 1985; 1990). Finally, a direct link between the olfactory bulb and the diagonal band was observed in the macaque monkey, and this is the only known direct sensory input to the basal forebrain (Carmichael *et al.*, 1994).

Importantly, input from the visual, auditory, somatosensory and gustatory senses enters the cortex through the thalamus, but this is not the case with olfaction. Olfactory input passes from the olfactory bulbs directly into the POC. The POC regions are directly connected with the presumed SOC (orbitofrontal and insular cortex) in the rat, but the POC and SOC do have an additional indirect link via the thalamus. However, the direct link between the primary and secondary olfactory areas is more prominent, and thalamic lesions do not induce anosmia or affect odour discrimination, suggesting that the transthalamic pathway is not the predominant route for transfer of olfactory sensory information (Price, 1985; Price *et al.*, 1991).

Overall, the neuroanatomy of olfaction is characterised by a higher degree of cortical and subcortical dispersion than the other senses, by an intimate association between the olfactory and the limbic system, by a unique cytoarchitectonic composition and a more distant relationship with neocortical structures

and by a direct input from the periphery to the POC and SOC that does not necessarily go through the thalamus. Clearly, the temporal lobe structures have an important role in this system.

Lesion studies

We have learned a great deal about the link between the temporal lobes and olfaction from lesion data. Olfactory functioning has been studied in various patient groups whose lesions involved the temporal lobes. However, the lesion data have often been inconclusive because the lesions were usually not strictly confined to the temporal lobes. Temporal lobe epilepsy (TLE) has been one of the commonly used models for the study of this relationship, because the olfactory system comprises some of the structures that are a frequent source of epileptogenic activity. In TLE, cerebral damage is often restricted to the temporal lobes.

At the Montreal Neurological Institute, patients with TLE typically undergo one of two surgical procedures: corticoamygdalohippocampectomy (CAH, also known as an anterior temporal lobectomy) and selective amygdalohippocampectomy (SAH), see Figure 2.1.

Both procedures involve removal of medial temporal lobe structures, and the difference between the two resection types is in the amount of temporal neocortex resected (Trop *et al.*, 1997). A CAH typically includes a resection of 4 to 5 cm of cortex along the Sylvian fissure together with amygdala and varying amounts of hippocampus, whereas in an SAH, the neocortex is left intact except for a small incision that allows access to the medial structures. Using postoperative MRI scans, Dade *et al.* (2002) measured the extent of remaining tissue in different temporal-lobe structures in 21 patients who had undergone surgery for epilepsy. These data are shown in Table 2.1, together with the average extent of the same structures in the unoperated hemisphere.

As can be appreciated from these data, temporal lobe resections include removal of essential olfactory structures such as the piriform cortex (the mean of

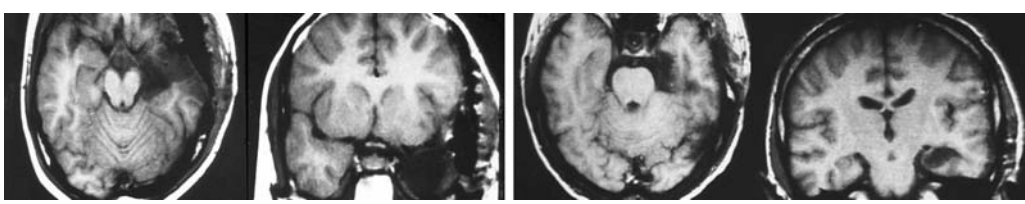

Figure 2.1 MRI scans showing a right corticoamygdalohippocampectomy (left two images: horizontal slice at left, coronal right) and a right selective amygdalohippocampectomy (right two images: horizontal slice at left, coronal right).

Table 2.1. MRI scan measurements: extent of tissue remaining in surgical hemisphere

Region of surgical resection	Left residual $N = 10$	Right residual $N = 11$	Measures of intact structures
Hippocampus [mean length (range)]	27 mm (16–39)	21 mm (8–38)	35 mm (17–40)
Entorhinal cortex [mean length (range)]	7 mm (0–15)	4 mm (0–10)	26 mm (23–30)
Parahippocampal cortex [mean length (range)]	19 mm (16–25)	15 mm (3–21)	22 mm (16–27)
Piriform cortex [tissue percentage (range)]	36 (0–78)	34 (0–100)	
Amygdala [tissue percentage (range)]	19 (0–33)	14 (0–33)	

From 'Olfactory learning: convergent findings from lesion and brain imaging studies in humans', by Dade *et al.* (2002, p. 88). Reprinted with permission.

spared piriform volume was 36% in left, and 34% in right resections), entorhinal cortex and the amygdala. Besides complete or partial removal of these structures, all patients had partial removals from the hippocampus and the parahippocampal gyrus, and those who underwent CAH had additional excisions along the superior temporal gyrus (mean 22 mm, range 5 to 50 mm) and along the inferior temporal gyrus (mean 43 mm, range 29 to 70 mm) (Dade *et al.*, 2002). Given that epilepsy surgery in the temporal lobe always encroaches on some of the crucial olfactory structures, patients with TLE do present an excellent model to study the relationship between olfaction and temporal lobes, and therefore the main findings obtained with these patients will be summarised here.

Olfactory functioning in temporal lobe epilepsy

Although not all reports from the literature have been consistent, it appears that damage to temporal-lobe structures does not necessarily lead to impairment in *olfactory sensitivity*. Several studies have shown that excisions from the left or right temporal lobe are not associated with decreased odour detection thresholds (Eskenazi *et al.*, 1983; Jones-Gotman & Zatorre, 1988, 1993; Kohler *et al.*, 2001; Zatorre & Jones-Gotman, 1991). In contrast, lesions to either temporal lobe were associated with *odour quality discrimination* impairments: these were either limited to the nostril ipsilateral to the lesion (Zatorre & Jones-Gotman, 1991), or were present regardless of the lesion side (Eskenazi *et al.*, 1983). Similarly, patients with unilateral temporal lobe excision consistently display deficits on tests of *odour identification* (Carrol *et al.*, 1993; Eskenazi *et al.*, 1983; 1986; Jones-Gotman & Zatorre, 1988; Jones-Gotman *et al.*, 1997; Kohler *et al.*, 2001). Olfactory findings from the patient H.M. support the notion that the temporal lobes are important for olfactory discrimination and identification: H.M. had bilateral medial temporal lobe damage and was completely unable

to discriminate among different odour qualities or to identify odours, even though his olfactory sensitivity, suprathreshold intensity discrimination and olfactory adaptation were normal (Eichenbaum *et al.*, 1983). Several studies have reported deficits in *odour memory* in epilepsy patients after unilateral resection from a temporal lobe (Abraham & Mathai, 1983; Carrol *et al.*, 1993; Dade *et al.*, 2002; Eskenazi *et al.*, 1983; 1986; Jones-Gotman & Zatorre, 1993; Rausch *et al.*, 1977), but evidence for a possible hemispheric asymmetry (the deficit being more pronounced after right temporal excision) was inconsistent. Notably, odour memory impairments after temporal lobe resections were observed with a variety of memory testing paradigms and over a range of delays (i.e. from 10-second to 24-hour delay intervals).

Very few studies have examined preoperative olfactory functioning in TLE patients. West *et al.* (1993) and Martinez *et al.* (1993) reported impairments in odour discrimination, identification and memory before surgery. Jones-Gotman *et al.* (1997) also found a deficit in olfactory identification in unoperated TLE patients: those with a left focus were impaired only on the left nostril, whereas those with a right focus were impaired on both nostrils. Taken together, these findings suggest that olfactory deficits arising from temporal-lobe dysfunction are often present before surgery.

Olfactory auras

Epileptic olfactory hallucinations (OH) are typically described as brief sensations of smell, lasting 5 to 30 seconds (Acharya *et al.*, 1998), although prolonged OHs lasting minutes to hours and even days, have also been described (Lehrner *et al.*, 1997; Manford & Shorvon, 1992; Potolicchio *et al.*, 1986). However, OHs in epilepsy most often occur before or early in the seizure as the first ictal manifestation or the 'aura', which is why they are frequently referred to as olfactory auras. Yet, OHs have also been described as part of the so-called epileptic prodromes, thus preceding seizures by a longer period of time (Lehrner *et al.*, 1997).

The reported incidence of epileptic olfactory auras varies greatly in the literature, from 0.6% to more than 30% (Acharya *et al.*, 1998; West & Doty, 1995). Despite this disparity across different studies, the general belief that olfactory auras are rare compared with other types of aura has been expressed many times (Daly, 1958; Gastaut *et al.*, 1955; Gupta *et al.*, 1983; Lennox & Cobb, 1933; Penfield & Perot, 1963). However, several authors have suggested that the reported numbers of olfactory hallucinations and illusions in epilepsy are most likely underestimated (Daly, 1958; Howe & Gibson, 1982; West & Doty, 1995).

The traditional view of epileptic olfactory auras has been that they are nearly always unpleasant (Jackson, 1871; Penfield & Jasper, 1954), and common auras

included odours of decay, excrement, burning objects, or chemical smells (Greenberg, 1992). However, a review of the literature reveals that neutral and pleasant descriptions also occur but are far less frequent (Acharya *et al.*, 1998; Daly, 1958; Greenberg, 1992; Mizobuchi *et al.*, 1999). These included food, plant, perfume, and environmental odours (Greenberg, 1992).

The neuroanatomical substrate of epileptic OHs has not been defined precisely, but a clear link has been made with temporal-lobe structures. Hughlings Jackson was among the first to describe OHs in epilepsy and to relate these to temporal-lobe abnormality (Jackson, 1871; Jackson & Beevor, 1889a, 1889b; Jackson & Stewart, 1899). One of the most illustrative cases was a patient who experienced a 'very horrid smell of burning dirty stuff' as part of her seizures (Jackson & Beevor, 1889a, 1889b). Post-mortem examination of her brain revealed a large right temporal-lobe tumor, which included the anterior part of the temporal lobe, the amygdala, and the white matter in the temporal lobe. Based on a series of cases with olfactory auras and the available literature at the time, Jackson proposed the 'uncinate region' to be the crucial brain region for the sense of smell.

Daly (1958) described a patient with epileptic OHs whose lesion was restricted to the right uncus and amygdala, leading him to affirm that the uncus was a cortical centre for smell. Penfield and Jasper (1954) held that 'the localisation of discharge is doubtless in or near the uncinate gyrus' when olfactory seizures occur (p. 26). Acharya *et al.* (1998) reported medial temporal spikes in the interictal EEG of all patients with olfactory auras; in addition, seizures with olfactory auras were localised to the temporal region. Twelve of their 13 patients with OHs had a visible MRI abnormality, and 11 of these had involvement of the amygdala. In another series of 12 patients with olfactory auras, 11 had structural lesions, all of which involved the medial temporal-lobe structures; five of these had amygdala involvement, whereas the lesion was restricted to the amygdala in two (Chen *et al.*, 2003). The side of temporal-lobe lesion appears not to be a determining factor in the occurrence of olfactory auras, as they have been reported with both left- and right-sided lesions (Acharya *et al.*, 1998; Chen *et al.*, 2003). For further detailed analysis of olfactory auras/hallucinations, see also Chapters 17 and 18.

Electrophysiological stimulation of the temporal lobes

The literature on electrophysiological stimulation of the temporal lobes abounds with reports of experiential phenomena, such as auditory and visual hallucinations, reminiscences and déjà vu experiences, but elicitation of OHs has been rare (Gloor *et al.*, 1982; Halgren *et al.*, 1978; Jasper & Rasmussen, 1958;

Penfield & Perot, 1963). Penfield and Jasper noted that stimulation of the olfactory bulb produced olfactory sensation regularly, whereas stimulation of the uncus produced it only occasionally. Gloor and colleagues (1982), stimulating both hemispheres, reported that only one of the 35 patients experienced OHs upon electrical stimulation of the left amygdala. Others also elicited OHs with stimulation of the amygdala (Andy, 1967; Andy *et al.*, 1975; Jasper & Rasmussen, 1958; Penfield & Jasper, 1954; Van Buren, 1961). Notably, the induction of olfactory hallucinations has not been restricted to olfactory bulbs and temporal-lobe structures; these phenomena have also been induced by stimulation of the insular cortex (Jasper & Rasmussen, 1958; Penfield & Jasper, 1954) and of thalamic nuclei (Nashold & Wilson, 1970).

Other methods revealing the role of temporal lobes in olfaction

Electroencephalographic (EEG) recordings in response to olfactory stimulation have been studied in humans and show reproducible olfactory event-related potentials (OERPs). Hummel *et al.* (1995) showed that these responses had longer latencies in patients with left- or right-sided temporal lobe foci than in healthy control subjects, but only after stimulation to the nostril ipsilateral to the epileptic focus. Their findings also indicated that TLE affected the processing of olfactory but not trigeminal information. OERP studies have greatly advanced our understanding of cognitive processing involving olfaction, and the main strength of this approach is the temporal precision with which events can be monitored. However, a limitation of surface or scalp EEG studies is that the spatial resolution of this method is quite imprecise. Surface OERPs are recorded from multiple sites on the scalp but seem to have the largest amplitude over parietal regions, at least in healthy participants (Hummel *et al.*, 1992), but even with topographic analysis the precise localisation of the brain areas generating these potentials is difficult to define.

The method of stereotactic EEG (SEEG) using depth electrodes implanted in the brain overcomes this problem because it combines the good temporal resolution of a standard EEG approach with an improved spatial resolution: the potentials are recorded directly from the brain regions of interest. This is an invasive procedure that is applied only in patients for whom it is expected to contribute to the presurgical diagnostic evaluation. At the Montreal Neurological Institute, SEEG studies are conducted in patients who are candidates for surgical treatment for epilepsy, and in whom other diagnostic methods (scalp EEG, magnetic resonance imaging, neuropsychological evaluation) did not lead to a conclusive localisation of the epileptic focus. Most frequent candidates for such a procedure are patients with bitemporal

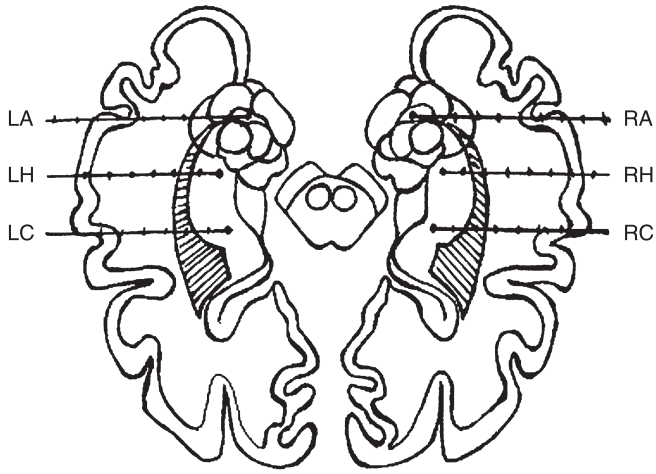

Figure 2.2 Typical placement of electrodes within the limbic structures of the temporal lobes in bitemporal epilepsy. Electrode LA goes through the second temporal gyrus, with its tip in the core of the amygdala. Electrode LH goes through the second temporal gyrus into the anterior hippocampus. Electrode LC, also through the second temporal gyrus, ends in posterior hippocampus or in the parahippocampus. RA, RH and RC are same placements in the right temporal lobe. Figure from 'Stereotactic intracranial recording (Stereo-electroencephalography)', by Olivier & Boling (2000). Reproduced with permission.

abnormalities, and less frequently, patients in whom the hemisphere generating epileptic activity is known but the site of focus within the hemisphere needs to be established. Usually there are several stimulation/recording sites along the length of the electrodes, and those that pass from the temporal neocortex into the amygdala and the hippocampus are the most relevant for SEEG studies of olfaction (Figure 2.2).

Hudry and colleagues (2001) were the first to demonstrate reproducible OERPs in the human amygdala, and these were limited to amygdala as none occurred in the temporal neocortex or hippocampus. The potentials were elicited exclusively by olfactory stimulation; sniffing in the absence of an odour did not produce an electrophysiological response. Furthermore, stimulus repetition and novelty modulated peak latencies and amplitudes (Hudry *et al.*, 2001; 2003), showing that the activity in the amygdala is influenced by recent odour experiences, and suggesting an amygdalar role in selective attention and short-term memory for odours. These results show that SEEG permits the recording of neural activity with excellent temporal and spatial resolution, providing a promising tool with which to refine our understanding of the role of the temporal lobes, and amygdala in particular, in human olfaction.

Summary of findings in TLE

Whilst the findings on detection thresholds remain inconclusive, there is no doubt that unilateral resection of medial temporal-lobe structures leads to impairments in olfactory discrimination, identification, and memory, suggesting a clear functional role of these brain regions in olfaction. Olfactory hallucinations and related experiences occur in patients with TLE, but relatively infrequently. Although the neuroanatomical substrate of these experiences is poorly understood, they have been most consistently associated with the amygdala and the uncus. In keeping with this, electrophysiological stimulation within the temporal lobes indicates that subjective olfactory experiences can be elicited by stimulation of the uncus and amygdala, whereas repeated stimulation of the hippocampus has not induced such experiences. Finally, olfactory evoked potentials have been recorded directly from the amygdala, suggesting a crucial role for this structure in olfactory processing.

Functional neuroimaging of temporal lobe: contributions to olfaction

Odour-induced activations in the piriform cortex

The use of functional imaging techniques to study human olfaction began in 1992, with publication of the first study by Zatorre and co-workers using positron emission tomography (PET). Zatorre *et al.* demonstrated odorant-induced activity in the piriform cortex bilaterally and in the right orbitofrontal cortex (Figure 2.3), corresponding to the primary and secondary olfactory cortical areas for the sense of smell.

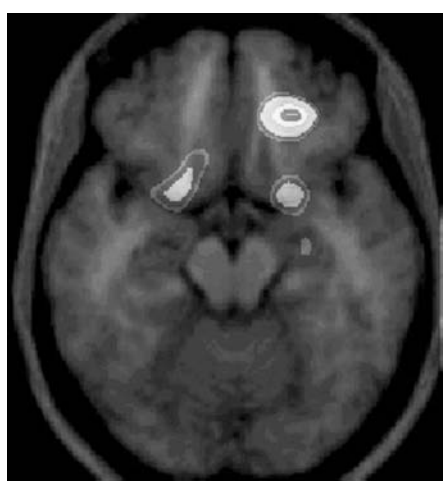

Figure 2.3 Cortical regions activated by olfactory stimulation: the piriform cortex bilaterally, and the right orbitofrontal cortex. Data reported in Zatorre *et al.* (1992). For a colour version of this figure please see Plate 1.

Soon after this landmark study, it became clear that *piriform cortex* is not invariably activated with olfactory stimulation, as several subsequent studies could not replicate the piriform activation (reviewed in Zatorre & Jones-Gotman, 2000). However other studies did demonstrate clear activation of the piriform cortex. Many of these reported bilateral POC activation, while others found it only on the right or only on the left.

The inconsistent activation (i.e. only left, only right, bilateral, or lack of POC activation) of the POC in response to odorants is puzzling; in particular, the lack of POC activation in the context of increased activity in other regions including the secondary olfactory cortex appears strange, but has been noted in a number of studies that used a broad range of odorous compounds and different experimental designs. Several hypotheses have been proposed to explain this inconsistent piriform activation: these included a fast habituation in piriform cortex (Poellinger *et al.*, 2001; Sobel *et al.*, 2000) and involvement of piriform activation in the control/baseline tasks (Sobel *et al.*, 1998). Sobel *et al.* (1998; 2000) showed that activation in the piriform cortex can be induced by sniffing, regardless of whether an odorant is present or not. However, Kareken and colleagues (2004) found no difference in activations of the piriform cortex and surrounding structures when odourless stimulation was presented, regardless of whether participants sniffed actively or not (the latter condition used the technique of velopharingeal closure). Furthermore, odorant exposure elicited activity in the POC regardless of active sniffing vs. passive delivery, indicating that odorant stimulation was a more important factor than sniffing in inducing POC activation. Cerf-Ducastel and Murphy (2001) showed that odorants delivered in aqueous solutions through the mouth (and thus presented retronasally) also induce activation in olfactory regions of the brain, including piriform and OFC, entorhinal cortex, hippocampus, and amygdala, confirming that a piriform response can be induced by odorants without sniffing.

Two studies showed a change in the functional neuroanatomy of the olfactory response over time (Poellinger *et al.*, 2001; Sobel *et al.*, 2000). Piriform activation in response to odorants declined rapidly despite continued stimulus presentation and detection. This finding in humans is consistent with Wilson's (1998) demonstration of a rapid habituation in the piriform region in the rat. Further, Poellinger and colleagues (2001) found that brain structures other than piriform cortex are involved in habituation: these included entorhinal cortex, amygdala, hippocampus and anterior insula.

Few studies have explicitly examined the specific functional contributions of different brain structures, and of the POC in particular, to olfactory processing. Some have suggested an involvement of the piriform cortex in higher-order,

rather than only in basic olfactory functions. Dade and colleagues (1998; 2002) showed piriform participation in recognition but not in encoding of odorants, suggesting its role in memory processing. In a series of studies, Gottfried and colleagues have demonstrated a role of the piriform in establishing cross-modal, visual–olfactory associations (Gottfried *et al.*, 2002b; 2003; 2004). Two studies have shown piriform cortex activation that did not result from direct, physically present, olfactory stimulation (Djordjevic *et al.*, 2005; Gottfried *et al.*, 2004). Gottfried *et al.* (2004) showed that visual stimuli alone, provided that they had been paired with odours during an encoding phase, can elicit activation in the piriform cortex during a retrieval (recognition) phase, suggesting that piriform cortex may act as a storage of sensory-specific (olfactory) memories. Djordjevic and colleagues (2005) showed activation of the POC during perceiving and also during *imagining* smells. Those findings demonstrated a parallel between olfactory imagery and mental imagery in other sensory domains, which had also been shown to activate primary cortical areas within their respective modalities.

Some recent functional neuroimaging findings have demonstrated functional heterogeneity of the piriform cortex in humans such as that shown in the piriform cortex of rodents (for a review, see Wilson & Sullivan, 2003). Gottfried and colleagues (2002a) found that the posterior piriform cortex was activated by odours regardless of their valence, whereas the anterior piriform cortex was activated only by pleasant and unpleasant, but not neutral odours. Furthermore, the anterior piriform cortex displayed a differential temporal response to pleasant and unpleasant odours: whereas the response to a pleasant odour was stable over time, the response to an unpleasant odorant decreased. In a subsequent study, Gottfried and Dolan (2003) found that activation in the left anterior piriform cortex was greater with unpleasant than with pleasant odorants. These dissociations were consistent with the notion that the posterior piriform cortex may be involved in basic olfactory processing, whereas the anterior piriform cortex may be more involved in processing the affective quality of odorants.

To illustrate the locations of piriform activations reported in functional neuroimaging studies, we have plotted those found to date in the literature on a horizontal and a coronal MRI slice (Figure 2.4). We included only activations that were reported in terms of standardised stereotaxic space based on the atlas of Talairach and Tournoux (1988), which allowed a direct comparability of findings across studies.

Odour-induced activations in the amygdala

Besides the piriform cortex, which is the major recipient of input from the olfactory bulb (OB), several other temporal-lobe structures receive direct

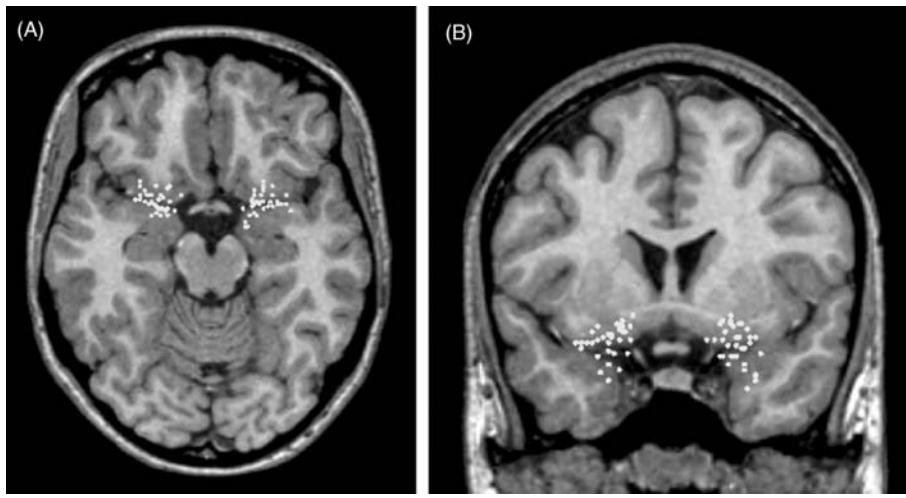

Figure 2.4 Location of odorant-induced piriform activations (36 left and 33 right) reported in 23 studies. Each dot represents one activation, and its location is determined by the reported coordinates. **A.** On the horizontal brain slice, *x* and *y* coordinates were plotted at $z = -16$, which was the average *z* coordinate of all 69 activations. **B.** On the coronal brain slice, *x* and *z* coordinates were plotted at $y = 3$, which was the average *y* coordinate of all 69 activations.

projections from the OB. These include periamygdaloid cortex, the anterior cortical nucleus and nucleus of the lateral olfactory tract of the amygdala, and a small anteromedial part of the entorhinal cortex. The anatomical demarcation of these structures in the context of PET and fMRI has been difficult, but activation in response to odorants has been reported repeatedly in the *amygdala* (for a review, see Royet & Plailly, 2004; Sobel *et al.*, 2003; Zald & Pardo, 2000; Zatorre & Jones-Gotman, 2000). The role of the amygdala in olfactory processing has been another topic of heated debate and is advanced in Chapter 3.

A unique feature of the olfactory system is that perception itself involves limbic structures, including the amygdala. The role of the amygdala in emotional processing has been long recognised, and it is therefore not surprising that the initial conceptualisations of its role in olfaction revolved around this notion. An early study showed large activation increases in amygdala bilaterally (Zald & Pardo, 1997) in response to a highly aversive odorant (a sulphide cocktail), whereas exposure to less aversive but still unpleasant odorants did not produce blood flow increases in the amygdala. Royet *et al.* (2000) showed that emotionally valenced (pleasant and unpleasant) odours, but not pictures or sounds, induced bilateral activation in the amygdala, suggesting a superior potency of olfactory over visual and auditory stimuli to activate the amygdala.

Similarly, Herz *et al.* (2004) found that memories evoked by odours elicited more activation in the left amygdala and parahippocampal gyrus than memories evoked by visual cues, consistent with a greater emotional salience of the memories induced by odours.

Interestingly, several recent studies (Anderson *et al.*, 2003; Gottfried *et al.*, 2002a; Rolls *et al.*, 2003; Wicker *et al.*, 2003) have reported findings that question the traditional view of the amygdala as the crucial structure for encoding affective aspects of odorants. Gottfried and colleagues (2002a) found that activity in the amygdala bilaterally was tuned to all odours (pleasant, neutral and unpleasant) regardless of their affective attributes, although some tendency for a stronger response with increasing odour unpleasantness was noted. Similarly, Gottfried and Dolan (2003) reported that activation in the left amygdala was elicited by all odours regardless of their emotional valence, whereas direct contrasting of brain activity induced by pleasant vs. unpleasant odorants did not produce any activation in the amygdala. Anderson *et al.* (2003) employed a different experimental design, using high and low concentrations of a pleasant and an unpleasant odorant, thus varying intensity and pleasantness independently. Their main finding was that amygdala activation was associated with the intensity and not the valence of odours. Rolls and colleagues (2003), using three pleasant and three unpleasant odours, also found activation in medial temporal-lobe structures to be associated with the intensity and not with the affective valence of odours. Finally, Wicker and colleagues (2003) found that the amygdala was equally activated by pleasant and disgusting odours when these were contrasted with neutral odours.

Other data show a basic sensory role of the amygdala in olfaction: Savic and colleagues have reported that passive smelling activates a cluster of structures that include piriform cortex and the amygdala (e.g. Bengtsson *et al.*, 2001; Savic & Berglund, 2004; Savic *et al.*, 2000). Occasionally, this cluster also included the insula and striatum. Taken together, these findings suggest that the amygdala together with some portions of the piriform cortex and some adjacent structures may participate in basic sensory olfactory processes such as passive smelling or odour detection.

In contrast, Royet and colleages (2003) compared pleasant and unpleasant odorants matched for intensity and found a stronger amygdalar response to unpleasant than to pleasant odorants. Given that the unpleasant odorants elicited stronger electrodermal responses than did the pleasant ones, these authors suggested that the amygdala responds preferentially to the arousal potency or the intensity of emotional reaction elicited by odours, rather than to odorant intensity or affective valence. Recent electrophysiological evidence (Hudry *et al.*, 2004) is consistent with this hypothesis: emotionally arousing odorants, whether

negative or positive, elicit shorter evoked potential latencies in the amygdala than do neutral odorants.

In yet another twist, Gottfried and colleagues (2003) demonstrated that the amygdala, together with the orbitofrontal cortex, also plays an active role in encoding the current reward value of predictive cues. Participants were scanned in three sessions whilst learning picture–odour associations, pre-satiety, and post-satiety. After the associations were formed, a pre-satiety session was conducted, following which subjects were fed to satiety with a meal that was the source of the target odour, thus reducing the motivational/reward value of that odour. Subsequently, fMRI showed differential activations to the same visual stimuli (associated with the target odour in the learning session) after selective satiation/devaluation of the target odour. These were observed in two brain regions: the amygdala and the orbitofrontal cortex. Responses decreased from before to after being fed to satiety with the corresponding food, indicating that the reward value of predictive stimuli may be represented in these structures.

Overall, recent findings seem to converge towards the notion that the role of the amygdala may be at least partially different, or more versatile, in olfaction compared to other senses. The amygdala may be primarily involved in basic sensory processing, including encoding odour intensity, whereas some other structures, such as orbitofrontal cortex and some portions of the piriform cortex, may be involved in processing the affective and reward value of odorants. However, it has also been suggested that the motivational/reward value of predictive cues may be represented in an amygdala–orbitofrontal network, and some findings do suggest involvement of the amygdala in processing affective olfactory features, particularly with respect to arousal potency. Thus it seems that the amygdala participates in multiple aspects of olfactory processing, including basic perception and higher-order processes of affect, learning and motivation. It is possible that different parts of the amygdala subserve these different aspects: this remains an open question for future research.

Odour-induced activations in other temporal-lobe structures

Odour-induced activations have been reported less often in the *entorhinal cortex* than in the piriform cortex or the amygdala (Cerf-Ducastel & Murphy, 2001; Levy *et al.*, 1997; Poellinger *et al.*, 2001; Rolls *et al.*, 2003; Sobel *et al.*, 1998). Given that a very small portion of entorhinal cortex receives olfactory inputs and that increases in activations induced by odorants in this structure have been reported only rarely, the precise role of entorhinal cortex in olfactory processing remains unknown.

Another structure of interest in understanding olfaction is the *hippocampus*, as it receives projections from the entorhinal cortex (Carmichael *et al.*, 1994; Price *et al.*, 1991). Some olfactory studies have reported activation in the hippocampus (Bengtsson *et al.*, 2001; Cerf-Ducastel & Murphy, 2001; Poellinger *et al.*, 2001; Small *et al.*, 1997; Sobel *et al.*, 1999; 2000; Zatorre & Jones-Gotman, 2000). Jones-Gotman and colleagues (Jones-Gotman *et al.*, 1993; Zatorre & Jones-Gotman, 2000) found that odour recognition memory yielded similar findings of bilateral piriform and right OFC activation as odour perception, with an additional activation in the right posterior hippocampus. However, some later studies examining odour memory did not find hippocampal activation (Dade *et al.*, 1998; 2002; Savic *et al.*, 2000), although Savic and colleagues (2000) reported activation of the subiculum–hippocampus during discrimination of odour quality. Gottfried and colleagues (2002b) reported activation that decreased over time in the anterior hippocampus bilaterally during appetitive, but not aversive olfactory learning. Interestingly, Gottfried and Dolan's (2003) findings suggested that the anterior hippocampus, together with rostromedial orbitofrontal cortex, participates in the cross-modal integration of visual and olfactory information: these two regions were selectively activated by congruent, but not incongruent pairs of odours and pictures presented simultaneously, and both showed increased neural activity with higher perceived congruency of odour–picture pairs. This congruency-specific activity in the anterior hippocampus was thus consistent with its role in the creation of associations between cross-modal, in this case visual and olfactory, sensory inputs.

Finally, olfactory responses have been identified in a variety of regions other than the primary and secondary olfactory regions, including *temporal neocortex*. Increased activations in response to odours have been reported in the superior temporal gyrus and temporal pole (e.g. Cerf-Ducastel & Murphy, 2001; Poellinger *et al.*, 2001; Sobel *et al.*, 2000). However, the role of the temporal neocortex in olfactory processing is poorly understood. One explanation could be that these areas have been activated not by odour perception but rather because of their role in cognitive or some other type of processing elicited by specific task demands.

Concluding comments

The study of human olfaction has come a long way over the last two decades: findings from a range of lesion studies have converged towards the notion that the temporal lobes play an important role in olfactory processing, as their removal leads to significant olfactory impairments. Functional neuroimaging

techniques have made a substantial contribution to defining the neuroanatomy of human olfaction. Several authors have proposed hypotheses about the functional significance of different temporal-lobe structures, including piriform cortex, amygdala and hippocampus, in olfaction. Some of the most exciting findings suggest a functional heterogeneity not only between but also within the key olfactory brain regions, and the clearest illustration of this is dissociation between anterior and posterior piriform cortex (Gottfried *et al.*, 2002a). We have also learned that affective aspects of odorants may be processed within the primary and secondary olfactory cortex, which is not true for other sensory systems (except perhaps for gustation), and that therefore the role of the primary and secondary olfactory cortex seems to be far more complex than as mere relays of sensory information. Moreover, the role of the amygdala may be not only anatomically but also functionally unique, and more multifaceted in olfaction than in other senses. On one hand, it appears that the amygdala contributes to processing affective and arousal properties of odorants, which is similar to its role in other sensory modalities. On the other hand, unlike in other senses, it is apparently involved also in basic sensory processing.

In this chapter, we attempted to illustrate how information from functional neuroimaging complements and extends the knowledge we have gained about olfaction from studying disorders of the temporal lobes. Such integration of approaches and findings promises to broaden our understanding of the 'Olfactory brain'.

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3

Role of the insula in smell and disgust

Maike Heining and Mary Phillips

Introduction

The emotion of disgust

Disgust is an important emotion, as it is believed to have evolved to protect the individual from danger in the form of harmful substances, including those detected in the olfactory and gustatory modalities. Disgust (literally, 'bad taste') has been defined in terms of a food-related emotion. It has been recognised as a basic emotion since Darwin (1872/1998), who wrote that disgust was '... something offensive to the taste'. A more recent definition of disgust is offered by Rozin & Fallon (1987): 'Revulsion at the prospect of (oral) incorporation of an offensive object. The offensive objects are contaminants; that is, if they even briefly contact an acceptable food, they tend to render that food unacceptable'. Sources other than ingestion, such as sex or defence against infection (Rozin *et al.*, 2000) have also been proposed. A different approach to disgust, diverging from its definition based on taste, argues that it is based on the senses of touch and smell and that the taste–disgust association is more recent (Miller, 1997).

Like other emotions, disgust has a characteristic facial expression which is recognised across all cultures as shown in Figure 3.1 (Ekman & Friesen, 1976). This facial expression involves facial muscles necessary for the avoidance of ingestion of contaminants and consists of the closing of the nostrils and opening of the mouth. Features of this facial expression appear to be innate, as nose wrinkling and upper lip raising can be observed in neonates. The purpose of the facial expression is to inhibit ingestion of the repulsive object, the nostrils closing off serves to reduce the input of an offensive odour, whereas

Figure 3.1 A typical facial expression of disgust, clearly showing the nose wrinkle and the upper lip curl.

the opening of the mouth allows expulsion of offensive objects. The facial expression is usually accompanied by nausea, a physiological manifestation of rejection by reverse peristalsis and disgust. This is often associated with the consequences of ingestion of harmful stimuli and serves to discourage further or future ingestion. According to Darwin, (1872/1998), the physiological concomitants of disgust are the phylogenetic remainders of a voluntary vomiting system.

The output system of disgust, including the characteristic facial expression, appears to have remained stable during cultural evolution, and the main changes during development and across cultures appear to be the input system – the stimuli that elicit disgust (Rozin *et al.*, 2000). For example, decayed or fermented food is generally regarded as disgusting, but different cultures have their own exceptions: cheese for Europeans, meat for the Inuit and fish in fish sauce for Southeast Asians.

As disgust appears to have evolved to enable the avoidance of harmful substances, recognition of disgust-provoking stimuli is important, not only in the olfactory and gustatory modalities, but also through the recognition of facial expressions of disgust in others to facilitate vicarious learning of the avoidance of these substances. A close link between systems specialised to react to harmful odours, whether detected directly by the individual or indirectly by way of conspecific facial expression, is likely to have aided survival. A neural system

specialised for the identification of and response to disgusting stimuli presented in different sensory modalities would therefore be plausible.

The neural correlates of disgust

Evidence that there might be a specific neural substrate underlying the emotion of disgust first came from a study involving patients with Huntington's disease, in which there is neurodegeneration of the striatum, an area of the basal ganglia. These patients demonstrate a disproportionate impairment in the recognition of facial expressions of disgust. This finding was extended to non-symptomatic carriers of the gene associated with Huntington's disease. More recently an examination of a patient with a lesion of the left insula and basal ganglia has highlighted the importance of the insula in addition to the basal ganglia in the recognition of both facial and vocal expressions of disgust and the experience of disgust in humans (Calder *et al.*, 2001). Functional neuroimaging studies have provided further evidence for the role of the insula and the basal ganglia in the identification of facial expressions of disgust (Calder *et al.*, 2001; Phan *et al.*, 2002). The involvement of the insula is of particular interest here, given its role in smell (see below) and taste. One recent functional neuroimaging study (Wicker *et al.*, 2003) contrasted the viewing of facial expressions of disgust with the inhalation of disgusting odours which induced feelings of disgust, and showed that the same area of the anterior insula was activated in response to both tasks. This supports the suggestion that the same brain circuit is involved not just in the identification of disgust in others, but also in the subjective experience of disgust.

The neural correlates of smell

As discussed in more detail in the previous two chapters, the neural correlates of olfaction have been investigated in animal, lesion and neuroimaging studies. The piriform cortex appears to be the primary olfactory cortex, and the orbitofrontal cortex the secondary olfactory cortex, with other areas such as the amygdala and the insula also believed to play a role in olfaction.

Compared with other sensory modalities such as vision or hearing, there have been relatively few neuroimaging studies of human olfaction. These have been discussed in the context of more general temporal lobe function in Chapter 2. The first such study which was performed in 1992 using Positron Emission Tomography (PET) reported bilateral activation of the piriform cortex and activation of the right mediolateral orbitofrontal cortex, corresponding to the primary and secondary olfactory cortex, respectively. Bilateral piriform and orbitofrontal cortex activations were also reported in the first functional

Magnetic Resonance Imaging (fMRI) study to investigate the neural correlates of human olfaction. Since then there has been some inconsistency with regard to piriform cortex activation across studies, with some studies reporting activation in piriform cortex, but others finding activation in this area to be elusive. An explanation for this inconsistency was proposed by Sobel and colleagues (Sobel *et al.*, 2000). Using a block design during fMRI, the time course of the response in the piriform cortex was investigated and it was found that responses to olfactory stimuli habituate rapidly. This finding has been confirmed by Poellinger and colleagues (2001). They reported a 10 s to 15 s increase in the activation after stimulus onset, which then rapidly diminished to sub-baseline levels. It was suggested that the hippocampus and anterior insula follow a similar time course during olfactory activation.

Activation in the orbitofrontal cortex in response to odours has been far more consistent (Zald & Pardo, 2000). However, it is unclear what role lateralisation of the activation plays, as some studies report right orbitofrontal cortex activation, some left, and some, bilateral activation (Brand *et al.*, 2001). Activation in the right frontal lobe has been reported to be greater in females compared with males (Yousem *et al.*, 1999), whereas another study investigating sex differences in response to odours did not find any orbitofrontal cortex activation (Bengtsson *et al.*, 2001).

The roles of the piriform cortex, orbitofrontal cortex, amygdala and the entorhinal/hippocampal region in olfaction have been emphasised in a recent review of PET and fMRI studies of the human olfactory system (Zald & Pardo, (2000); and see Chapter 2). Another region that has been consistently activated in most functional neuroimaging studies of olfaction but has received little attention is the insula. A recent study investigating the integration of smells and tastes also reported insula activation (Small *et al.*, 2004). Judging by the regularity with which studies report insula activation in response to olfactory stimulation, this area must clearly play a role in the perception of odours.

Smells are rarely devoid of emotional salience, and odours have been shown to modulate the startle reflex in humans differentially, with unpleasant odours enhancing the startle reflex amplitude and pleasant odours reducing the amplitude (Kaviani *et al.*, 1998). Odorants have also been shown to induce basic emotions and elicit changes in autonomic nervous system activity, measured by various skin responses, respiratory frequency and heart rate (Vernet-Maury *et al.*, 1999). This suggests a strong hedonic component of odours. Despite this, few neuroimaging studies of olfaction have investigated the affective component, and findings broadly indicate that many of the brain regions associated with emotion perception are also involved in the perception of olfactory stimuli: the orbitofrontal cortex, amygdala and the insula.

It has been suggested that the amygdala participates in the hedonic processing of olfactory stimuli, especially aversive olfactory stimuli (Zald & Pardo, 2000), as the amygdala receives input from the piriform cortex which has been activated during exposure to unpleasant stimuli in other sensory modalities (Calder *et al.*, 2001; Phan *et al.*, 2002). The orbitofrontal cortex, which is thought to be involved in reward processing per se (Rolls, 1999), has been implicated in affective processing in general in previous neuroimaging studies, and is also thought to play a role in the processing of the affective component of odours. This link between reward and the processing of the affective component of odours in the orbitofrontal cortex has been shown very elegantly in an fMRI study investigating sensory specific satiety (O'Doherty *et al.*, 2000). In this study, subjects were scanned during exposure to two pleasant odours, vanillin and banana, before eating bananas to satiety. The fMRI scan was then repeated, and while activation to vanillin remained stable in the orbitofrontal cortex, the activation in response to the banana odour decreased, demonstrating that as the banana odour loses its reward value and its pleasantness, the activation pattern in the orbitofrontal cortex changes (O'Doherty *et al.*, 2000).

Royet and colleagues (2001) reported activation of the left orbitofrontal cortex in response to the hedonic judgement of odours. Unlike most other studies, subjects had to make a conscious decision whether an odour was pleasant or unpleasant, and they were exposed to both pleasant and unpleasant odours during the PET scan.

Regarding the neural correlates of perception of emotionally salient odours, activation of the left medial frontal lobe, inferior frontal cortex, and bilateral insulae have been demonstrated during olfaction per se, with pleasant odours producing increased left insula activation compared with unpleasant odours (Fulbright *et al.*, 1998). Another study reported increased blood flow in the left orbitofrontal cortex and bilateral amygdalae and in the insula (Zald & Pardo, 2000) in response to the perception of unpleasant (although not specifically disgusting) odorants. Left lateral orbitofrontal cortex has also been shown to have increased activation in response to unpleasant odours regardless of intensity in another study, whereas right medial orbitofrontal cortex showed greater response to pleasant than unpleasant odours regardless of intensity (Anderson *et al.*, 2003).

Although previous studies have investigated neural responses to unpleasant or aversive olfactory stimuli, only two (Heining *et al.*, 2003; Wicker *et al.*, 2003) have specifically investigated the neural responses to disgusting stimuli. With the exception of pheromones, some of which are thought to convey fear, anger and sexual attraction in animals and possibly also in humans, disgust is the only emotion that can be directly translated from visual and auditory stimuli

to olfaction. Both these studies report insula activation in response to disgusting smells. However, there is some discrepancy about the lateralisation, with one study reporting right insula activation in response to disgusting odours (Heining *et al.*, 2003) and the other study reporting mainly left insula activation in response to such odours (Wicker *et al.*, 2003).

As the olfactory system of the human brain is closely associated with the limbic system, potential areas of overlap between olfactory and emotion processing occur in the insula, amygdala and the orbitofrontal cortex. Since odours are rarely devoid of emotional significance, it is probable that the involvement of the orbitofrontal cortex, amygdala and insula demonstrated in the neural response to olfactory stimulation reflects, at least in part, processing of the emotional component of these stimuli.

The functional anatomy of the insula

Involvement of the insula in the perception of disgust and in the processing of smells has been detailed above. This section will explore the insula, its connections, and its functions in more detail.

As shown in Figure 3.2, the insula is part of the cerebral cortex and is situated at the base of the lateral sulcus. It is covered by the frontal, temporal and parietal opercula. Animal studies and human neuropathological and functional neuroimaging studies have helped elucidate the functional role of the insular cortex.

The insula has been shown to be involved in odour and taste aversion learning in animals (Calder *et al.*, 2001). Insula activation has also been demonstrated

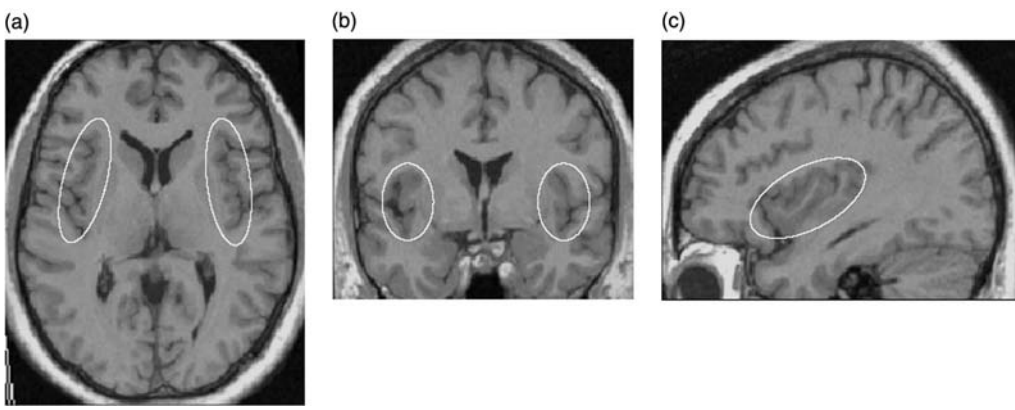

Figure 3.2 This figure shows the location of the insular cortex encircled in white. (a) Axial view. (b) Coronal view. (c) Sagittal view.

in human neuroimaging studies in response to both odours and tastes. In human stimulation studies, the insula has been shown to modulate behaviour such as swallowing, salivation, oesophageal contraction and vomiting. Stroke patients with a lesion confined to the posterior insula can present with a variety of symptoms, such as somatosensory deficits, gustatory disorders, dizziness, cardiovascular disorders and neuropsychological deficits including aphasia. Patients with insula tumours have reported symptoms such as nausea, retching and vomiting, or alternating diarrhoea and constipation. Functional neuroimaging studies in humans have demonstrated activation of the insula in response to visceral stimulation such as oesophageal distension. These findings show a close association of various functions of the insula with the manifestation of the experience of disgust, namely salivation, nausea, retching, and with the main senses eliciting disgust – namely smell and taste.

The anterior insula is also thought to be part of a nociception network, consisting of the thalamus, primary and secondary somatosensory cortices, the insula and the anterior cingulate gyrus. Nociceptive fields have been revealed in the insula by single cell recordings and local field potentials in rats and monkeys. Lesions to the insula cause a reduction in the affective component of pain and in appropriate responses to painful stimuli, and the anterior insula has been consistently activated in response to painful stimuli in human neuroimaging studies (Peyron *et al.*, 2000). Results of these studies suggest an integrative role of the insula, combining information about the nature of the painful stimulus from the secondary somatosensory cortex and thalamus with contextual information from other sensory modalities, modifying the response, especially autonomic, to noxious stimuli, and being involved in the affective component of pain, facilitating pain-related learning and memory. The close association of the posterior insula with somatosensory function has been supported by a recent neuroimaging study showing activation of the posterior insula in response to tactile stimuli (McGlone *et al.*, 2002). Middle and posterior insula activation has also been associated with temperature perception and was shown to correlate with perceived thermal intensity.

The insula also receives input from visual association and auditory cortices (Mufson & Mesulam, 1982), and has been shown to be activated in response to both auditory and visual stimuli, and patients with insula lesions have demonstrated a reduced emotional response to threatening visual and auditory stimuli. Activity within the insula can be modulated by both awareness of visual stimuli and autonomic arousal, as patients with peripheral autonomic denervation do not show insula activation in response to threatening stimuli (Critchley *et al.*, 2002). Furthermore, the insula has been implicated in crossmodal integration of senses in human neuroimaging studies (Calvert, 2001).

As the insular cortex receives input from several autonomic regions, and sends efferents to brain regions that play a role in regulating autonomic responses, it has been suggested that it is critical for visceral representation (Cechetto & Saper, 1990). Furthermore, it has been proposed that activation of the insular cortex during emotion is associated with the autonomic changes that occur in response to an emotion (Damasio, 1999).

Functional neuroimaging studies have also highlighted the role of the insula during recall of internally generated emotion, and during the experience of guilt, a complex emotion which, like the experience of shame, may involve self-directed disgust (Power & Dalgleish, 1997). There is therefore accumulating evidence for the role of the insula in mediating behaviour to aversive, including disgust-related, stimuli. The insula is ideally located to integrate information from different sensory modalities and from the autonomic system, and could therefore be involved in both the perception of disgust from various sensory modalities and the subjective experience of disgust.

Smell, disgust, the insula and psychiatric disorders

In recent years there has been increased interest in the emotion-processing abnormalities of psychiatric disorders (Phillips *et al.*, 2003). The main focus of research has been on fear and sadness, which have been considered important as underlying disorders such as anxiety disorder and depressive disorder, respectively. However, evidence for abnormal perception of disgust is beginning to emerge as relevant in the genesis of specific psychiatric conditions such as obsessive-compulsive disorder (OCD) or phobias (Phillips *et al.*, 1998), and is receiving more attention (special issue of *Journal of Anxiety Disorders*, 2002). In the remaining sections of this chapter, the focus will be on two psychiatric disorders which have been linked to both abnormal processing of disgust and to olfactory deficits: OCD and schizophrenia.

Obsessive-compulsive disorder (OCD)

The OCD is characterised by the persistent intrusion of intense and unwanted thoughts or images (obsessions), and repetitive, ritualistic behaviours or mental acts (compulsions) (DSM-IV, 1994). It is clinically heterogeneous and a symptom-dimensional approach has been proposed to take into account at least four symptom dimensions: contamination/washing, aggressive/checking, hoarding, and ordering/symmetry (Mataix-Cols *et al.*, 2004).

It has been suggested that disgust may play an important role in the psychopathology of OCD (Phillips *et al.*, 1998). There is a connection between

disgust and obsessions and compulsions in healthy individuals (Mancini *et al.*, 2001), even when controlling for gender, age, anxiety and depression. Washing and checking behaviours were particularly associated with disgust sensitivity, whereas anxiety and depression scores best predicted impulses and rumination. These findings also support the symptom-dimensional approach to OCD, and the hypothesis that at least some of those symptom dimensions, especially the contamination/washing symptoms, are related to disgust processing.

It is debated whether there is a specific deficit in the recognition of facial expressions of disgust in patients with OCD, with some studies finding this effect and others failing to replicate this finding. This could also be due to the heterogeneous nature of patients included in those studies.

Brain regions most commonly associated with OCD in neuroimaging studies include the orbitofrontal cortex and the basal ganglia (Saxena & Rauch, 2000). Several functional neuroimaging studies have investigated the brain responses to disgusting stimuli in patients with OCD compared to healthy individuals. Some studies have used generally disgusting stimuli, whereas others have employed stimuli that would only be perceived as disgusting by individuals with OCD. Increased insula activation was reported in response to disgusting stimuli in both control and OCD groups, with a greater increase in the right insula in the patient group than in the controls. However, when symptom-specific stimuli were employed such as photographs of ashtrays or sinks, which only evoke disgust in OCD patients with contamination/washing symptoms, insula activation was reported only in patients with those symptoms, but not in the control group or in OCD patients without these symptoms. A recent neuroimaging study specifically examining the different symptom dimensions in OCD found a correlation between anterior insula activation and washing rituals (Mataix-Cols *et al.*, 2004).

Structural neuroimaging studies have provided some evidence of anatomical abnormalities in patients with OCD, but these findings have been inconsistent, possibly due to the phenotypic heterogeneity of the patient groups. A recent study investigating structural brain alterations in OCD has taken the heterogeneous nature of OCD into account and correlated clinical variables with anatomical changes (Pujol *et al.*, 2004). However, the only significant correlation was between aggressive/checking symptoms and a decrease in the grey matter volume of the right amygdala compared with the rest of the OCD group. Overall, OCD patients showed a reduced grey matter volume in frontal cortex and insula, and an increase in striatal and anterior cerebellar volume.

Patients with OCD showed a significant impairment in olfactory identification compared to healthy individuals, and most were classified as mildly to

moderately microsmic (Barnett *et al.*, 1999). Again, OCD patients were investigated as a homogeneous group without looking at different symptom dimensions. However, OCD patients have been shown to have normal odour detection threshold sensitivity. It is therefore unlikely that the impaired ability to identify odours is caused by a decrease in olfactory acuity. Furthermore, the magnitude of impairment was considerably smaller than in patients with schizophrenia or with lesions of the orbitofrontal cortex.

There appears to be evidence of an abnormality in both emotion and olfactory processing in patients with OCD. The brain regions highlighted by neuroimaging studies of OCD are the orbitofrontal cortex and the basal ganglia, and to a lesser extent the insula. Both the insula and basal ganglia have been associated with the perception and experience of disgust (Calder *et al.*, 2001; Phan *et al.*, 2002), and the insula and orbitofrontal cortex have been implicated in the processing of olfaction and emotion processing. Results suggest that abnormalities in disgust processing may play an important role for some but not all OCD patients, i.e. especially for those patients with washing rituals and/or contamination obsessions. Inconsistencies in the disgust and smell literature in OCD may be due to studies not looking at specific symptom dimensions but OCD as a whole. As OCD is such a heterogeneous illness, investigating specific deficits or abilities in olfactory function and emotion perception might therefore provide valuable information about the brain systems involved in mediating the different symptom dimensions.

Schizophrenia

As described in more detail in Chapter 16, patients suffering from schizophrenia often appear to misinterpret social cues and exhibit poor social skills, reflected in symptoms such as persecutory delusions. It has been suggested that specific abnormalities in the identification of emotionally salient information in combination with misinterpretations of others' intentions and impaired emotional regulation could underlie some of the symptoms and social problems reported in patients with schizophrenia (Phillips *et al.*, 2003).

Impaired recognition of facial expressions of emotion in patients with schizophrenia has been documented extensively (Mandal *et al.*, 1998). However, the extent to which there is a differential deficit for processing specific emotions is as yet unclear. Some studies have reported lowered recognition rates for facial expressions of fear, disgust, and neutral (Kohler *et al.*, 2003), with disgust the only emotion where performance was worse for high intensity of expression compared to low intensity of expression. Another study looking at paranoid

symptoms in schizophrenia spectrum disorders reported a bias to misperceive emotion in others as disgust (Peer *et al.*, 2004). However, studies regarding a specific impairment of emotion recognition in patients with schizophrenia have not been consistent and it has been argued that these effects can be explained by a generalised deficit (Johnston *et al.*, 2001).

A flattened affect and anhedonia have long been recognised as core features of schizophrenia (Phillips *et al.*, 2003). However, diminished experience of emotion in schizophrenia has remained an understudied issue for a long time with little empirical evidence available as to whether patients or subgroups of patients with schizophrenia experience the full range of feelings at a 'normal' intensity. It is thought that affectively flat or anhedonic patients do not suffer from overall reduced affect, but show a reduced experience of positive emotions and an increased experience of negative emotions compared to healthy individuals (Suslow *et al.*, 2003), whereas patients without negative affective symptoms only showed an increased experience of negative emotions compared with healthy controls. More specifically, the negative emotions which schizophrenic patients experienced more frequently than healthy individuals were fear and disgust. Anhedonic patients also had higher sadness, guilt and shame scores than healthy controls. Guilt and shame have been conceptualised as self-directed disgust (Power & Dalgleish, 1997). As disgust is a defensive emotion, the increased frequency of experiencing disgust in patients with schizophrenia could be due to an increased need to defend oneself from interpersonal infringement (Suslow *et al.*, 2003).

Another facet of schizophrenia is olfactory dysfunction in patients, ranging from deficits in smell identification and threshold sensitivity to impaired memory for odours (Moberg *et al.*, (1999); see also Chapter 16 for further detail). Regions of the brain that have been implicated in the pathophysiology of schizophrenia, including the insula, mediate olfactory processing. These deficits in olfactory function are seen early on in the disorder, and are present even in individuals at high risk of psychosis who go on to develop schizophrenia (Brewer *et al.*, 2003). Olfactory function in schizophrenia has also been investigated as part of the neural mechanisms of anhedonia (Crespo-Facorro *et al.*, 2001). Patients with schizophrenia reported experiencing unpleasant odours in a similar manner to healthy participants but showed impaired experience of pleasant odours. This was not directly reflected in the pattern of brain activation in response to these olfactory stimuli, with patients failing to activate limbic regions including the insular cortex in response to unpleasant odours, and recruiting frontal cortical regions instead. Other functional neuroimaging studies have reported decreased blood flow in the insula during memory and verbal fluency tasks.

The insular cortex has also been implicated in structural abnormalities in the brains of individuals with schizophrenia. Structural imaging studies of chronic patients have reported a bilateral reduction of the volume of the insula compared to healthy controls. Furthermore, morphological abnormalities, which were correlated with the severity of psychotic symptoms, have been found in the insula in unmedicated patients during the early stages of the illness (Phillips *et al.*, 2003).

As has been shown above, there is evidence for deficits in both emotional processing (with some studies reporting specific abnormalities with regards to disgust), and olfactory processing in schizophrenia. The insular cortex is thought to be involved in both these processes, and neuroimaging studies have described structural as well as functional abnormalities in this region. It has been suggested that these abnormalities in the structure and function of the insula might underlie the abnormal peripheral and behavioural responses to emotional stimuli that have been described in schizophrenia (Crespo-Facorro *et al.*, 2000).

Conclusion

There is considerable overlap between the brain systems mediating emotion and olfactory processing. Parts of these systems have been implicated in the psychopathology of psychiatric disorders, illustrated above in OCD and schizophrenia, and many studies have reported emotion-processing abnormalities in psychiatric patients. The emotion of disgust has been understudied, but is important because it links directly to our chemical senses, and many patients with psychiatric disorders who have an olfactory deficit also appear to have abnormal disgust processing. The control of odour identification and disgust recognition by a common brain system is plausible as the risk of disease and contamination can be conveyed to individuals both by facial expressions of disgust and by smells emanating from harmful substances. The insular cortex is a promising candidate for this role, as it is involved in the expression of autonomic patterns in response to affective stimuli, with a predominant role in disgust, and in the integration of sensory events, principally the chemical senses, with appropriate emotional responses. Future studies comparing olfactory abilities in neuropsychiatric disorders that impact brain systems involved in olfaction and emotion will help elucidate the magnitude and specificity of olfactory deficits in different disorders or specific symptoms of disorders, and could be used to provide some insight into differences and commonalities of brain regions involved in the psychopathologies.

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4

Olfaction and memory

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The scent was so heavenly fine that tears welled into Baldini's eyes. He did not have to test it; he simply stood at the table in front of the mixing bottle and breathed. The perfume was glorious. It was to Amour and Psyche as a symphony is to the scratching of a lonely violin. And it was more. Baldini closed his eyes and watched as the most sublime memories were awakened within him. He saw himself as a young man walking through the evening gardens of Naples; he saw himself lying in the arms of a woman with dark curly hair and saw the silhouette of a bouquet of roses on the windowsill as the night wind passed by; he heard the random song of birds and the distant music from a harbor tavern; he heard whispering at his ear, he heard I-love-you and felt his hair ruffle with bliss, now! Now at this very moment! He forced open his eyes and groaned with pleasure. This perfume was not like any perfume known before. It was not a scent that made things smell better, not some sachet, some toiletry. It was something completely new, capable of creating a whole world, a magical rich world, and in an instant you forgot all the loathsomeness around you and felt so rich, so at ease, so free, so fine . . .

-from *Perfume* by Patrick Süskind

Introduction

As Süskind has reminded us in his evocative description of the power of scent, the slightest hint of perfume can transform the present into the past; it can re-create entire sensory experiences by providing an emotional link between past events initially experienced through separate senses; it can make memories seem real and tangible. In the *Remembrance of all Things Past*, Proust's description of dipping a mnemonically rich Madeleine into his tea and being completely

transported by its aroma back to his childhood, is one of the most frequently cited passages of literature. These experiences illustrate the unique power of scents, odours, smells or aromas as mnemonic cues that can revive, refresh, retrieve and re-create entire episodes of one's life.

In this chapter, we parse the nature of olfactory memory in an attempt to understand its uniqueness and richness. We briefly summarise neurobiological underpinnings of olfactory memory before discussing specific issues pertaining to components of the olfactory memory system including a discussion of the nature of olfactory memory encoding and retrieval in relation to semantic processes and an assessment of the relationship between emotion and olfactory memories.

The proust phenomenon and the uniqueness of olfactory memory

We begin with the Proust phenomenon. Why does a whiff of vanilla-and-butter in the Madeleine transfix us so? Included in the notion of the Proust phenomenon are that memory for odours do not decay as quickly as memories for other sensory modalities (Engen & Ross, 1973), that odours evoke older memories (Rubin *et al.*, 1984) and that memories evoked by odours are more emotionally loaded (Herz & Cupchik, 1995). In other words, olfactory memory may enjoy a unique position owing to its neuroanatomical and psychological underpinning.

A growing body of evidence suggests that a discrete memory system may exist for olfaction, and that memory systems may differentiate into a diverse array of component subsystems (Lehrner *et al.*, 1999). Olfactory stimuli are more potent cues of autobiographical memories than stimuli presented to other sensory modalities (Chu & Downes, 2000). However, it is not clear whether this effect is accounted for by variance in encoding and consolidation or ease of retrieval. In addition, working memory may also play an important role in the Proust phenomenon. Evidence suggests that there are distinct olfactory long-term and working memory systems (White, 1998). In order to re-live the past in the manner of Proust or Monsieur Baldini, just retrieving multiple fragments of an autobiographical episode may not be sufficient for a Proustian moment. Working memory may provide the glue that integrates bits and pieces of the past that are retrieved into a Gestalt so that the past can be re-experienced here and now. To understand the Proust phenomenon and olfactory memory in general, evidence from encoding and retrieval studies as well as working memory and priming data should be considered in the context of neuroanatomy.

Neuroanatomy of olfactory memory

The first clue to the olfactory system's relation to memory is the neuroanatomical overlap between the structures and circuits involved in memory processes

and the pathways involved in olfaction (see Chapters 1 and 2 for further detail). From the olfactory bulb, where chemical receptors detect environmental odorants, olfactory signals are sent through the lateral olfactory tract to the pyriform cortex, which constitutes the primary olfactory cortex as outlined further in Chapter 1. From the pyriform cortex, the system bifurcates to transmit information to both the lateral hypothalamus and the dorsal medial thalamus. A final level of convergence arrives in the orbitofrontal cortex (OFC), where taste and olfactory sensations from the tongue and nose create unified perceptions of flavour. Therefore, the olfactory system is widely distributed, involving preprocessing of olfactory information in the olfactory bulb, thalamus and pyriform cortex prior to reaching the OFC (Jones-Gotman & Zatorre, 1988). Case studies have identified olfactory memory deficits resulting from both orbitofrontal and temporal cortices (Savage *et al.*, 2002), but it is the particular heteromodal characteristic of the OFC that results in the integration of olfactory with other sensory information that may be relevant to the Proust phenomenon and the uniqueness of olfactory memories.

Developmentally, the OFC is derived from two separate moieties, and its structure and function in mature primates reflects its dual beginnings (Sanides, 1969). The OFC develops from olfactory and hippocampal cores. The olfactory-derived sub-sections seem to be generally concerned with stimulus recognition, while the hippocampal-related areas seem to be concerned with spatial and relational functions (Zald & Kim, 1996b). Anatomical connectivity studies in primates have identified the lateral regions as being comprised of these olfactory generated areas, while the medial regions of the orbital surface are generally related to the areas derived from the hippocampus (Sanides, 1969). The gyrus rectus of the OFC is an association area between the medial and orbital frontal cortices, but its dense connections with the medial OFC give it a prominent role in the orbitofrontal functional system (Zald & Kim, 1996b). Cytoarchitectonic and neurophysiological investigations of the OFC have elucidated a relatively high degree of cellular specificity and functional demarcation within these ventral regions of cortex (Carmichael & Price, 1995; 1996; Chiavaras *et al.*, 2001; Frey & Petrides, 2000; Price *et al.*, 1996; Schoenbaum *et al.*, 1998).

The OFC is a heteromodal association area that receives sensory information that has already undergone primary and secondary processing from other brain centres (Baylis *et al.*, 1995; Carmichael & Price, 1994; Rolls *et al.*, 1996). Gustatory, olfactory, auditory and visual inputs to the OFC show a high level of specificity, and specific cells exist within each modality that respond to certain stimuli, but not to others (Rolls, 2000; Thorpe *et al.*, 1983; Zald & Kim, 1996a). Efferents from the OFC are also widely distributed, and significantly influence functions of other areas of the brain. The OFC projects to many of the areas

whence it receives projections, including limbic, frontal and temporal cortices as well as subcortical nuclei (Carmichael & Price, 1995; 1996; Cavada *et al.*, 2000; Frey & Petrides, 2000; Price *et al.*, 1996). This pattern of connectivity signifies that the OFC is a convergence area for limbic and sensory structures. This is especially important in terms of mediating emotional and mnemonic interaction with the environment (Yamamoto *et al.*, 1984) and in affective decision-making. To summarise, the functional significance of OFC arises from its unique position in the frontal executive system (Fuster, 1997) and as an association area for sensory and emotional information (Carmichael & Price, 1995; Frey & Petrides, 2000; Zald & Kim, 1996b).

The role of the OFC in gustatory and olfactory processing is well established. The OFC handles simultaneous representation of several sensory modalities into a salient mnemonic representation. Taste, smell, and flavour are represented in distinct areas of the OFC, often with a high degree of specificity (Yamamoto *et al.*, 1984). Pre-processed olfactory information from the pyriform cortex is projected to the agranular posterior regions, and these areas project to more anterior aspects within the OFC (Carmichael & Price, 1994), providing a region of extensive associative olfactory processing. Gustatory information arriving from frontal and insular cortices also project to the posterior regions of the OFC (Baylis *et al.*, 1995), providing close associations between olfactory and gustatory processing cells. In fact, the proximity with which olfactory and gustatory cells process information provides specific processing of either smell or taste information, or shared processing of both modalities for specific stimuli (Rolls & Baylis, 1994). This polymodal association is responsible for experiencing flavour, the mixing of smell and taste that is so important in hedonic processing of appetitive stimuli. Experiencing all of the sensory and emotional aspects of food would require perceiving its visual, olfactory, gustatory and tactile (and sometimes even auditory) characteristics. The polymodal association attributes of the OFC make it an ideal system for processing and cross-indexing these inputs. Does the OFC, however, require the complete collection of sensations to access the emotional associations elicited by food stimuli? The data show that just the taste of food (Yamamoto *et al.*, 1984) or even just the visual presentation (Thorpe *et al.*, 1983) activates similar, specific cells in the OFC.

Given the OFC's high degree of sensory specificity and its role as a mediator between stimulus input and behavioural output, many studies have investigated the unique role of the OFC in stimulus association learning and memory (Rolls *et al.*, 1996). Single OFC neurons have been found to activate responses to stimuli only after they have been associated with negative affective outcomes, such as unpleasant taste (Thorpe *et al.*, 1983). This finding indicated that orbitofrontal neurons are somehow engaged in associating stimuli with their

outcomes after this outcome has become learned or expected (O'Doherty *et al.*, 2002; Rolls, 2000; Thorpe *et al.*, 1983; Watanabe, 1996). The OFC neurons have even been examined that associate a stimulus with a certain spatial location (Lipton *et al.*, 1999) because they respond when the animal is taken back to the location of stimulus presentation. This suggests that these neurons encode information about stimulus associations in memory for future retrieval. The olfactory system is further recognised in human emotional regulation and dysfunction because of its relationships with the limbic and frontal systems (Arnold & Trojanowski, 1996). The olfactory system is linked to hedonic evaluations (Royet *et al.*, 2000), given that we have a well-developed process for recognising scents, and deciding whether they are either pleasant or unpleasant. More recent primate data on error recognition (Rosenkilde *et al.*, 1981), learning (Watanabe, 1998) and relative reward and preference decisions (Tremblay & Schultz, 1999) have implicated the OFC in these behaviours, so it is important to examine the specific role of olfaction in these behaviours in order to produce more specific models of olfactory influence on OFC emotional inference.

There is a further specialisation of the OFC in relation to hemispheric laterality. The right hemisphere makes a substantial contribution to retaining olfactory percepts. Response latency, in particular to identifying olfactory memories, has been linked to enhanced performance in the right hemisphere (Olsson & Cain, 2003) and olfactory deficits are seen most often when there is a right OFC insult (Zatorre & Jones-Gotman, 1991; see also Chapter 2).

Several facets of olfactory processing, such as odour detection (Eichenbaum *et al.*, 1983), discrimination (Abraham & Mathai, 1983), and memory (Dade *et al.*, 2002), occur in the anteromesial temporal lobes. Some evidence suggests a distinctive role for right temporal cortex in olfactory memory (Rausch *et al.*, 1977) given the left hemispheric advantage in verbal memory tasks and the right hemisphere advantage for nonverbal memory (Buchanan *et al.*, 2001). But detecting hemispheric specialisation also depends on the types of olfactory tasks. For example, odour naming or identification tasks would involve verbal processing, and therefore would recruit the left hemisphere. In a study of patients with either left or right amygdala damage, Buchanan *et al.* (2003) found impaired performance on an odour-name matching task in left temporal lobectomy patients, supporting the specialised role of the left amygdala in verbal–odour associations. These findings were independent of generalised memory impairments, suggesting an olfactory-specific memory deficit following amygdala damage. However, this study did not find support for the broader role that the amygdala may play in olfactory processing, as there was no difference between normal controls and right temporal lobectomy patients in an odour-recognition task (Buchanan *et al.*, 2003). Thus, there may not be a specific

advantage of the right hemisphere in olfactory processing. In addition, Dade *et al.* (2002) showed both left and right temporal lobe participation in olfactory memory. More specifically, the pyriform cortex, the entorhinal cortex, the periamygdaloid cortex, and the anterior cortical nucleus of the amygdala play a pivotal role in olfactory processes (Savic, 2001).

Lastly, in addition to the OFC and the temporal lobe, the role of the hippocampus in episodic memory (including olfactory memory) retrieval must be emphasised. Along with the frontal cortex, the hippocampus provides the primary circuit where short-term memories are transferred into long-term memories. As described further in Chapter 2, damage to the hippocampus (Levy *et al.*, 2003) and medial temporal lobes (Mouly *et al.*, 2001) impairs olfactory memory.

Encoding of olfactory stimuli in relation to semantic processing and affect

A growing body of evidence indicates that a discrete memory system may exist for the olfactory domain and that the olfactory memory system may bifurcate into a diverse array of component subsystems (Lehrner *et al.*, 1999). In order for memories to form, encoding must occur and, considering the uniqueness of the olfactory perceptual system, it is important to understand how or if encoding of olfactory stimuli may be different from encoding in other sensory modalities.

Auditory and visual sensory information reach the OFC after having undergone significant processing. The olfactory system is exclusive in that it has more *direct* contact to the external environment via olfactory receptor cells, and it directly projects to the brain via the olfactory bulb. Moreover, the sensory input is relayed directly to the cortex and is not initially relayed to the thalamus (Powell *et al.*, 1965). Lastly, cortical olfactory areas are phylogenetically older than other sensory cortical areas. This implies both an anatomical and functional proximity to the limbic system that is much closer than other sensory modalities. Therefore, the olfactory encoding process seems qualitatively different from encoding in visual or auditory modalities. Whether the perception and encoding of stimuli significantly affect how they are stored can be debated and in this context the role of language in olfactory encoding must be carefully considered. However, the picture is rather complicated.

The role of language in encoding olfactory stimuli remains to be elucidated. Moreover, it is not clear whether aspects of odour perception, such as pleasantness or familiarity, influence the labelling of odour during the encoding stage. Rosenbluth *et al.* (2000) showed that children who were blind early in childhood significantly out-performed controls on an olfactory recognition task. This study concluded that the difference in performance arose from an advantage in labelling the odours. Murphy and Cain (1986) found that blind subjects recalled 31% more odours from memory than sighted controls. This advantage

is not accounted for by increased olfactory sensitivity in blind individuals. Wakefield *et al.* (2004) found that blind children named 20% more odours than their sighted counterparts and odour perception (i.e. pleasantness, familiarity) did not account for this difference. This result suggests that blind individuals may have an advantage in accessing memory for non-visual stimuli (Wakefield *et al.*, 2004). Does language facilitate olfactory memory? To begin to address this question, we need to look further into semantic processes.

There is conflicting evidence for the role of semantic networks in olfactory encoding. Human subjects are notoriously poor at correctly labelling olfactory stimuli. Engen (1983) reported that subjects encode the same odour differently on successive presentations. Moreover, different subjects generated different labels for the same odours (Engen, 1983). It has been proposed that odours are encoded in relation to perception and independent of semantic networks (Engen & Ross, 1973). However, Royet *et al.* (1999) examined the neural correlates of semantic versus perceptual processing for odours and found that these two subsystems interact in a positron emission tomography (PET) study. In the perceptual condition, subjects had to decide whether an odour was familiar or not. In the semantic condition, subjects had to judge whether an odour corresponded to a comestible item or not. In the control detection condition, subjects were asked to decide whether the perceived stimulus was made of an odour or was just a puff of air. Subtracting familiarity from control, conditions showed that familiarity judgements were associated with the activity of the right OFC, the subcallosal gyrus, the left inferior frontal gyrus, the left superior frontal gyrus, and the anterior cingulate. Subtracting familiarity from comestibility conditions showed that comestibility judgements (i.e. semantic) activated the primary visual areas. In contrast, for familiarity judgements, a decrease in regional cerebral blood flow (rCBF) was observed in the primary visual cortex. Also a decrease in rCBF was observed in the OFC area for comestibility judgements. These complicated results suggest that OFC and visual cortex functionally interact in odour processing in a complementary way. Therefore, attempting to parse 'perceptual' from 'semantic' odour processing may be difficult to achieve. Moreover, familiarity judgements require some semantic processing and are not purely perceptual in nature as they evoke memories. Passively smelling odours activate the amygdala, pyriform cortex and cingulate cortices but familiar odours (rated after the scanning session) activate the left frontal cortex and left parietal cortex (Savic & Berglund 2004), suggesting that familiarity recruits different neural circuits. This suggests that encoding of odours may be linked to semantic processing (Savic & Berglund, 2004).

Magnetoencephalographic (MEG) and electroencephalographic (EEG) studies provide further insight into the relationship between semantic encoding and

olfaction. Lorig (1999) proposed that olfactory processes share some of the neural substrates with language processes. Furthermore, interference occurs when both processes occur at the same time. In a study investigating this possible interference, Lorig *et al.* (1998) used olfactory and visual stimuli as distractions during a verbal processing task. There were differences in both EEG and verbal responses when olfactory distracters were present, but not when visual distracters were present, suggesting interference between semantic and olfactory systems (Lorig *et al.*, 1998). Walla and colleagues (2003) found reduced MEG response in a semantic (deep) encoding task during chronic odour stimulation compared to performance on the same task in the absence of odour stimulation. But the authors of this study point out that olfactory stimulation may have modulated attention and the MEG results are an indication of this modulation. In a corresponding study, Walla *et al.* (2003) showed that there was no difference in activity in a non-semantic (shallowly encoded) version of the same task, suggesting that the first effect was independent of modulation of attention by olfactory stimulation. Together, these findings suggest that odour interferes with verbal processes differentially in that odours disrupt semantic but not non-semantic processes (Walla *et al.*, 2003). The authors propose three possible reasons why odours disrupt semantic processes, even when no cognitive demands are associated with the odours. First, odours may alter cortical regions associated with semantic processes. Second, odours may modulate cortical regions associated with semantic processes. The third option is that odours may compete with cortical regions associated with semantic processes (Walla *et al.*, 2003). Other studies suggest that olfactory processes and language processes are related in an inhibitory manner. Lehrner and colleagues (1999) found a weak relationship between naming consistency and odour recognition, whereas the relationship between odour identification and recognition was stronger, suggesting poor semantic memory may underlie both poor odour recognition and identification. But verbal process may inhibit olfactory recognition process. Parr and colleagues (2002) found that superior odour recognition in wine experts was not aided by semantic memory and lexical knowledge for wine-relevant odours. This might occur because experts' superior perceptual skills in identifying odours may protect them from verbal interference when they are forced to identify the odorants. In other words, novices may rely on verbal representations of the odorants at the expense of the odorants, but perceptual expertise in the experts may protect them from '*verbal overshadowing*', a concept proposed by Melcher and Schooler (1996) as a possible explanation for the inhibitory relationship between verbal and olfactory processes. Verbal overshadowing is thought to occur when subjects are forced to identify complex stimuli that are difficult to capture verbally. Verbal overshadowing

is hypothesised to decrease as perceptual expertise for odours increases (Melcher & Schooler, 1996). In other words, the relationship between verbal and olfactory processes may become less inhibitory as experiential knowledge increases.

Affective attributes of olfactory stimuli may interact with the role of semantic networks in olfactory processing. Olfactory stimuli invite initial automatic, affective evaluation, which may then influence verbal coding. Engen (1987) found that category labelling for odours was less consistent than labelling of other senses. He offered three conditions in which category labelling is achieved: (1) the stimulus is perceived in terms of similar smells; (2) the stimulus is perceived in terms of context; and (3) the stimulus induces the sensation of smell (Engen, 1987; Mohr *et al.*, 2001). In order to rule out these confounds associated with real odours, Mohr *et al.* (2001) investigated the semantic accessibility of imagined olfactory stimuli and compared them to that of imagined auditory stimuli. This study found that pleasant associations are more frequent in an imagined smell fluency task (i.e. generating 'smell' words) when compared to an imagined auditory fluency task (i.e. generating 'auditory' words). Given that the number of associations generated in both tasks was equal, these findings suggest that accessing verbal associates to olfactory or auditory stimuli does not differ, but that the difference lies in the semantic network architecture (Mohr *et al.*, 2001).

The anatomical proximity of olfaction to the limbic system makes it more likely that odours are affectively coded. The prevalence of pleasant associations with olfactory stimuli can be explained with two theories of hedonic value in memory: *the mere exposure paradigm* (Zajonc, 1968) and *repression theory* (Holmes, 1970). The mere exposure paradigm supposes that repeated exposure to a stimulus shifts hedonic judgements to pleasantness. The repression theory postulates that unpleasant memories degrade faster than pleasant memories. In terms of the mere exposure paradigm, previous exposure to the generated imagined stimuli leads to increased pleasantness. But this explanation alone does not account for the difference between the olfactory fluency task and the auditory fluency task. The close proximity to the limbic system would make the olfactory system more accessible to affectively coded information than it is the case for the auditory system. In terms of the repression theory, a stronger neuronal inhibition for odours as compared to sounds would push association accessibility towards the pool of pleasant memories (Mohr *et al.*, 2001).

It may be impossible to tease apart the semantic networks and olfaction because this initial affective categorisation of odours may be autonomic. Odours can induce both positive and negative affects which then modulate autonomic responses such as skin conductance, heart rate, and startle reflexes (Alaoui-Ismaili *et al.*, 1997; Ehrlichman *et al.*, 1995). Neuroimaging studies

(Fulbright *et al.*, 1998; Zald & Pardo, 1997) and electrophysiology studies (Hummel & Kobal, 1992) have found differential cerebral activation when processing pleasant versus unpleasant odours. Moreover, differences in processing pleasant versus unpleasant odours have also been shown in studies of response time (Bensafi *et al.*, 2002b). Zatorre and colleagues (2000) found hypothalamic activation when subjects were asked to make hedonic judgements of olfactory stimuli. Since odours are primarily experienced in terms of affective judgements, hedonic categorisation is pivotal in odour grouping (Bensafi *et al.*, 2002a). Bensafi and colleagues (2002a) investigated the involuntary nature of hedonic judgements of odours and found increased heart rate with exposure to unpleasant odours. This suggests that heart rate increases in the context of rejection (Bensafi *et al.*, 2002a). Moreover, physiological responses for judgements of familiarity differed from physiological responses for judgements of hedonic tone, suggesting that neural networks for familiarity and hedonic tones are different and that cognitive processing of odours does not inhibit autonomic responses to odours (Bensafi *et al.*, 2002a).

Retrieving olfactory memories

Mounting evidence suggests that odours are more emotional and stronger memory cues than other sensory stimuli. Olfactory cues for memories may be more affective than cues presented to other modalities (Herz, 1998; Herz & Cupchik, 1995). Odour-cued memories are rated as more pleasant and are recalled less frequently than memories cued via other modalities (Rubin *et al.*, 1984). Emotional potency of odour-evoked memory is correlated with specific activation in the amygdala during recall (Herz *et al.*, 2004). Odour cues to personal memories elicited greater activation in the amygdala–hippocampal complex than comparable but non-personally relevant odours. These findings show that activation of the amygdala–hippocampal complex is accounted for by the emotionality of the elicited memories and is not related to olfactory artefacts (Herz *et al.*, 2004). These data suggest that the amygdala–hippocampal complex may be part of the neural substrates involved in a distinct olfactory memory system

To elucidate the role of context in olfaction memory retrieval further, Vermetten & Bremner (2003) investigated flashbacks induced by hallucinated smells in three patients with Post Traumatic Stress Disorder (PTSD). Memory for smells in PTSD has four features: (1) specific, (2) long-lasting, (3) state dependent, and (4) context-dependent (Vermetten & Bremner, 2003). In two of these cases, hallucinated smells precipitated a traumatic memory with associated emotions. This suggests that olfactory memories are deeply embedded and that long-term effects of olfactory memory related to trauma can be evoked upon

re-exposure to cues. Moreover, this phenomenon does not extinguish with time. Vasterling *et al.* (2000) found that patients with PTSD showed olfactory identification deficits. This finding is consistent with reported dysfunction of the fronto-limbic system in PTSD and is discussed further in Chapters 6 and 14.

Age may modulate olfactory memory retrieval. Maylor *et al.* (2002) examined a set of young subjects (mean age 21) and a set of older subjects (mean age 84) in an autobiographical memory recall task either with or without the appropriate olfactory cues. Across the two groups, twice as many memories were recalled when accompanied with the appropriate odour than without. Therefore, it seems that olfactory cuing is remarkably intact in old age and that memory retrieval is enhanced by exposure to associated odours. This finding supports the idea that olfactory memory is more resistant to decay over time.

Olfactory priming: semantic or perceptual?

The memory studies described in the preceding sections probe explicit memory for odours. However, olfaction may also play an important role in the implicit and unconscious component of memory. Implicit memory can be studied using priming paradigms. In general, priming occurs when the processing of a previously encountered stimulus (the prime) influences the processing of a second stimulus (the target). The target can be either identical to the prime or related in some way to the target. Priming relies on a *spread of activation process*. (Koenig *et al.*, 2000; McNamara *et al.*, 1992). Perceptual priming occurs when the prime and the target share perceptual qualities, whereas semantic priming occurs when the prime and the target are semantically related. It is postulated that perceptual priming and semantic priming are mediated by two discrete subsystems. Perceptual priming spreads a pattern of activation through a subsystem that stores modality-specific traces, which correspond to perceptual attributes of a specific stimulus. Semantic priming activates an associative memory subsystem that stores memory traces that are independent of sensory modality (Kosslyn *et al.*, 1992; Tulving & Schacter, 1990).

Attempts to demonstrate such potential priming effects through the olfactory subsystem have produced mixed results (Cain *et al.*, 1995; Olsson, 1999). Koenig and colleagues (2000) demonstrated a robust priming effect for the olfactory modality when olfactory stimuli were previously encountered in the study session (perceptual priming). However, no semantic priming effect was observed when the *label* for olfactory stimuli was previously encountered in the study session. Thus, intramodal (olfactory−olfactory) priming operates at a pre-semantic level and is perceptual in nature.

There are known hemispheric effects on priming for auditory and visual modalities. Olsson and Friden (2001) found a hemispheric (nostril) difference

for response latencies when subjects were asked to make judgements of edibility for either primed or control odours. In this study, priming was demonstrated when odours were presented to the right nostril but not the left nostril. Furthermore, edibility judgements (which would require greater semantic processing) were more accurate when odours were presented to the left nostril. This is consistent with visual priming studies in that right hemispheric priming is dependent on perceptual similarity between the prime and the target (Olsson & Friden, 2001). However, Olsson and Friden (2001) did not find a hemispheric difference in a unirhinal odour repetition priming task.

Cross-modal integration

The olfactory memory system may rely upon cross-modal integration, and incongruent cues could attenuate olfactory memory retrieval. Morrot *et al.* (2002) found that in the absence of visual cues, subjects incorrectly described white wine odours using red wine terms. This is consistent with past studies of incongruent versus congruent cues. Identification of single odours improves when relevant semantic information is also presented (Cain, 1979). Basic properties of olfactory perception (such as intensity and thresholds) are modulated by visual and cognitive factors (Dalton, 1996; 2000; Distel & Hudson, 2001; Zellner & Kautz, 1990), suggesting multiple sites of integration. There is some evidence that olfactory information aids visual episodic memories, and that it provides a contextual salience to the memory storage and retrieval systems (Gottfried *et al.*, 2004). The effect of olfactory information on verbal memory encoding and retrieval may also be modulated, in part, based on the presence or absence of associated olfactory information (Bonfigli *et al.*, 2002).

As outlined by Gottfried and Dolan (2003), the hippocampus is one of several areas where integration of information occurs. It can be accessed directly or indirectly from all sensory modalities. Lesion studies show that post-surgical epilepsy patients with damage to hippocampus and adjacent medial temporal structures are impaired on a variety of cross-modal odour tasks (Eichenbaum *et al.*, 1983). Another possible site of integration is the OFC. The OFC has been shown to receive afferent inputs from the pyriform cortex and visual association areas in non-human primates (Carmicheal & Price, 1995). Moreover, a functional magnetic resonance imaging (fMRI) cross-modal study showed OFC activation in an olfactory–visual associative learning task (Gottfried *et al.*, 2002). Gottfried and Dolan (2003) found that olfactory detection was faster and more accurate when presented with semantically congruent visual stimuli. They also found activation in anterior hippocampus and rostromedial OFC during congruency-specific tasks. These results suggest both the hippocampus and OFC are involved in cross-modal integration.

As discussed previously, another possible site of integration may be the prefrontal cortex. Traditionally, the prefrontal cortex is divided into two anatomical parts: the dorsolateral prefrontal cortex and the ventrolateral prefrontal cortex, although the functionality of these two divisions is not as clear. Goldman-Rakic (1995) proposed a functional division based on segregated areas that process a specific type of knowledge. Specifically, this model supposes that the dorsolateral prefrontal cortex is reserved for spatial functioning while the ventrolateral cortex processes verbal information. This model assumes that different sensory modalities can contribute to one informational domain. Single cell recording studies in non-human primates indicate, however, that there is no specific division of cells responding to spatial versus non-spatial working memory (White & Wise, 1999).

Alternatively, Petrides (1995) offers a 'two-level hypothesis,' dividing the lateral frontal cortex with respect to its executive functions, such that the mid-dorsolateral and mid-ventrolateral frontal cortex are divided according to the processes being carried out. Dade and colleagues (2001) found that olfactory working memory activates dorsolateral and ventrolateral PFC, but differs from face working memory with regards to activation in the parietal lobe. More specifically, overlap was found in the dorsolateral, ventrolateral and frontal polar cortices suggesting that, in general, the same functional prefrontal regions are used in visual and olfactory working memory tasks (Dade *et al.*, 2001).

Conclusions

Bringing together the evidence from encoding and retrieval studies as well as incorporating olfactory working memory and olfactory priming permits a broader conceptualisation of the olfactory memory system and how it is integrated with other memory systems. Neuroanatomical overlap between the structures and circuits involved in memory encoding, recognition and retrieval and the pathways involved in olfaction suggest that components of the olfactory memory system are highly integrated and may modulate one another. Olfactory perceptual qualities, such as hedonics and familiarity, are autonomic in nature and influence olfactory stimulus encoding. The context in which olfactory stimuli are encoded is likely to influence olfactory memory retrieval. In turn, olfactory memory retrieval can modulate the experience of olfactory qualities such as hedonics and familiarity. Finally, olfactory, affect and semantic processing are intimately intertwined and thus disentangling the complex relationships among these three domains is likely to be almost as challenging as the dark quest undertaken by Grenouille in his attempt to distill the ultimate essence of the human scent in 'Perfume' (Süskind, 1976).

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5

Olfactory neurogenesis: a window on brain development

François Féron, Richard McCurdy, John McGrath and Alan Mackay-Sim

Introduction

It is understandable that members of the public are surprised to learn that a biopsy taken from inside the nose may be able to provide clues into neurological and psychiatric disorders. Those with the knowledge of the development of Freudian psychoanalysis may have a particular shudder of recognition at any project that links psychiatry with surgical procedures on the nose. Wilhelm Fliess (1858–1928) was a Berlin-based Ear, Nose and Throat specialist (oto-rhino-laryngologist), who was preoccupied with the influence of biological rhythms on health and disease. He also developed a bizarre theory linking the erectile tissue in the nose with sexuality. Sigmund Freud, the father of psychoanalysis, corresponded with Fliess over many years. They shared a belief that surgery on the nose could interrupt 'reflex nasal neuroses', and thus be an effective treatment for various neurotic disorders thought to be connected to sexuality. The details of this theory do not warrant further scrutiny apart from one incidence that became pivotal in the development of psychoanalysis. Freud had sent one of his most celebrated patients (Emma Eckstein) to Fliess for the nasal surgery as a treatment for her 'psychological' condition. In an act of gross negligence, Fleiss left a nasal pack *in situ* after the surgery and did not provide appropriate follow-up or after-care. After much suffering, another surgeon discovered the mistake, and the nasal pack was removed. When the pack was removed, the patient had a life-threatening nasal bleed and Freud felt so sickened that he had to leave the room. Fortunately for all concerned, Emma Eckstein survived. Later, Freud wrote a glaringly self-serving analysis of a dream he had about this episode. It was this

self-analysis that laid the foundation for his work on dream interpretation (Zucker & Wiegand, 1988).

It is not widely appreciated that an Ear, Nose and Throat surgeon made such an important contribution to the 'psycho-analytic revolution' of psychiatry. However, collaborations between Ear, Nose and Throat surgeons and psychiatrists have recently made important contributions to our understanding of neuropsychiatric disorders. This chapter will outline a programme of research that examined olfactory neuroepithelium in schizophrenia as an example of the heuristic value of this research. While the chapter will focus on schizophrenia, the techniques can be applied to many different brain disorders.

How can we study brain development in schizophrenia?

The neurodevelopmental hypothesis of schizophrenia proposes that genetic and epigenetic factors alter early brain development, leaving the affected individual at increased risk of developing schizophrenia (McGrath & Murray, 2003; McGrath *et al.*, 2003). It has been suggested that disruptions in key events during brain development related to neuronal proliferation, migration, differentiation and cell death may underlie some of the subtle neuroanatomical and cytoarchitectural features associated with schizophrenia (Jones & Murray, 1991; Weinberger, 1995). However, researchers interested in linking altered neurodevelopment with neuropsychiatric disorders face several major hurdles. First, many of the key processes underlying early brain development are not open to scrutiny in vivo. In addition, by the time schizophrenia becomes clinically apparent, most of the central processes in brain development are long finished. While neurogenesis in the adult human brain (Eriksson *et al.*, 1998) might theoretically be used to investigate fundamental aspects of the neurodevelopmental hypothesis, harvesting neural precursors from the human brain is ethically unjustifiable, dangerous and technically difficult. Animal models (e.g. transgenic mice, early life brain lesions or exposure to infection, toxins, etc.) can provide an indirect window on what may be happening in neurodevelopmental disorders, but the validity of these models remains suboptimal (Lipska & Weinberger, 2003). A model for brain development can be found in the human olfactory epithelium, the organ of the sense of smell, and this is the model discussed below. The human olfactory epithelium remains in a state of embryo-like development throughout adult life such that new neurons are being continually formed (a process called neurogenesis) under the influence of growth factors and other regulatory molecules that shape development of the embryonic brain. Of note, and also discussed below, is the continuing neurogenesis now recognised to play an important role in the adult brain which continues to contribute to interneurons in the olfactory bulb into adulthood. It is possible

that the altered olfactory function in persons with schizophrenia may result from alterations in the continuing neurogenesis present in the olfactory epithelium and olfactory bulb.

The neurodevelopmental hypothesis of schizophrenia

The neurodevelopmental hypothesis of schizophrenia has been reviewed elsewhere but it is reconsidered again here because it is central to our thesis that olfactory neurogenesis provides a valid model for neurodevelopmental factors that may be operating in early brain development.

Developmental abnormalities

Various 'minor physical anomalies' have been noted in schizophrenia and other psychiatric disorders (Lane *et al.*, 1997; McGrath *et al.*, 2002). These developmental anomalies are subtle variations in soft-tissue, cartilaginous and bony structures that are the result of an uncertain mix of genetic and environmental factors that operate prenatally. Minor physical anomalies are of interest because they may represent persistent evidence of fetal maldevelopment, and may also serve as markers of early events influencing brain development (Lyon *et al.*, 1989). Specific anomalies may provide clues to the timing of the disruption; for example, the major features of the palate are essentially complete by 16 to 17 weeks. Minor physical anomalies occurring in schizophrenia and other developmental disorders include variations in the shape and proportions of the head, face, mouth, fingers, hands and toes and aberrant dermatoglyphics (Green *et al.*, 1994). For example, various dermatoglyphic measures are different in schizophrenia patients and well controls (Fananas *et al.*, 1990; Mellor, 1992; Weinberger & Marenco, 2003), including affected and non-affected monozygotic twin pairs (Rosa *et al.*, 2000).

Early last century, Kraepelin observed that a high palate and low set ears were more common in patients with schizophrenia (Weinberger, 1995). A closer analysis revealed an overall narrowing and elongation of the mid- and lower-face, a widening of the skull base and numerous minor physical anomalies in the eyes, ears and mouth in schizophrenia patients compared to well controls (Lane *et al.*, 1997; McGrath *et al.*, 2002). Also, the ratio of skull width to skull length was significantly larger in those individuals with psychotic disorders compared to the healthy controls (McGrath *et al.*, 2002). The odds of having a psychotic disorder were increased in those with wider skull bases, lower facial heights, protruding ears and shorter and wider palates. The relationship between facial features and psychosis is also indicated in Velocardiofacial Syndrome (VCFS), or 22q11 deletion syndrome, that is associated with an increased frequency of

schizophrenia (Bassett *et al.*, 1998; Gothelf *et al.*, 1997) and bipolar mood disorder (Carlson *et al.*, 1997).

Recently, Waddington and colleagues have drawn attention to the close links between the brain growth and the development of the face, providing a developmental-progressive basis to the relationship between craniofacial dysmorphogenesis and schizophrenia (Waddington *et al.*, 1999). Epigenetic exposures that can affect the bony structures of the face and cranium include prenatal viral exposures, obstetric complications (Sperber, 2001), protein malnutrition (Miller & German, 1999), maternal contact (Helm & German, 1996), hyper-vitaminosis A (Thorogood *et al.*, 1982) and low prenatal vitamin D (Engstrom *et al.*, 1982). The correlation between individual measures of minor physical anomalies and brain morphology is weak, with one study reporting a correlation between dermatoglyphic ridge count and ventricular volume as measured (van Os *et al.*, 2000), but other studies reporting no such association (McGrath *et al.*, 2002; Rosa *et al.*, 2000).

Brain morphology in schizophrenia

Morphological differences in anatomical features of the schizophrenic brain are well documented (Bogerts, 1993). Recent reviews of magnetic resonance imaging (MRI) studies collated the most replicated findings of altered global and regional neuroanatomy in schizophrenia (Lawrie & Abukmeil, 1998; Wright *et al.*, 2000). Brains from schizophrenia patients have reductions in overall size, volume and weight, and are shorter through the anterior–posterior axis, compared to brains from healthy controls. Other alterations in brain anatomy include increased ventricular size and reductions in the volume of limbic structures such as the hippocampus, amygdala, parahippocampus (Lawrie & Abukmeil, 1998; Wright *et al.*, 2000) and olfactory bulb (Turetsky *et al.*, 2000). The problems experienced by schizophrenia patients in the higher integrative and associative brain functions, for example speech and thought disorder, hallucinations and poor motivation, are associated with these structural and functional deficits (Bogerts, 1993). Another interesting difference in the anatomy of the schizophrenic brain is the lack of normal asymmetric features (Bogerts, 1993; Lawrie & Abukmeil, 1998; Wright *et al.*, 2000; Zaidel, 1999). The normal structural asymmetry includes a longer Sylvian fissure and larger right frontal and temporal lobes – differences that are absent in schizophrenia patients. The brain volume differences in schizophrenia are not correlated with the duration of the illness (Lawrie & Abukmeil, 1998) and exist in first episode patients (Nopoulos *et al.*, 1995). These findings suggest that the structural brain differences probably result from abnormalities in brain development associated with, and leading to, schizophrenia pathogenesis.

Olfactory epithelium as a model for neurodevelopment

Our favoured model for neurodevelopment is the adult olfactory epithelium, which provides access to developing neural tissue in living patients. The olfactory neuroepithelium is capable of regeneration and there is a continual renewal of the sensory neurons (Graziadei & Monti Graziadei, 1978). As a model for neurodevelopment, the olfactory neuroepithelium is pertinent because all the elements of neuronal cell lineage, migration and survival are regulated by the same growth factors that act on the developing brain (Mackay-Sim & Chuah, 2000). When olfactory mucosa is cultured in explanted slices of tissue, cells leave the explant and form a sheet of epithelioid cells around it. These cells are born in vitro and express markers of the olfactory basal cells, presumptive neuronal precursors, as well as markers of developing neurons (Caggiano *et al.*, 1994; MacDonald *et al.*, 1996; Newman *et al.*, 2000). Some neurons born in these cultures take a bipolar morphology and express proteins of mature olfactory sensory neurons (Féron *et al.*, 1998; MacDonald *et al.*, 1996; Murrell *et al.*, 1996). Some cells express markers of olfactory ensheathing cells, the glia of the olfactory nerve (MacDonald *et al.*, 1996; Pixley, 1992). Like neurogenesis in the developing nervous system, neurogenesis in the adult olfactory neuroepithelium is tightly regulated (Mackay-Sim, 2003; Mackay-Sim & Chuah, 2000). It is similar to the developing nervous system in that there is an overproduction of immature neurons, limited neuronal survival dependent on factors from axonal targets, neuronal survival dependent on activity, neuronal precursor proliferation, and cell survival dependent on thyroxine and on autocrine and paracrine growth factors and cytokines (Mackay-Sim, 2003; Mackay-Sim & Chuah, 2000).

Thus, we argue that cultures of adult olfactory neuroepithelium provide a convenient and informative model for studying key features of neural development. In particular, properties of olfactory neuroepithelium cultures of individuals with psychotic disorders may have heuristic value with respect to unravelling functions related to both early brain development and even with respect to current brain function, given the continuing neurogenesis now known to occur in adult brain (see the section on 'Neurogenesis in the brain: role in Schizophrenia').

Biopsy of the human olfactory epithelium

Based on the mapping studies of human olfactory mucosa (Féron *et al.*, 1998; Leopold *et al.*, 2000), we now have a clearer understanding of the distribution of the olfactory mucosa in the nose. Over the last seven years, we have biopsied more than 60 persons under local anesthesia as participants in our studies of olfactory neurogenesis in psychosis. Additionally, we have biopsied more than

250 persons under general anesthesia who were undergoing surgery for septoplasty or turbinectomy. All samples were obtained under a protocol approved by the ethics committees of the hospital and university. We have taken biopsies from persons as old as 82 years and in all cases we have identified olfactory epithelium in the biopsy material. In all cases where we have tried, we have been able to grow this tissue in vitro to produce neuronal progenitors and neurons. It is notable that in adults, the olfactory epithelium was found more anterior and more inferior than is generally recognised (Féron *et al.*, 1998) — an observation confirmed by electrophysiological analysis of odour-evoked potentials from the nasal cavity (Leopold *et al.*, 2000). In a recent study, we surveyed participants about their experiences after nasal biopsy under local anesthesia. Of the 30 individuals questioned, about one-third experienced mild, self-limiting bleeding and/or discomfort after the biopsy procedure. One subject had a post-operative nasal bleed that required the insertion of a nasal pack overnight. We recommend that research teams undertaking this procedure ensure that the participants are monitored after the procedure and that they have ready access to the research team in case of serious adverse events.

On gross inspection, the olfactory mucosa is not clearly demarcated from respiratory mucosa. There is a fine patchwork of intermingling microscopic areas of respiratory and olfactory mucosa. The ratio of respiratory to olfactory mucosa is highest in the superior nasal cavity, and lowest in the inferior regions. There is a concentration of olfactory mucosal zones in the front of the middle turbinate but the higher and further back the biopsy is taken, the more likely one will find larger areas of olfactory mucosa present (Perry *et al.*, 2002). We recommend taking biopsy specimens on the most posterior areas of the septum and the superior turbinates only. Even in the dorso-posterior regions of the adult nasal cavity, where the probability of finding olfactory epithelium was highest, only 40% of the specimens contained olfactory epithelium exclusively. Considering the small surface area within each biopsy specimen (1 mm^2), it is apparent that the olfactory and respiratory tissues are intimately dispersed in the adult nasal cavity. Comparison of fetal and adult tissues suggests that invasion of respiratory tissue into olfactory epithelium increases with age.

Neurogenesis in adult olfactory epithelium: a model for neurodevelopment in schizophrenia

Olfactory mucosa is the only part of the nervous system that is readily available via biopsy, yielding neurons, glia, and neuronal progenitor cells, without leading to any sensory deficits (Féron *et al.*, 1998). It is also available at autopsy and can

produce viable cultures from people of all ages for at least a day postmortem (Murrell *et al.*, 1996). This availability has been exploited to reveal some aspects of human diseases of aging and neurodevelopment. For example, neuroblast cell lines were derived from human olfactory epithelium (Wolozin, *et al.*, 1992) and were shown to have altered processing of the amyloid precursor protein in Alzheimer's disease (Wolozin *et al.*, 1993). More recently, histology of the olfactory epithelium revealed fewer olfactory neurons and more neuronal precursors in Rett's syndrome, a neurodevelopmental disorder leading to profound motor and cognitive deficits (Ronnett *et al.*, 2003).

In schizophrenia, olfactory epithelium has also been exploited to reveal evidence in support of a neurodevelopmental aetiology for this disorder (Arnold *et al.*, 2001; Féron *et al.*, 1999). Our group has demonstrated the utility of olfactory mucosal culture as a tool to explore the neurodevelopmental hypothesis of schizophrenia (Féron *et al.*, 1999). We found that compared to healthy controls, slices of olfactory mucosa from patients with schizophrenia were less likely to attach to the culture dish (30% versus 73.5% in patients and controls, respectively) and within the attached cultures, there was significantly more cell proliferation (as measured by mitotic activity) in the patient group versus the controls (0.7% versus 0.3% of cells were mitotic in patients and controls respectively). The reduction of attachment to the plastic culture wells in the schizophrenia group suggested the decreased cellular adhesion, a finding consistent with two studies that reported reduced adhesion in skin fibroblasts in schizophrenia compared to healthy controls (Mahadik *et al.*, 1994; Miyamae *et al.*, 1998). Altered cell proliferation in cultures of olfactory epithelium in schizophrenia (Féron *et al.*, 1999) is consistent with an altered trajectory of brain development in these patients. Histology of postmortem olfactory epithelium in aged humans with schizophrenia revealed greater proportions of immature and mature neurons in this tissue when compared to the precursor cells, indicating dysregulated neurogenesis in this tissue (Arnold *et al.*, 2001). It is interesting to note that Rett's syndrome and schizophrenia are both disorders of neurodevelopment but each appears to alter the ratios of neuronal precursors and neurons in characteristic ways. This suggests that the measurable dynamics of olfactory neurogenesis may be identifiable in different disorders, further illustrating the potential for this tissue as a tool for investigating the aetiologies of different neurodevelopmental disorders.

Neurogenesis in adult brain: role in schizophrenia?

The long held dogma that the adult mammalian brain cannot generate new neurons was first questioned by evidence for mitotic cells in the forebrain

subventricular zone of the adult rodent and mitotic precursor cells were shown to give rise to neurons in the dentate gyrus of the hippocampus and olfactory bulb (Altman, 1969; Altman & Das, 1965; Kaplan & Hinds, 1977). It was not until the early 1990s that new evidence (Reynolds & Weiss, 1992; Richards *et al.*, 1992) confirmed the formation of new neurons in the adult brain, with general acceptance of this concept only in the last 10 years.

It is now well recognised that neurogenesis continually provides new neurons not just to the olfactory epithelium but also to the olfactory bulb. Within the olfactory bulb, neuronal precursors migrate from its core to the periphery where they differentiate into local interneurons, olfactory granule cells, and periglomerular cells (Alvarez-Buylla & Garcia-Verdugo, 2002). Significantly, the majority of the granule cells are produced postnatally and newly generated interneurons are found during adulthood (Bayer, 1983; Kaplan & Hinds, 1977). Progenitors that give rise to olfactory interneurons reside in the anterior area of the subventricular zone (Luskin, 1993) and migrate tangentially along a restricted pathway named the rostral migratory stream (Doetsch & Alvarez-Buylla, 1996; Lois & Alvarez-Buylla, 1994; Luskin & Boone, 1994). Within this rostral migratory stream, neuroblasts are assembled in chains ensheathed by slowly dividing astrocytes (Garcia-Verdugo *et al.*, 1998; Lois *et al.*, 1996; Peretto *et al.*, 1999; Rousselot *et al.*, 1995). Migrating and dividing cells express markers of immature neurons such as doublecortin and the polysialylated form of neural adhesion molecule (Bonfanti & Theodosis, 1994; Doetsch & Alvarez-Buylla, 1996; Gleeson *et al.*, 1999; Hu & Rutishauser, 1996). Once in the olfactory bulb, neuronal progenitors migrate along radial glia and differentiate into fully mature and electrophysiologically active interneurons (Carleton *et al.*, 2003).

Forebrain neurogenesis in adulthood has been observed in every examined mammalian species, and neural stem cells have been isolated from the human brain (Bernier *et al.*, 2000; Johansson *et al.*, 1999; Kukekov *et al.*, 1999; Nunes *et al.*, 2003; Pagano *et al.*, 2000; Pincus *et al.*, 1997; Roy *et al.*, 2000). Migration of neuron precursors along the rostral migratory stream is well documented in non-human primates (Alvarez-Buylla & Garcia-Verdugo, 2002; Kornack & Rakic, 2001; Pencea *et al.*, 2001) though to date, not in humans. A recent study performed postmortem on nine human brain samples did not find any evidence of chains of migrating neurons in the olfactory peduncle or a structure similar to the rostral migratory stream of other mammals (Sanai *et al.*, 2004). However, it cannot be excluded that neuronal precursors migrate individually. Indeed, a previous report has described the presence of individual neural precursors in the adult human olfactory bulb (Liu & Martin, 2003). Furthermore, considering the relatively poor sense of smell of human species,

it is likely that the replacement of bulbar interneurons, if it occurs, is a rare event that cannot be detected easily with the contemporary techniques.

Regulation of neurogenesis in adult brain

Many studies have indicated that hormones could be regulators of adult neurogenesis. Prolactin, a hormone that increases during the first half of pregnancy and postpartum, stimulates neurogenesis in the female subventricular zone contributing to new interneurons in the olfactory bulb (Shingo *et al.*, 2003). Erythropoietin infusion into the adult lateral ventricles decreases the number of neural stem cells in the subventricular zone, increases the number of newly generated cells migrating to the olfactory bulb and increases the number of new olfactory bulb interneurons (Shingo *et al.*, 2001). Progesterone reduces proliferative activity within the subependymal layer (Giachino *et al.*, 2003). Pituitary adenylate cyclase-activating polypeptide promotes neural stem cell proliferation in the subventricular zone as well as in the dentate gyrus of the hippocampus (Mercer *et al.*, 2004).

Vitamins are also suspected to play a role in adult neurogenesis. Vitamin A deficiency increases cell proliferation in the rat olfactory epithelium (Asson-Batres *et al.*, 2003), while vitamin E deficiency induces neural precursor proliferation and cell death in the rat dentate gyrus (Cecchini *et al.*, 2003; Ciaroni *et al.*, 1999; 2002).

Several growth factors regulate adult neurogenesis in vitro. Epidermal growth factor or basic fibroblast growth factor induce survival and self-renewal of neural stem cells from adult subventricular zone (Kuhn *et al.*, 1997; Reynolds & Weiss, 1992) (for a recent review, see Galli *et al.* (2003)). After removal of these factors, the progeny differentiate spontaneously into astrocytes, neurons, and oligodendrocytes (Doetsch *et al.*, 1999; Kilpatrick & Bartlett, 1993; Morshead *et al.*, 1994; Vescovi *et al.*, 1993). The growth factors, sonic hedgehog and fibroblast growth factor 8, then induce neuronal precursors to develop into dopaminergic neurons (Kim *et al.*, 2003).

In vivo, subventricular zone progenitors give rise to olfactory bulb interneurons and their destiny can be modified by growth factor administration. Intracerebroventricular administration of epidermal growth factor and transforming growth factor α dramatically increase subventricular precursor proliferation (Craig *et al.*, 1996) while basic fibroblast growth factor is less potent (Kuhn *et al.*, 1997) but also has a proliferative effect after subcutaneous delivery (Wagner *et al.*, 1999). Epidermal growth factor and basic fibroblast growth factor differ in molecular mechanism and induce different lineages: the former induces production of more astrocytes in the olfactory bulb and

in striatum of infused animals whereas the latter induces more olfactory bulb interneurons (Craig *et al.*, 1996; Kuhn *et al.*, 1997).

In addition to these well-studied ligands, other growth factors have emerged as potential regulators of bulbar neurogenesis. The ciliary neurotrophic factor supports neural stem cell renewal via Notch signaling (Chojnacki *et al.*, 2003; Hitoshi *et al.*, 2002; Shimazaki *et al.*, 2001) while Ephrin molecules, when infused in the lateral ventricle, increase cell proliferation and decrease neuroblast migration (Conover *et al.*, 2000). A highly glycosylated molecule expressed on differentiating neurons during development, mCD24, decreases cell proliferation in the subventricular zone (Belvindrah *et al.*, 2002). Furthermore, it has been demonstrated that neurogenesis and gliogenesis in the forebrain are regulated by two antagonistic growth factors. Bone morphogenic proteins, expressed by subventricular cells, promote astroglial lineage whereas noggin, produced by ependymal cells, antagonises this (Gross *et al.*, 1996; Lim *et al.*, 2000; Shou *et al.*, 1999).

Several factors have been identified that regulate neuronal precursor migration. The polysialylated form of neural cell adhesion molecule (NCAM) expressed by olfactory interneuron precursors, is a key player during the rostral migration (Bonfanti & Theodosis, 1994; Chazal *et al.*, 2000; Doetsch & Alvarez-Buylla, 1996; Lois *et al.*, 1996; Rousselot *et al.*, 1995) and not surprisingly, NCAM mutant mice display a decreased number of newly generated granule cells as well as impaired odour discrimination (Gheusi *et al.*, 2000). The protein reelin, known for guiding and positioning neuronal precursors during development, acts during adulthood as a detachment signal for chain-migrating interneuron precursors in the olfactory bulb (Hack *et al.*, 2002). Moreover, two soluble proteins of the slit family are considered to be the prime candidates for guiding neuroblasts within the rostral migratory stream (Hu & Rutishauser, 1996; Mason *et al.*, 2001; Wu *et al.*, 1999) while the extracellular matrix glycoprotein tenascin-R initiates both the detachment of neuroblasts from chains and their radial migration (Saghatelyan *et al.*, 2004).

Finally, the list of factors influencing olfactory bulb neurogenesis should include neurotransmitters. Glutamate and serotonin modulate adult neurogenesis within the hippocampus (Banasr *et al.*, 2004; Bernabeu & Sharp, 2000; Brezun & Daszuta, 1999; Cameron *et al.*, 1998; Gould, 1999). Serotonin depletion increases cell proliferation and neurogenesis in the dentate gyrus and olfactory bulb (Banasr *et al.*, 2004; Brezun & Daszuta, 1999), and when the cholinergic input to the dentate gyrus and the olfactory bulb is damaged, there are fewer granule cells and more apoptotic cells in the granule cell layers of these structures (Cooper-Kuhn *et al.*, 2004).

Neurogenesis in olfactory bulb affects olfactory function

As discussed in Chapter 16, olfaction in schizophrenia is impaired. At present the locus of this olfactory dysfunction is not known. The observed changes in neurogenesis in the olfactory epithelium may provide clues, but it is possible that changes to the olfactory bulb or higher centres may contribute. Of relevance in this regard is a recent study of neurogenesis and olfactory function in aged mice (Enwere *et al.*, 2004). Two-year-old mice showed impairments in olfactory function; namely making discriminations between closely related odours. They also have less proliferation in the subventricular zone and fewer interneurons newly contributing to the olfactory bulb, even though they have more interneurons in total. Of interest, here is the reduced expression of the epidermal growth factor receptor in the aged mice compared to the younger controls. Independently of age, mice lacking the ligand for this receptor (transforming growth factor a) also showed reduced neurogenesis and a similar olfactory deficit (Enwere *et al.*, 2004). Another mutant mouse with reduced neurogenesis (leukemia inhibitory factor heterozygote) and reduced new olfactory bulb interneurons also exhibited olfactory dysfunction independently of age (Enwere *et al.*, 2004). It was concluded that reduced neurogenesis in the olfactory bulb must contribute directly to reduced olfactory function. We speculate that neurogenesis may be impaired in the adult schizophrenic brain, specifically in the olfactory bulb, and this may contribute to the olfactory dysfunction. There is no direct evidence for this although the olfactory bulbs are reported to be smaller in schizophrenia (Turetsky *et al.*, 2000) and neurogenesis in the nose is impaired (Arnold *et al.*, 2001; Féron *et al.*, 1999) (see also Chapter 16). There is now evidence that the rate of neurogenesis in the rodent olfactory bulb may be related to the rate of neurogenesis in the olfactory epithelium of the same animal (Mandairon *et al.*, 2006). If this were true in humans, the olfactory epithelium would indeed be a 'window into the brain'.

Since neurotransmitters influence adult neurogenesis, it can be expected that a disease-induced neurotransmitter depletion or excess might impair neurogenesis in the patient's brain. Three recent studies of brains of individuals with neurodegenerative diseases (Parkinson, Huntington and Alzheimer) support this hypothesis, although the findings are not completely concordant. A reduced number of proliferating subependymal zone cells and neuronal precursor cells in the olfactory bulb and dentate gyrus was found in the brains of patients with Parkinson's disease (Hoglinger *et al.*, 2004; and see Chapters 14 and 15) while an increased cell proliferation and neurogenesis was observed in the subependymal layer of human Huntington's disease brains (Curtis *et al.*, 2003). Consistent with the latter report but in contrast with animal models, another study showed that neurogenesis is increased in the hippocampus of individuals

with Alzheimer's disease (Jin *et al.*, 2004). It is possible that the differences in neurogenesis implied by these observations may be explained by the nature of the neurotransmitter pathways disrupted in each disorder. More studies, using larger cohorts, need to be performed in order to clarify this issue. However, the data from the study by Hoglinger *et al.* (2004) raises the possibility that impairment of olfactory bulb neurogenesis, in addition to striatal depletion of dopamine, contributes to olfactory impairment in Parkinson's disease.

Conclusions

The ability to examine in vitro the dynamic process of neuronal birth, differentiation and death in neuroepithelium from individuals with psychosis provides a powerful tool for understanding neurobiological correlates of schizophrenia and bipolar disorder. It will also provide measurable neurobiological factors associated with affective and non-affective psychoses which may serve as informative endophenotypes for future genetic studies (Gottesman & Gould, 2003). Additionally, there is a growing interest in the possible links between neurogenesis and affective disorders. Medications widely used to treat psychosis and depression have recently been shown to promote neurogenesis and to be neuroprotective in the rat brain. These include lithium (Chen *et al.*, 2000), olanzapine and risperidone (Wakade *et al.*, 2002), fluoxetine and tranylcypromine (Duman *et al.*, 2001). While the evidence is far from complete, these curious properties of psychotropic medications have led some researchers to speculate that disrupted neurogenesis in the adult brain may be implicated in the pathogenesis of affective disorders (Duman *et al.*, 2001; Manji *et al.*, 2000). Conversely, the neuroprotective properties of compounds such as lithium have led to speculation that its therapeutic effect is related to its reduction of neuronal cell death in bipolar disorder (Manji & Duman, 2001). The ability to examine mitosis and cell death in olfactory neuroepithelial cultures from individuals with affective disorders lends itself to exploring these hypotheses.

The observed differences in cell biology in the olfactory neuroepithelium in psychosis also lend themselves to deeper analysis using gene and protein expression arrays. Pertinent to this are recent attempts to investigate the genetic bases of neurogenesis, determination of cell fate and differentiation during development (Blackshaw & Livesey, 2002), procedures which could be applied to olfactory neuroepithelium cultures. With these technologies, one could compare the differential expression of genes and proteins between different patient groups (Hakak *et al.*, 2001; Mirnics *et al.*, 2000; Vawter *et al.*, 2001) and one could investigate the effects of psychotropic agents on the expression of genes or

proteins such as the impact of lithium on the anti-apoptotic protein Bcl-2 (Manji *et al.*, 2000).

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6

Olfactory processing and brain maturation

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Introduction

Olfactory deficits are found in neurodegenerative disorders, predominantly in later life, as well as in disorders with an onset in childhood or adolescence. The former will be considered in detail in Chapters 14–16. It is clear that the neuropathological changes accompanying neurodegenerative disorders are implicated in causing such deficits in olfactory abilities. In contrast, the processes underlying olfactory abnormalities in disorders of early development are less clear and are best understood in the context of dynamic brain maturational changes that are occurring at this time. Thus, neurobiology relevant to the deficits observed in disorders having a neurodevelopmental basis, such as the autistic spectrum disorders, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) and schizophrenia, may relate more to abnormalities in the processes of brain maturation rather than to specific neuropathological processes, or to an interaction between brain maturation and other processes relevant to these conditions.

We suggest that in order to understand the nature of the deficits observed in various aspects of olfactory function in early developmental disorders, it is important to consider the nature of the normal brain structural and functional changes that are occurring at the time of their onset. It is likely that interruption of these normal processes by the emergence of such disorders at critical times of maturation adversely affect the development of olfactory functions. Interruption of normal neurodevelopment, reflected by olfactory deficits, may manifest as developmental arrest, developmental lag or possibly functional deterioration following onset of these conditions.

In this chapter, we review the limited available data about the maturation of olfactory function in the context of the emergence of disorders of neurodevelopment and discuss, where data is available, how the neurobiology of each of the disorders may lead to the observed deficits in olfactory abilities. Further, consideration of the staggered maturational trajectories of the various aspects of lower- and higher-order olfactory function (acuity, discrimination, memory, identification) is a prerequisite to understanding the nature and extent of the deficits observed in early onset disorders. Thus, childhood-onset disorders involving brain structures relevant to olfaction are likely to have a greater impact on olfactory functions maturing during childhood (e.g. olfactory acuity and memory) as well as adversely affecting functions maturing later during adolescence. For those disorders occurring in adolescence, the impact on olfactory function may be limited to those domains that have not yet matured (e.g. olfactory identification). Further, the impact of pre- or peri-natal insult(s), as suggested in disorders like schizophrenia, needs to be considered in terms of the interaction of brain maturation with the processes relevant to the disorder. Thus, such early neurodevelopmental insults affecting olfactory-related neural systems may only become manifest as olfactory deficits at a time when such function would normally be reaching maturity ('growing into deficit').

Development of limbic-prefrontal networks in adolescence

The critical phase of early adolescent development can be likened to a second revolution of neural development, in which neural change occurs predominantly in anterior brain networks, particularly frontal systems, relative to the development of posterior spinal column networks during early childhood (Giedd *et al.*, 1999; Klingberg *et al.*, 1999; Paus *et al.*, 1999; Reiss *et al.*, 1996; Yakovlev & Lecours, 1967). Consistent with this, early development primarily involves the mastery of motor co-ordination and language, while later development is focused on mastering executive cognitive abilities, including cognitive and emotional control (see Sowell *et al.* (2001); Spear (2000); Steinberg (2005); Wood *et al.* (2004)). During this stage of development, there is increased complexity of symbolic representation of the self (motor, cognitive, emotional, social). These changes closely parallel the brain structural changes identified recently using high-resolution magnetic resonance imaging (MRI) scanning, as discussed below. With regard to olfaction, this period is associated with improved ability to process and code olfactory information. Given that olfaction in humans is considered important in regulating hedonic states (Hvastja & Zanuttini, 1989), as well as being a determinant of the emotional

atmosphere within which cognitive processes occur (Davis, 1975), the interaction of the olfactory system with the processes of development are relevant to understanding disorders of cognition and emotion.

Normal brain maturational processes during adolescence

We recently reviewed the normal brain changes occurring during childhood and adolescence and discussed their relevance to understanding the brain changes in emerging psychiatric illness (Wood *et al.*, 2004). Adolescence is an important time when higher-level cognitive changes are evolving and maturing, in concert with maturation of social interaction, and increase in risk-taking behaviour (Spear, 2000). While higher intellectual or 'executive' functions are available to the young child, these functions show maturation most rapidly from age 11–12 through to early adulthood (De Luca *et al.* (2003); Stuss (1992); Travis (1998); Wood *et al.* (2004)), accompanied by structural brain changes in both grey and white matter, involving myelination and cortical synapse elimination (Huttenlocher, 1984). This remodelling is especially pronounced in regions associated with social cognition, response inhibition, monitoring, emotion regulation and the capacity for abstract, reflective and hypothetical thinking (Paus, 2005). The neurobiological processes that are thought to underlie these developments include increases in myelination and connectivity (especially between prefrontal and limbic structures), and synaptic pruning (loss of grey matter), reflecting increased efficiency, and specialisation (Paus, 2005). The apoptotic elimination of excess synapses results in remodelling and refinement of the neural circuitry, which is thought to strengthen the remaining functional connections and reduce competition from suboptimal associations. While the result of this, essentially Darwinian, process is improved and more efficient neuronal communication, it is important to note that this also leads to reduced redundancy available in the brain. This may be particularly relevant to understanding the longitudinal trajectory of behavioural and neuropsychological features observed in young people developing psychopathology (Pantelis *et al.*, 2003; 2005).

Myelination begins during the second trimester of gestation, continuing well into the third decade of life (Benes *et al.*, 1994; Yakovlev & Lecours, 1967), progressing in a graded fashion from inferior to superior and posterior to anterior, with the cerebellum developing first and the frontal lobes last (Yakovlev & Lecours, 1967). These processes are consistent with the observed changes on MRI that have illustrated maturational changes in vivo during adolescence (Giedd *et al.*, 1999; Giedd, 2004; Gogtay *et al.*, 2004; Reiss *et al.*, 1996; Sowell *et al.*, 2003). Using diffusion tensor imaging to examine axonal integrity in the

frontal lobes of children and adults, Klingberg *et al.* (1999) found that white matter continues to increase into the second decade of life in this region, with the white matter increase located in dorsal prefrontal rather than orbitofrontal cortex (Reiss *et al.*, 1996). While both these prefrontal regions are implicated in early onset disorders, such as autistic spectrum disorders, ADHD, OCD and schizophrenia (Barnett *et al.*, 1999; Brewer *et al.*, 1996; 2001; In submission; Gansler *et al.*, 1998; Karsz *et al.*, In submission; Kopala *et al.*, 1989; 1992; 1993; 1994; Moberg *et al.*, 1999; Murphy *et al.*, 2001; Pantelis & Brewer, 1996; Pantelis & Maruff, 2002; Suzuki *et al.*, 2003), the impact on DLPFC versus OFC in these disorders may be dependent on the developmental stage of the brain at time of their onset. Structurally, orbito-frontal cortex (OFC) *matures* later than dorsolateral prefrontal cortex (DLPFC), although *myelination* occurs earlier than that occurring in DLPFC (Yakovlev and Lecours, 1967). The OFC is thought to be the last area of the brain to complete *maturation* — which probably includes all three major processes occurring in the brain at that time — i.e. synaptic pruning, loss of neurons, and myelination (Gogtay *et al.*, 2004).

Given that the predominant brain regions developing during adolescence are the frontal lobes, the development of neuropsychological functions mediated by these regions will be relevant to disorders developing during this stage of brain maturation (Pantelis *et al.*, 2001; 2003). These 'executive functions' include higher-order processes, such as strategic planning, problem solving, inhibitory control, cognitive flexibility, abstract thinking, concept formation, working memory and self-monitoring, as well as higher-order olfactory processing. All of these functions are necessary for successful independent, goal-directed, volitional behaviour (Anderson, 1998).

The development of executive function (for review: Wood *et al.*, 2004) is characterised by 'spurts' in executive abilities beginning from as young as twelve months of age, with the majority of functions becoming available to the child from age around eight (Ardila & Rosselli, 1994; Case, 1992; Luciana & Nelson, 1998), though these functions have disparate developmental trajectories (e.g. De Luca *et al.*, 2003; Levin *et al.*, 1991; Wood *et al.*, 2004), thereby paralleling the brain structural changes observed. Simple planning, attentional set-shifting and hypothesis testing are available to the child at an earlier stage than other abilities, including temporal ordering, affective decision-making and complex strategy formation (Anderson *et al.*, 1995; Chelune & Baer, 1986; Espy, 1997; Levin *et al.*, 1991; Luciana & Nelson, 1998; Stuss, 1992; Welsh & Pennington, 1988). The development of working memory capacity improves slowly but steadily over the adolescent years and into adulthood (De Luca *et al.*, 2003; Luciana & Nelson, 1998), in concert with the structural changes observed in DLPFC. Understanding the maturation of various olfactory abilities in the context of brain structural

and functional changes will be important in understanding the nature and pattern of deficits observed in neurodevelopmental disorders, considered in detail below.

Nature of olfactory abilities in childhood and adolescence

In order to understand the nature of the deficits observed in various aspects of olfactory function in early developmental disorders, we have suggested above that it is important to consider the nature of the normal brain structural and functional changes that are occurring at the time of their onset and the implications that these changes have for olfactory information processing. Limited data is available with regard to normal olfactory function during development, and the following literature is structured according to the hierarchical nature of olfactory processing from basic sensation to higher-order identification.

Olfactory sensation (sensory perception)

Olfactory sensation refers to the ability to detect olfactory sensory information, regardless of threshold. Such ability is available to the newborn, however, there are few studies to inform our understanding of the development of such function. Detection of an olfactory stimulus in newborns can be assessed by examining the orienting response. Schall *et al.* (1998) demonstrated that newborn infants are able to orient to the presence of familiar as opposed to non-familiar amniotic fluid by comparing bottle-fed versus maternal milk-fed 3-day-old infants. By examining orienting response to a neutral control stimulus (distilled water) they were able to demonstrate that this response was triggered by an orienting response to the familiar odour rather than avoidance of a non-familiar odour. These results were interpreted to support the hypothesis that the human fetus can detect and store the unique chemosensory information available in the prenatal environment. However, such a response may be governed by genetically determined preference for maternal odours. Unfortunately, the investigators did not examine whether the bottle-nurtured infants in their study responded preferentially to type (breast versus bottle) of milk rather than to amniotic fluid or to a control stimulus. This would have helped to determine if infants were able to learn and respond to new odours.

It has also been suggested that other salient characteristics of some odours, such as pleasantness versus unpleasantness, are learnt (Bartoshuk & Beauchamp, 1994; Engen, 1982) from within the first few days of birth (Balogh & Porter, 1986; Schleidt & Genzel, 1990). Others have found that by three years of age, odour preference patterns are essentially the same as those of adults

(Schmidt & Beauchamp, 1988). However, it is unclear from the available studies whether this relates to newer olfactory learning.

Olfactory sensitivity (threshold detection)

In contrast to the literature on identification ability, the available evidence suggests that children and young adults possess sensitivity comparable to that of persons in their thirties (Beauchamp *et al.*, 1991; Schall, 1998). However, this is confounded by the type of odorant utilised and methodological differences, such as method of odorant delivery. For example, while Koelega (1994) found relative insensitivity of prepubescent children for 4 to 5 odorants compared to subjects aged 15 and 20 years, the musk-based steroidal odorants utilised are more likely to be detected post-puberty (see also Dorries *et al.*, 1989 who utilised androstenone). Such changes to sensitivity to some odours may be determined by hormonal or maturational changes. Using a pressurised injection technique for delivery of odours, Strauss (1970) concluded that threshold detection ability for non-steroidal substances increases progressively from age 8–10 through to adulthood (21–39 years). However, this technique has been widely criticised as olfactory sensitivity was likely confounded by pressure detection. In contrast, the better controlled studies report no increase in sensitivity for non-steroidal odorants (Cain *et al.*, 1995; Dorries *et al.*, 1989; Koelega & Koster, 1974; Larsson & Backman, 1997).

As discussed earlier, differences in odour salience may affect sensitivity, which appears relevant to the person's stage of development. For example, infants have higher levels of olfactory acuity for certain odorants (e.g. breast milk) rather than others (Beauchamp *et al.*, 1991; Koelega, 1994; Richman *et al.*, 1995; Schall, 1998). As indicated above, prepubescent children are as sensitive to non-steroidal odours as adolescents and adults, while the ability to detect certain steroidal substances is only apparent post-pubertally.

Olfactory memory

Memory of odours in adults is discussed in more detail in Chapter 4. The literature examining olfactory memory in childhood is sparse, but it would seem that the ability to recognise odours appears less affected by the passage of time than are auditory or visual memories. However, Hvastja & Zanuttini (1989) found that children's odour memory decay over time appears more marked with increasing age from 6.5 to 10.5 years. They considered that this was probably caused by increased proactive interference as subjects accumulate a higher number of olfactory experiences. Apparently, as age increases, this more rapid decay is offset by better immediate recognition (Hvastja & Zanuttini, 1989). It is possible that improved olfactory identification (OI) around the pubertal and

post-pubertal period is also relevant to improved odour memory ability; thus, the improved ability to symbolically represent olfactory information improves memory for odours. The hedonic characteristics of odours, which are partially learned, may also influence individual memory abilities. Finally, the rate of new learning of odours appears diminished compared to the other sensory modalities (vision and hearing) up until adulthood (Cain *et al.*, 1995). However, there are no adequate data to inform how the rate of olfactory learning changes developmentally.

Olfactory discrimination

There is only one study on olfactory discrimination ability in children that utilised a match-to-sample odour discrimination task (MODT). Such tasks are easier than identification tasks as successful performance relies less on the processing and storage of information. Richman and colleagues (1995) examined seventy-five normal subjects aged 2 to 18 years. They utilised five odorants as the standard odour set, and mean test scores on the MODT increased as a function of age until mid-adolescence with a similar pattern across the genders. The task was found to have limitations for use in the 2- to 5-year-old group. Further work is required to assess discrimination ability of steroidal substances in children.

Olfactory identification

Tasks of olfactory detection are quite simple in that they require relatively limited cognitive or verbal skill from the subject. In contrast, tasks such as identification of odours rely upon extended experience with the olfactory world and acquisition of a vocabulary to categorise it (Cain *et al.*, 1995). The available literature suggests that children perform progressively better at identification into their teens (de Wijk & Cain, 1994; Doty *et al.*, 1984; Richman *et al.*, 1988; 1992). As discussed above, factors that impede odour identification include a relative slowness in learning to assign names to odours, failure to retrieve the name in spite of a well formed association, and difficulty discriminating similar stimuli (Hvastja & Zanuttini, 1989). In contrast, associations between olfactory stimuli and emotion are made more readily and such associations may account for individual differences in ability to identify certain smells. Olfactory identification ability (OIA) of children aged 3.5 to 5 years increases with age (Richman *et al.*, 1992), and children aged 8 to 14 years perform worse than young and middle-aged adults in unprompted identification of odours, with average performance much like elderly adults (Cain *et al.*, 1995). The most comprehensive study that demonstrates maturational development of OIA is provided by Doty and colleagues (1984), and is shown in Figure 6.1. This study

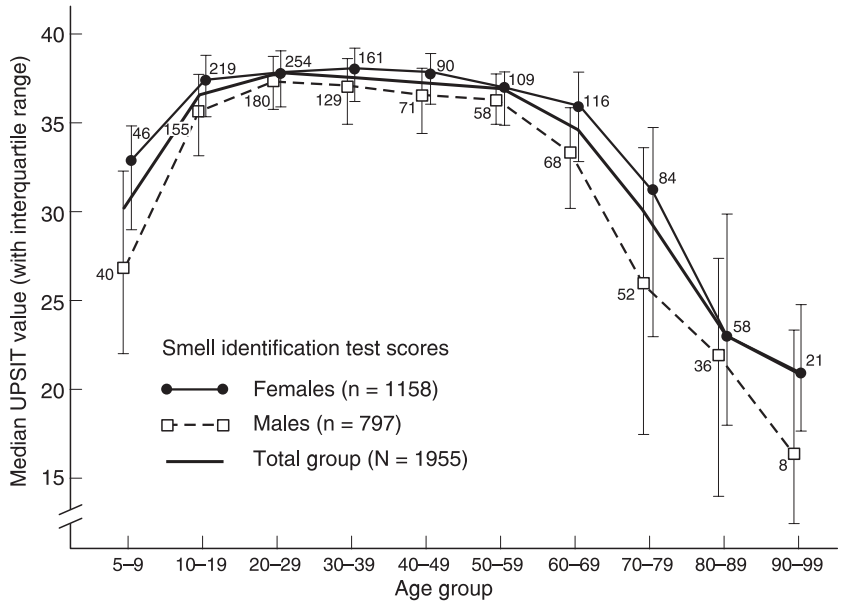

Figure 6.1 Scores on the University of Pennsylvania Smell Identification Test as a function of age in a large heterogeneous group of 'normal' subjects. Numbers by data points indicate sample sizes. From Doty *et al.*, 1984; see Chapter 13: Figure 13.5.

is useful in that individual scores for subjects can be ranked according to these normative data, and is discussed in detail in Chapter 13. However, it should be noted that these data are cross-sectional and there are no currently available longitudinal studies in children or adolescents.

Summary

In summary, it appears from the limited available data that sensitivity and threshold abilities for non-steroidal odours are established early in childhood. In contrast, odorants that have a steroidal base are less detectable until the onset of puberty. Olfactory memory develops early, but has a continuing maturational trajectory, which may partly relate to the maturation of OIA, though the available data are still limited. The relationship between olfactory memory and limbic/emotional processes is discussed in further detail elsewhere (Chapters 1 and 4).

Olfactory discrimination and identification abilities appear to develop slowly through childhood and then more rapidly at the onset of adolescence. These findings are consistent with the maturation of prefrontal regions through adolescence and early adulthood that are described above. It is hypothesised that any disruption to the normal maturation of OFC would be reflected in

diminished OIA. Indeed, olfactory identification deficits (OID) may be a useful index of compromise of OFC neural systems, and have been identified in a number of purported neurodevelopmental disorders, including psychiatric disorders of childhood (e.g. autism, Apserger's Disorder, ADHD) and disorders in adolescence (e.g. OCD, schizophrenia). Understanding the normal maturation of olfactory abilities, as discussed above, is relevant to understanding the nature and timing of the disturbances in neuropsychiatric disorders. The next section discusses the implications of these principles to disorders of childhood and adolescence.

Olfactory deficits in developmental disorders

The maturational trajectories of various olfactory abilities described above are consistent with changing survival needs from birth (dependence) to adolescence (independence), with higher-order olfactory appreciation becoming apparent with sexual maturation (see Chapter 13). Given the maturational trajectory of olfactory abilities, does this help us to understand the nature of olfactory deficits in various neurodevelopmental disorders? In turn, does the observed pattern of olfactory deficits in these various disorders inform understanding about when and which (prefrontal-limbic) neural systems are implicated? Can the nature, extent and timing of deficits, considered within a maturational context provide information about the timing and nature of the compromise in disorders of neurodevelopmental origin? Thus, is there a failure of maturation of functions, suggesting developmental arrest, lag, or stunted development (dysmaturation)? For example, it would be hypothesised that disorders with an earlier onset would manifest abnormalities in olfactory functions maturing at that time.

Autistic spectrum disorders

Autistic spectrum disorders are early-onset, low-prevalence neurodevelopmental disorders that implicate neural dysfunction of prefrontal brain regions (Dawson *et al.*, 1998; see Chapter 14). Autism occurs in early childhood, with onset prior to age three, while Asperger's disorder is identified later as speech is generally unaffected. The available studies have identified intact odour detection but impaired OIA in Asperger's disorder individuals assessed after adolescence (mean age at assessment = 33.0 years) (Suzuki *et al.*, 2003). In a recent study of high functioning children with autism assessed in childhood (age 5 to 9 years; mean = 6.4 years), Brewer *et al.*; In submission found that OI was not different to an age- and gender-matched control group. Given that OI has not yet matured

at this age, it was not surprising that there was no difference found. In this study, however, the normal relationship found between age and OIA in the control population was not found in the children with autism. These results suggest that some process may disrupt the normal maturational development of olfactory ability, although this will require longitudinal investigation. There are no other studies investigating other olfactory abilities, however, it may be predicted that deficits in other olfactory domains (e.g. olfactory memory) may be apparent in this group, especially as medial temporal structures are also implicated (Bachevalier & Merjanian, 1994). There are no studies of olfaction in pervasive developmental disorders of childhood.

Attention deficit hyperactivity disorder (ADHD)

ADHD is a behavioural disorder that affects young children with an onset before the age of seven years. The only study in children has been conducted by our group, in which children aged 12.2 years on average; range 7 to 17 years were assessed (see also Chapter 14). The children with ADHD showed poorer OIAs relative to an age- and gender-matched normal control group (Karsz *et al.*, In Submission). These findings are interesting as OI is maturing during this time. Presumably, as in the autism study, OI impairments would not be evident in these children had they been assessed at an earlier age. In a preliminary report of older individuals with ADHD (age 28.9 years at time of assessment), Gansler *et al.* (1998) reported OID compared with normal controls. Furthermore, Murphy *et al.* (2001) assessed OIA in a group of young adults with ADHD relative to a control group, and after IQ was controlled for, group differences in OIA were no longer significant. There are no other available studies examining other olfactory functions in this group.

Schizophrenia

Schizophrenia is a disorder of neurodevelopmental origin (Weinberger, 1987) with an onset in late adolescence or early adulthood (see Chapters 14 and 16). The mean age of onset of illness in males is around the early 20s while for females it is in the later 20s (APA, 1994), although this may not represent a robust biological finding due to the confounding effects of marital status and premorbid personality differences (Jablensky & Cole, 1997). Olfactory identification deficits have been consistently reported in this disorder in chronic patients, first-episode psychosis (see Chapters 14 and 16) and, more recently, in individuals assessed before the onset of schizophrenia (Brewer *et al.*, 2003). Males tend to have more severe deficits and this is consistent with a later age of illness onset in women, as well as an earlier maturational trajectory of OIA

in females (see Chapter 12). Interestingly, no association was found between OIA and either duration of untreated psychosis or length of prodrome in first-episode psychosis patients (Brewer *et al.*, 2001). This is consistent with our own high-risk study of pre-psychotic individuals (Brewer *et al.*, 2003), suggesting that there is a failure of normal maturation of OIA in young people who will eventually develop schizophrenia. It is also relevant that the age equivalent capacity of patients with chronic schizophrenia is similar to that of normal 5- to 9-year-old children (Brewer *et al.*, 1996). While OID are stable after the onset of illness (Brewer *et al.*, 2001), there are no longitudinal studies over the transition to illness. Taken together, these studies highlight the utility of OI to probe the development of prefrontal-limbic pathways, and support the notion of a breakdown of limbic-prefrontal function early in the aetiology of psychosis (see Pantelis *et al.*, 2002; 2003).

The limited olfactory acuity studies in schizophrenia (Geddes *et al.*, 1991; Isseroff *et al.*, 1987; Kopala *et al.*, 1992; Serby *et al.*, 1990) report some deficits with modest effect sizes (for review, see Moberg *et al.*, 1999); however, assessment of acuity in these studies has not been standardised, and further investigation is required to make more definitive claims regarding acuity status in schizophrenia. There is also some evidence suggesting that olfactory discrimination and olfactory memory may be impaired (For reviews, see Moberg *et al.* (1999; 2003)), though again, the available data is less convincing than the investigations regarding OI. In the recent well-designed study, Rupp and colleagues (2005) comprehensively examined a number of olfactory abilities in male patients with chronic schizophrenia, including detection threshold, quality discrimination, subjective ratings of odour quality, as well as familiarity and edibility judgements and odour identification. Impairments were found in sensitivity, discrimination, familiarity and edibility judgements and identification. There were no differences between nostrils. These results suggest that there are deficits across a number of olfactory domains, which may implicate early neural compromise of relevant systems. However, further studies are needed that control for differences in task complexity and sensitivity to degree of deficit.

The findings outlined above suggest an altered developmental trajectory for OI, and by implication, prefrontal-limbic pathways, in emerging schizophrenia. This is somewhat surprising given the heterogeneity not only of the established illness, but also of the developmental trajectories of other Axis I illnesses that are mediated by prefrontal-limbic dysfunction. Olfactory identification deficits would be expected in these other illnesses, but their differing nature and timing of presentation may inform our understanding of the various neurobiological processes involved.

Conclusions

This chapter has examined olfactory abilities and deficits from a neurodevelopmental perspective. It is suggested that deficits in various disorders need to be understood in the context of normal versus abnormal maturational trajectory of these abilities. Further, the staggered nature of maturation of various olfactory abilities is considered. The implication is that earlier onset disorders of neurodevelopmental origin will manifest olfactory abnormalities that can be predicted from the maturational age of the individual at the time of illness onset or the time of the proposed abnormality. For example, in schizophrenia, a range of deficits may be apparent that are consistent with an early neurodevelopmental insult (see Pantelis *et al.*, 2005). The nature and degree of deficit may also be informative about the nature of any proposed neural compromise. To date, the available studies to inform these hypotheses are limited and further work should focus on longitudinal studies of olfactory abilities from childhood to adulthood in individuals at high risk for various disorders of neurodevelopment.

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7

Probes of behaviour regulation: olfactory models in addiction

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The utility of olfactory probes for understanding disorders involving orbitofrontal compromise has been outlined in Chapter 6. In this chapter, we discuss how such investigations may also be applied to addiction, where current neurobiological models implicate dysfunction within the orbitofrontal cortex (OFC) as a core underlying feature (Lubman *et al.*, 2004). Hence, the focus of the chapter is not on olfaction per se, but more broadly upon compromise of OFC structure and function. The aim is to model one example of how olfactory testing could be applied to investigations of OFC function and related behavioural outcomes. Specifically, we discuss how abnormalities within the OFC and associated limbic pathways may perpetuate substance use disorders (SUD), as well as having a potential causal role in the development of SUD in at-risk youth. The utility of olfaction in mapping adolescent prefrontal development is also described, with particular reference to impulse control, disinhibition, compulsion and other aspects of decision-making that are mediated by orbitofrontal processes.

Drug use in young people

Adolescence is a period of significant change, encompassing the transition from total dependence on parents to relative independence. To navigate this journey successfully, the young person must develop a number of core skills necessary for adulthood, as well as negotiate a series of emotional and social hurdles. Whilst several characteristic adolescent behaviours (such as increased risk-taking, novelty-seeking and peer-directed social interactions) are frequently blamed on modern youth culture, researchers now recognise that these behaviours are

also prominent in other adolescent mammals. This commonality across species suggests that these characteristic behaviours serve an important evolutionary adaptive function that promotes independence, survival and reproductive success (Spear, 2000).

Enhanced novelty-seeking and risk-taking during adolescence may be viewed as important ontogenetic adaptations that encourage the young person to explore new environments and situations, enhancing their knowledge and skill base through experiential learning. Although risk-taking may be considered to be an important developmental process, it is also associated with a number of potentially adverse outcomes, such that the young person must learn to tread a steady course. This is highlighted in studies of adolescent risk-taking, where high rates of 'reckless behaviour' are frequently recorded. For example, Arnett (1992) found that more than 50% of young people admitted to participating in risky behaviours, including unprotected sex and criminal activities (mostly minor). Such high-risk behaviours contribute to the increased morbidity and mortality rate associated with adolescence and young adulthood.

Epidemiological studies of experimental substance use report similar high rates during adolescence. For example, in a study of Australian secondary students, 94% of 16- to 17-year olds reported a lifetime history of alcohol use, whilst 47% described using an illicit substance at least once (White, 2001a, 2001b). Similarly, the 2001 Monitoring the Future Study found 80% of 12th graders (aged 17–18 years) in the United States had drunk alcohol, 61% had smoked cigarettes and 54% had used an illicit drug (Johnston *et al.*, 2002). Whilst these figures are alarming, such high rates suggest that experimentation with substances may be considered normative during the adolescent period, especially when viewed under the rubric of adolescent risk-taking. Block and Shelder (1990) have explored this notion further, demonstrating that young experimental users are more socially competent than both frequent users and abstainers, supporting the notion that experimental substance use during this period may be developmentally appropriate.

Fortunately, most young people only experiment with substances for brief periods, with only a minority developing substance-related problems. For those who do continue to use heavily, ongoing use may lead to psychological dependence (or addiction), characterised by the development of a strong desire or sense of compulsion to continue using despite a clear understanding of the potential risks. Other interests or responsibilities are also frequently neglected as individuals experience significant difficulties in controlling their use. Given the enormous personal and social costs associated with substance abuse, understanding the mechanisms that predispose and maintain SUD is clearly important.

Current neurobiological models of addiction

Neurobiological research into addictive processes has tended to focus on the brain's reward system, consisting of dopaminergic neurones projecting from the ventral tegmental area to the ventral striatum (including the nucleus accumbens), amygdala and septal nuclei, and prefrontal and cingulate cortices (Everitt *et al.*, 2001a). This system mediates the behavioural consequences of natural rewards (food, water, sex and nurturing behaviour), and appears to be a critical component of drug-induced reward (Everitt *et al.*, 2001a). By directly or indirectly inducing dopamine release within this system, addictive drugs can become potent behavioural reinforcers. This 'hijacking' of the brain's natural reward system explains how drugs of abuse can directly influence behaviour and promote ongoing drug-taking.

With chronic drug use, incremental neuroadaptations are suggested to occur within this system, rendering it sensitised (i.e. over-responsive) to drugs as well as related stimuli (Robinson & Berridge, 2000). This process of sensitisation results in excessive incentive salience being ascribed to the act of drug-taking, and transforms ordinary 'wanting' into severe drug craving. These neuroadaptations are thought to be independent of those underlying the phenomena of tolerance and withdrawal, suggesting that the desire for continued use is unaffected by the development of tolerance to its pleasurable effects or the amelioration of withdrawal symptoms. Importantly, these neuroadaptations have been shown to persist long after detoxification (Everitt *et al.*, 2001a; Volkow & Fowler, 2000), which may help explain the substantial relapse rate amongst abstinent users.

Whilst this model accounts for the ongoing desire for drugs, as well as the craving that occurs even years after ceasing use, it does not fully explain the uncontrolled nature of substance-related behaviours, whereby active drug-taking continues in the face of significant and immediate adverse consequences. This failure to regulate the motivational drive of the reward system suggests dysfunction within brain regions underlying inhibitory control over behaviour. In line with this notion, recent neuroimaging studies have demonstrated that frontal cortical regions are directly affected by long-term exposure to drugs of abuse (Goldstein & Volkow, 2002; Volkow *et al.*, 1992). In particular, the anterior cingulate cortex (ACC) and the OFC, brain regions critically involved in inhibitory decision-making processes, have been implicated. Specifically, these regions process the reward value and/or affective valence of environmental stimuli, assess the future consequences of one's own actions and inhibit inappropriate behaviours (Krawczyk, 2002). We, together with a number of other groups, have proposed that dysfunction within these brain regions is a key

neural mechanism underlying addiction (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999; Lubman *et al.*, 2004). However, what remains unclear is whether dysfunction within these brain regions is a direct consequence of chronic drug use and/or reflects premorbid vulnerability. In the following sections, we will explore these notions further, particularly focusing on the OFC. We will discuss how tasks such as olfactory identification, which probe normal and abnormal OFC function, may offer insights into the development and maintenance of SUD.

Role of the OFC in addiction

Both volumetric and functional imaging studies highlight abnormalities within the OFC in addicted populations. Recently, Franklin and colleagues reported decreased OFC volumes in patients with cocaine dependence compared to a cocaine-naïve group, a finding that is supported by a number of other research groups (Bartzokis *et al.*, 2004; Franklin *et al.*, 2002; Matochik *et al.*, 2003). More diffuse but less robust findings of frontal lobe abnormalities have also been reported in alcoholic individuals and polysubstance abusers (Kubota *et al.*, 2001; Liu *et al.*, 1998; Pfefferbaum *et al.*, 1997). Functional imaging studies conducted in addicted samples also highlight dysfunction within the OFC, although the pattern of activity observed appears to vary depending on the experimental condition (Lubman *et al.*, 2004). Significant *under*-activity in the OFC has been reported amongst current cocaine addicts and alcoholics, as well as in those abstaining for lengthy periods (Volkow *et al.*, 1988; 1992; 1997). In contrast, studies employing provocation paradigms in addicted populations, such as cue-exposure (i.e. presentation of drug-related imagery or paraphernalia), highlight *over*-activity in a number of brain regions, including the OFC. These studies report a correlation between OFC activity and subjective reports of craving and the urge to use drugs (Childress *et al.*, 1999; Daglish *et al.*, 2001; Garavan *et al.*, 2000; Grant *et al.*, 1996; Maas *et al.*, 1998; Wang *et al.*, 1999). Studies investigating metabolic changes during early withdrawal have also reported significant increases in OFC metabolism, which appear to correlate with self-rated measures of craving (Volkow *et al.*, 1991). The similarity across studies is not surprising considering that the withdrawal period is characterised by a heightened preoccupation with drug use, significant craving and an increased risk of relapse.

Direct pharmacological challenge with drugs of abuse also produces activation within the OFC in addicted populations. For example, the 'rush' associated with acute cocaine administration has been associated with activation within most

regions of the lateral prefrontal cortex (Breiter *et al.*, 1997), whilst intoxication with cannabis has been associated with increases in OFC metabolism in chronic marijuana users (Volkow *et al.*, 1996). Similarly, methylphenidate produces a craving state in cocaine abusers that correlates with increases in OFC metabolism (Volkow *et al.*, 1999). Interestingly, it is becoming evident that increased activity within the OFC is not only related to acute drug intake, but also appears to be associated with the expectation of drug reward. For example, London and colleagues found that in a sample of polydrug abusers expecting to receive cocaine, administration of placebo was also associated with increases in OFC metabolism (London *et al.*, 1990).

In parallel with these imaging studies, neuropsychological tasks that probe the integrity of the OFC have also recently been applied to addicted populations. The most widely reported has been the Iowa Gambling task, a decision-making paradigm that examines aspects of reward-related response selection, inhibition and impulsivity (Bechara *et al.*, 1994). In this task, participants are required to select from four piles of cards. Selection from two of the piles (the advantageous decks) results in small wins and small losses at irregular intervals, whereas selection from the other two piles (the disadvantageous decks) results in big wins and big losses. Over time, selection from the advantageous decks results in a net gain, whilst selection from the disadvantageous decks results in a net loss. The OFC has been shown to be critical to the successful performance of this task (and related paradigms) in healthy individuals across a number of imaging studies (Elliott *et al.*, 2000; Rogers *et al.*, 1999b). Not surprisingly, patients with OFC lesions perform poorly on this task, preferentially choosing the disadvantageous deck despite significant losses (Bechara *et al.*, 1994). Addicted subjects demonstrate similar behavioural responses (Bechara *et al.*, 2001; Bechara & Damasio, 2002; Grant *et al.*, 2000; Petry, 2001; Petry *et al.*, 1998). Thus, when faced with a choice of whether to pursue a course of action that brings the potential for immediate reward at the risk of future negative consequences or a low risk strategy involving long-term gain, addicted individuals tend to choose instant gratification, implying impairment in OFC integrity.

Deficits on this task (and thereby OFC dysfunction) appear to be related to duration of use. For example, Rogers and colleagues found that competent decision-making was negatively correlated with years of abuse amongst a group of chronic amphetamine users (Rogers *et al.*, 1999a). Similarly, Rupp and colleagues have recently reported olfactory identification deficits (further implicating the OFC) in alcohol-dependent subjects (Rupp *et al.*, 2003). In this study, the severity of olfactory deficits correlated with the duration of use, and was independent of associated amnestic or dementing syndromes. However, although both studies implicate the OFC in addiction, it is unclear whether

this is a result of premorbid vulnerability (i.e. poor premorbid OFC functioning is associated with a worse prognosis), the neurotoxic effects of chronic stimulant/alcohol use (i.e. longer use results in increasing damage to OFC structures) or both. Further work is essential, especially as these findings have important prevention and treatment implications.

Patients with OFC lesions also demonstrate a dissociation between knowledge and behaviour on the Iowa Gambling task and other paradigms that test reward-based decision-making (Bechara *et al.*, 1997; Rolls *et al.*, 1994). In fact, even though patients can readily describe the inappropriateness of their strategy, they continue to make disadvantageous choices. This is in keeping with the animal literature, where lesions to the OFC results in perseverative responding to previously rewarded stimuli, even following extinction (Butter, 1969; Dias *et al.*, 1996). This impairment in decision-making is similar to the behavioural choices typically enacted by addicts, who continue to make disadvantageous responses despite being able to clearly describe the likely consequences of their actions. This is consistent with the notion that the addictive state involves a behavioural 'loss of control' and disruption of brain circuits involved in compulsive behaviour. Given the OFC is also involved in other disorders characterised by compulsive and repetitive behaviours (such as obsessive-compulsive disorder (OCD): see Chapter 14) (Pujol *et al.*, 2004), its abnormal activation in the addicted subject could explain why drug-taking occurs in spite of potential immediate and significant adverse consequences, and in the absence of pleasurable drug effects. For example in OCD, a patient who engages in excessive hand-washing may be cognitively aware that their hands are clean (or even damaged by excessive scrubbing), but nevertheless feels driven to continue with the washing ritual. Similarly, addicts describe being driven to use their drug of choice, often taking the substance even when it is no longer pleasurable, and despite a clear understanding of potential serious adverse outcomes. This inability to regulate the excessive motivational drive seen in both addiction and OCD suggests that OFC dysfunction is likely to be a core component of both compulsive conditions. It would therefore be expected that olfactory identification deficits (OID) would be common to individuals exhibiting such compulsions. Limited data on addicted populations is available in this regard, however OID have been found in studies of OCD (see further discussion in Chapter 14). Given improvements in OI ability throughout adolescence (in parallel with OFC development), further research is required to explore the utility of assessing OID as an early marker of risk for the development of compulsive and/or addictive behaviours.

Whilst, the OFC appears to be highly active during drug administration, withdrawal and exposure to cues, it is relatively under-active at other times, including during periods of abstinence. This is consistent with the

neuropsychological literature, with deficits in OFC function reported across a range of addicted populations. There is also some preliminary evidence that these deficits may correlate with the duration of substance use, and that similar pathology is characteristic of other compulsive disorders (see Chapter 14). However, what still remains to be determined is the relationship between functional activation and behavioural performance of the OFC during provocation. We have previously suggested that the OFC is likely to be 'flooded' by intense motivational drives during provocation/cue exposure, resulting in the release (disinhibition) of behaviour that is overly dominated by 'pre-potent' and 'stimulus-driven' tendencies (Lubman *et al.*, 2004). This leads to impulsivity (experienced as a loss of control) without consideration of potential negative outcomes, resulting in recurrent compulsive drug-taking. This model may explain why addicts in treatment can vociferously insist that their drug-using days are over but reinstate drug use within days or even hours. Such lapses typically occur in the context of exposure to drug-related environments or strong affective states. However, despite the intrinsic appeal of this model, further studies are required to rigorously examine the role of the OFC in addiction, including its involvement in relapse. This will require a prospective arm to any further neurobiological research in human addicts, but offers the potential of significantly informing relapse prevention strategies, including plans that may be individually targeted.

OFC-related vulnerability and its role in maintaining addictive behaviour: what we already know and future directions

Although imaging and neuropsychological studies demonstrate abnormalities in OFC function within addicted populations, it is unclear whether these deficits are related to premorbid vulnerability, a direct consequence of chronic exposure to addictive substances, or a combination of both. This will be an extremely important area of research, especially in terms of early intervention and public health policy, and has been relatively neglected to date.

To this end, there is a growing literature on risk factors for SUD, which include studies of temperament and personality. These studies highlight a relationship between impulsivity and related constructs (such as sensation-seeking) in childhood and the development of later substance use problems in adulthood (Tarter, 2002; Tarter *et al.*, 1999). In fact, studies of both adolescents and adults consistently report an association between impulsivity and substance-related problems (Cloninger *et al.*, 1998; Henderson *et al.*, 1998; McGue *et al.*, 2001). More recently, researchers have suggested that it is a specific domain of impulsivity, termed 'rash-spontaneous impulsivity' (the tendency to act rashly

and without consideration of consequences; see Dawe *et al.* (2004) for a review) that is more directly associated with SUD. Such behaviours would also be expected to be related to OID. Indeed, Larsson and colleagues found that neuroticism, impulsivity and lack of assertiveness were negatively related to odour identification ability (Larsson *et al.*, 2000). Recent neuroimaging studies also suggest a role for the OFC in such constructs (i.e. impulsivity and constraint). For example, Horn and colleagues found that self-reported impulsivity correlated with activity in the lateral OFC (Horn *et al.*, 2003), whilst Bechara and colleagues noted that OFC volume inversely correlated with trait impulsivity/aggression scores in patients with antisocial personality disorder (Bechara *et al.*, 2001). Whilst these data suggest that certain temperament or personality characteristics may be associated with an increased vulnerability to addiction as a result of differential OFC functioning, and to olfactory identification ability, future studies need to examine OFC integrity specifically and more comprehensively, particularly in at-risk populations. Such studies need to delineate to what extent these factors enhance premorbid vulnerability and/or maintain drug-seeking behaviour. In this regard, future research should also consider whether such vulnerability is related to differences in OFC maturity (e.g. by measuring age-appropriate gains in olfactory identification), and to what degree this process may be further disrupted by recurrent drug-taking.

In terms of maturational processes within the brain, we now know that significant remodelling (particularly in frontal regions) occurs throughout adolescence, with substantial pruning of grey matter and concurrent myelination of white matter tracts. These structural changes are associated with improvements in cognitive processing (Casey *et al.*, 2000), with the development of more complex cognitive (e.g. inhibitory/impulse control) and affective abilities (e.g. regulation of motivational drive and affect). As discussed in Chapter 6, improvements in olfactory identification ability (mediated by OFC-related networks) closely parallels the development of prefrontal cortical function through adolescence, thus offering researchers a sensitive probe of OFC development in at-risk groups.

The maturational changes observed in brain structure and function during adolescence are essential for ongoing learning and the acquisition of relevant developmental tasks. However, this developmental plasticity also leaves the adolescent brain vulnerable to stressors and external agents, potentially disrupting the normal trajectory of maturational processes. Although structural brain changes have been more commonly reported in adult drug users, there is growing evidence from both the animal and human literature that adolescence is specifically associated with an increased sensitivity to the neurotoxic properties of addictive drugs. For example, in an elegant set of experiments, Slotkin and

colleagues have shown that brief episodic exposure to nicotine in adolescent rodents produces enduring cellular and neuritic damage in cortical regions, even at plasma concentrations one-tenth of that observed in regular smokers (Slotkin 2002). Importantly, these findings were not replicated in adult animals, even when administered at higher dosages for prolonged periods.

Similarly in humans, there is growing evidence that an earlier onset age of substance abuse may be related to more marked neurobiological and cognitive deficits. For example, Ehrenreich and colleagues found that early-onset cannabis users (smoking before age 17), but not those with a late-onset (smoking after age 17), had significantly slower reaction times than controls in a visual scanning task (Ehrenreich *et al.*, 1999). Similarly, Pope and colleagues found that early-onset long-term heavy cannabis users differed significantly from late-onset users on a number of measures, most notably verbal intelligence quotient (IQ) (Pope *et al.*, 2003). These findings are consistent with the neuroimaging literature, with early-onset cannabis users (but not late-onset) demonstrating reduced brain grey matter on magnetic resonance imaging (MRI) (Wilson *et al.*, 2000). De Bellis and colleagues reported similar findings in a sample of adolescents and young adults with alcohol use disorders. In this study, hippocampal volume correlated positively with age at onset and negatively with duration of use (De Bellis *et al.*, 2000). Whilst these studies are consistent with the concept of increased sensitivity to the neurotoxic effects of addictive substances during adolescence, future studies should consider carefully to what degree normal maturational processes are disturbed following the onset of drug use. In particular, given the strong evidence linking the OFC to addictive processes, future research should specifically examine how early substance use affects OFC functioning and maturation, and whether any delay is permanent or recovers over time.

At the same time, there is also evidence that adolescents are less sensitive to some of the behavioural effects of acute drug use (e.g. adolescent rodents are less vulnerable than adults to the sedative effects of alcohol), allowing them to use substances at higher doses for longer periods than their adult counterparts. Thus, young people may be able to indulge for longer periods than adults, despite being more vulnerable to substance-induced cognitive impairments, and perhaps, brain damage. In fact, Bartzokis and colleagues have recently reported that cocaine-dependent subjects (aged 19 to 47) do not demonstrate the normal pattern of age-related increases in white matter within frontal and temporal brain regions (a process that normally occurs well into the fifth decade of life) (Bartzokis *et al.*, 2002), suggesting that continued cocaine use may arrest normal white matter maturation. Whether or not this effect is more pronounced with an earlier onset of use requires further study.

Thus, although limited, there appears to be some evidence that the OFC has a critical role in both vulnerability and maintenance of SUD. Adolescence is a developmental period associated with increased risk-taking and experimentation with drugs, and is also a time of increased vulnerability to the development of SUD. Specific temperament and personality characteristics, such as impulsivity and low constraint, appear significantly to increase the risk of SUD during this period, which may in part be related to delayed OFC maturation or dysfunction. This is consistent with the research of Everitt and colleagues, who have recently proposed that recurrent drug use progresses to compulsive drug-taking as a result of dysfunctional prefrontal cortical structures (including the OFC) (Everitt *et al.*, 2001b). They postulate that increases in striatal dopamine that occur with chronic drug use leads to the progressive engagement of ventral striatal structures (via a process called 'spiralling'), ultimately transforming a repeated behaviour into a recurrent habit (that is difficult to cease). Delayed maturation or damage to OFC structures may therefore facilitate this process, increasing the likelihood of ongoing substance use and drug addiction.

Further, experimentation with drugs also occurs during a period of substantial brain development and remodelling. Whilst adolescents are less sensitive to some of the behavioural effects of acute drug use, they appear to be more vulnerable to the neurotoxic effects of such drugs, resulting in cognitive impairment and structural brain damage. Studies suggest that early-onset users are particularly at risk, and early use may significantly disrupt cognitive and cortical development. Neuropsychological and imaging studies of addicted subjects consistently report dysfunction within the OFC, suggesting that this region may be particularly sensitive to the chronic effects of drugs, and early use in particular, may significantly impair its maturation. Thus, chronic drug use may further damage a region implicated in 'at-risk' adolescents, and contribute to the maintenance of addictive behaviour. Although no studies to date have examined the impact of substance use on OFC maturation, there appears to be a strong case for mapping prefrontal development in at-risk adolescents using olfactory probes.

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Section II

Social functioning: role of evolution, genetics and gender

8

Primate olfaction: anatomy and evolution

Timothy Smith and James Rossie

Introduction

Primate origins

The living primates are commonly divided into two suborders: Strepsirrhini comprising the lemurs, lorises and galagos; and Haplorhini containing tarsiers and anthropoids (Table 8.1, Figure 8.1). These two groups had diverged from one another by the beginning of the Eocene period (Rose & Bown, 1991), where they are represented by the adapoids and omomyoids respectively. Together, the living and fossil strepsirrhines and haplorhines are known as 'crown primates' or 'euprimates'. Any primates preceding the divergence of the two euprimate suborders would be called stem primates, and a growing body of evidence suggests that the plesiadapiforms, a diverse radiation known mainly from the Paleocene period, are such a group (Bloch & Boyer, 2002). While the origin of stem primates constitutes the true origin of the primate order, most adaptive scenarios of 'primate origins' have focused on anatomical differences between euprimates and other mammals.

Of the several theories that have been developed to account for the origin of primates (see Cartmill (1992) and Sussman (1999) for more thorough discussion and original references), two have specific bearing on the topic of this chapter. The arboreal theory (e.g. Jones, 1916; Smith, 1927) holds that the features which distinguish primates from other mammals (divergent hallux and pollex, regressive rostrum, more forward-facing position of the orbits (known as 'orbital convergence')) are adaptations for an arboreal existence. In this view, the reduction of the rostrum was due to the diminished importance of olfaction in an arboreal milieu, along with recession of the jaws (Le Gros Clark, 1959).

Table 8.1. Taxonomy (extinct species in **bold**)

Cohort Euarchonta
- Order Dermoptera (culugos or 'flying lemurs')
- Order Scandentia (tupaiids or 'tree shrews')
- Order Primates
  - Semiorder Plesiadapiformes
    - ***Plesiadapis***, ***Ignacius***, ***Microsyops***, etc.
  - Semiorder Euprimates
    - Suborder Strepsirrhini
      - Infraorder Adapiformes
        - Superfamily Adapoidea
          - ***Adapis***, ***Notharctus***, ***Leptadapis***, etc.
      - Infraorder Lemuriformes
        - Superfamily Lemuroidea
          - *Lemur*, *Eulemur*, *Indri*, *Microcebus*, *Daubentonia*
        - Superfamily Lorisoidea
          - *Loris*, *Perodicticus*, *Galago*, etc.
    - Suborder Haplorhini
      - Hyporder Tarsiiformes
        - Superfamily Omomyoidea
          - ***Necrolemur***, ***Shoshonius***, ***Dyseolemur***, etc.
        - Superfamily Tarsioidea
          - *Tarsius*
      - Hyporder Anthropoidea
        - Infraorder Paracatarrhini
          - Superfamily Parapithecoidea
            - ***Parapithecus***
        - Infraorder Platyrrhini
          - Superfamily Ceboidea
            - ***Tremacebus***, *Cebus*, *Callicebus*, *Ateles*, *Saguinus*, etc.
        - Infraorder Catarrhini
          - Superfamily Propliopithecoidea
            - ***Aegyptopithecus***, ***Catopithecus***
          - Superfamily Cercopithecoidea
            - ***Victoriapithecus***, *Colobus*, *Cercopithecus*, *Papio*, etc.
          - Superfamily Hominoidea
            - ***Proconsul***, ***Sivapithecus***, *Hylobates*, *Pongo*, *Pan*, *Gorilla*, *Homo*

More recently, Cartmill (1970) has demonstrated that transition of a terrestrial, insectivore-like, ancestor to an arboreal habitat does not favour the expression of the primate traits mentioned above (it has not done so in squirrels, for instance). Rather, it is the combination of visually directed manual capture of prey in

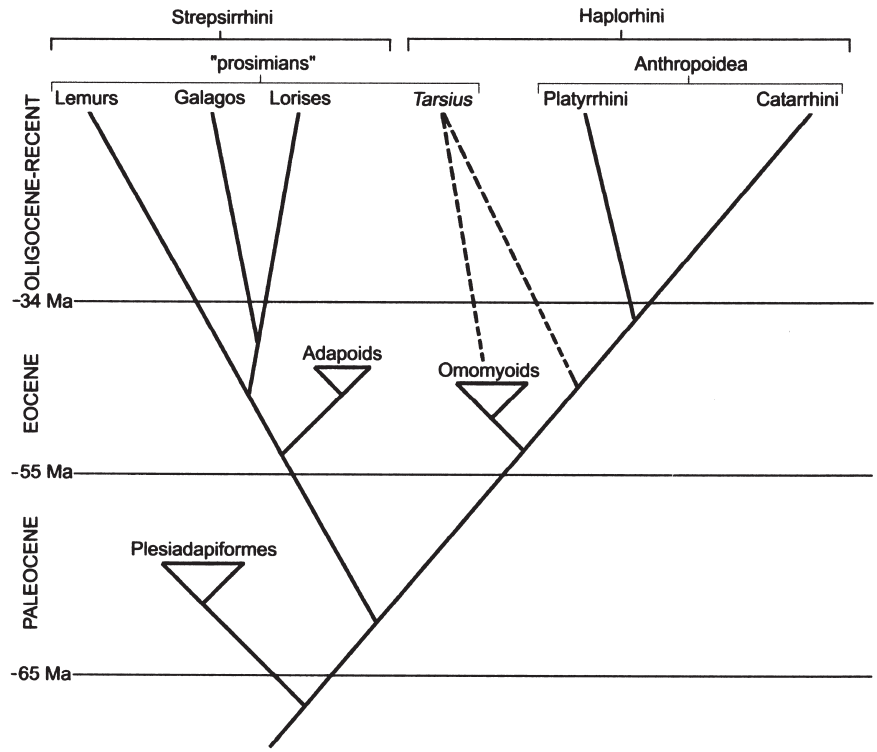

Figure 8.1 Simplified phylogeny of Primates. The two widely held views of the position of *Tarsius* are represented by dashed lines. While most researchers prefer the haplorhine/strepsirrhine classification scheme, the older prosimian/anthropoid dichotomy is depicted for the sake of reference.

a fine-branch setting that explains the hallmark primate features. More importantly for our purposes, it was shown that arboreal life does not favour a reduction in olfactory abilities (Cartmill, 1970). Cartmill's explanation for reduction of the nasal region is purely structural – it resulted from the crowding of the nasal cavity by the progressively convergent orbital cones.

Whatever be the cause of olfactory regression in primates, it is not a homogenous property of the order, but a trend, and the degree to which it distinguished the first primates from their immediate relatives depends on the identity of both parties (plesiadapiformes or tupaiids). Moreover, it is clear that substantial alterations in nasal anatomy have occurred within the order Primates since its origin (Cartmill, 1970; Cave, 1967; Le Gros Clark, 1959). Some authors have considered all primates 'microsmatic' (olfactory sense reduced) compared to other mammals (see Negus (1958)). Other authors have considered only a subset of primates to be microsmatic (usually haplorhines; Cartmill (1970);

Cave (1967; 1973); Turner (1891)). These categorical assessments of olfactory abilities are often based on questionable assumptions regarding the relationship between bony morphology and olfactory sensitivity. Regardless, the question remains: do the *proportionally* small snouts of primates in general, and of haplorhines in particular, reflect a relatively poor sense of smell? This chapter examines the evidence of olfactory regression over the course of primate evolution with the aim of understanding the human sense of smell in an evolutionary context.

Anatomy of primate olfaction

Introduction to primates

Primate noses are a frequent topic of discussion in primate higher taxonomy. The haplorhine/strepsirrhine dichotomy described above is based on shared derived characteristics (synapomorphies) of tarsiers and anthropoids (Haplorhini; Figure 8.2), including a reduction in the size and complexity of the nasal cavity. In the following section, we discuss the evolutionary morphology of primate olfaction, including the taxonomic variability of the main and accessory (vomeronasal) olfactory systems.

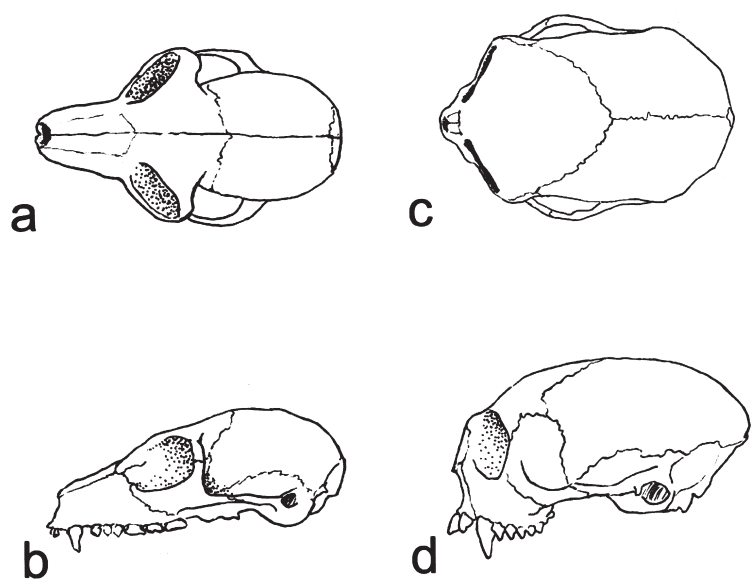

Figure 8.2 Dorsal (top) and lateral (bottom) view of a generic lemur (a, b) and tamarin (c, d). From a dorsal position, note that the two orbits are oriented more in the same direction in the tamarin (c) compared to the lemur (a) (and see Figure 8.9). From a lateral perspective, note that the orbits are more vertically oriented in the tamarin (d) compared to the lemur (b).

External nose

The terms 'strepsirrhine' and 'haplorhine' are themselves descriptive anatomical terms, regardless of taxonomic importance. They refer to characteristics of the skin found around the nostrils and the upper lip (Pocock, 1918). As in most other mammals, strepsirrhines exhibit a rhinarium, a moist patch of skin that surrounds the nostrils, and usually extends inferiorly to form a small portion of the upper lip. The rhinarium is typically highly glandular and well innervated (although it does not contain olfactory receptors, contra Ankel-Simons (2000)). There is a midline rhinarial groove that extends to a notch in the upper lip. At this notch, the rhinarium attaches to gingival mucosa between the central incisors via a mucosal fold, the philtrum. This necessitates a gap between the central incisors that continues into a midline palatal groove. This palatal groove leads to the incisive papilla (Hofer, 1980), which is found at the terminus of a canal that communicates with the duct of an accessory olfactory organ, the vomeronasal organ (VNO, see below). Thus, the rhinarium has an indirect association with the accessory olfactory (vomeronasal) system, but has no similar relationship to the main olfactory system. More details may be found in the excellent description by Ankel-Simons (2000).

Haplorhinism represents a more simplified condition, since there is no rhinarium present (Ankel-Simons, 2000). Instead, a continuous upper lip is present, with skin including hair follicles and a continuous layer of muscles of facial expression (e.g. *orbicularis oris* – Hofer (1977)). Moreover, there is no gap between the upper central incisors of living haplorhines. Thus, this association of the external nose with the VNO is lost in living haplorhines.

Another external nasal mechanism may relate to VNO function in some primates. In primates that retain a VNO with receptor neurons, the marginoturbinal is continuous posteriorly with an atrioturbinal at the margin of the bony nasal aperture and, subsequently, with the maxilloturbinal, resulting in a continuous turbinal structure that divides the nasal fossa into an upper and lower pathway. Muscles attaching to the cartilaginous marginoturbinal at the entrance of the external nares can either close the nostrils or redirect airflow (Maier, 1980; Seiler, 1976). Such control over the nostrils is thought to play a role in the function of the VNO in some mammals (Dagg & Taub, 1970; Estes, 1972; Moulton, 1967). Although flehmen (see Estes (1972)) has not been observed in any haplorhines, it may suffice to be able to redirect chemostimuli inferiorly toward the nasopalatine duct, into which the ducts of the VNO open. Catarrhines have lost the atrioturbinal and reoriented the maxilloturbinal such that this path of chemostimulus access no longer exists (Maier, 1980; Rossie, 2005). It is noteworthy that the VNO has been lost or is vestigial in catarrhines (see p.142 and Smith *et al.* (2001)).

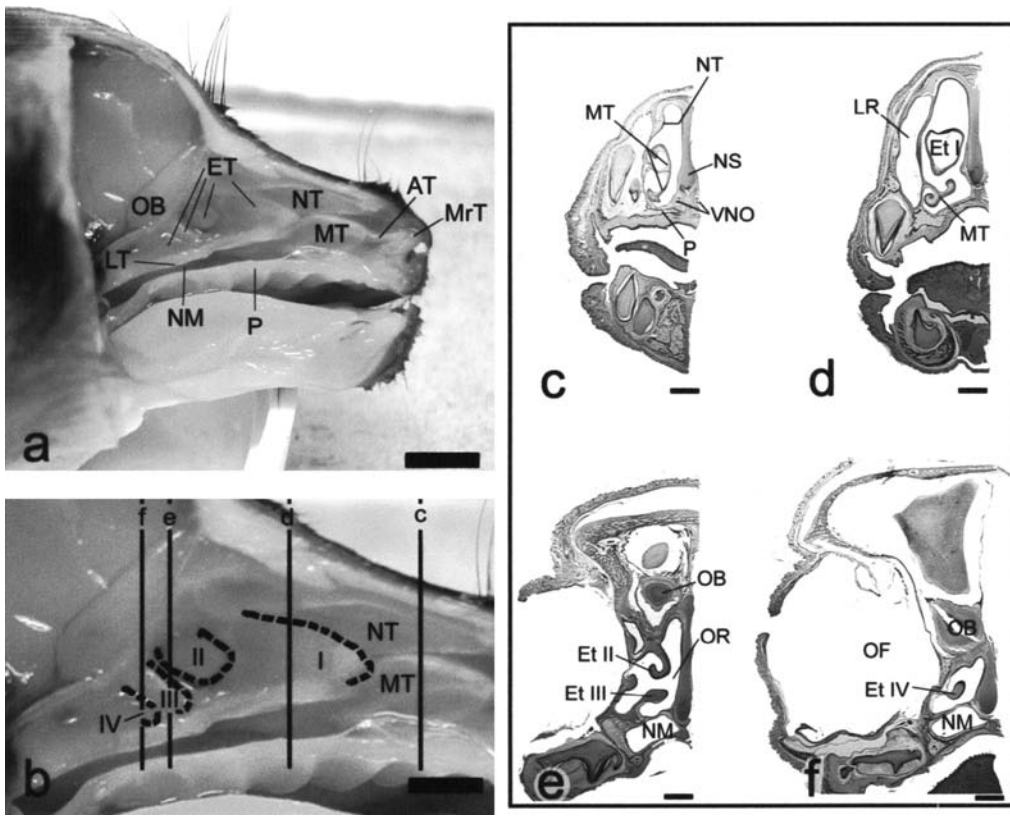

Figure 8.3 (**a**) Parasagittal view of the head of a neonatal black lemur (*Eulemur macaco*) showing the lateral nasal wall, and the position of the ethmoturbinals (ET) relatively to the olfactory bulb (OB) in the anterior cranial case, the olfactory recess (OR) and the more anterior turbinals (NT, nasoturbinal; MT, maxilloturbinal; Mrt, marginoturbinal; AT, atrioturbinal). A detail view (**b**) shows four planes (c–f) which grossly show features seen on the serially sectioned, contralateral side. Shown are coronal views of the NT and MT anteriorly (**c**), followed posteriorly by ethmoturbinal I (**d** – ET I), and the remaining ethmoturbinals (**e** – ET II and ET III; **f** – ET IV). LR, *recessus* lateralis; LT, *lamina transversalis posterior*; NM, nasopharyngeal meatus; OF, orbital fossa; P, palate. Scale bars: a, 5 mm; b, 2.5. mm; c–f, 1 mm.

Nasal fossae

Anatomical background

The mammalian nasal fossae are located on either side of a midline nasal septum, and thus represent right and left sides of the entire nasal cavity (Figure 8.3). The nasal fossae each have medial walls consisting of the nasal septal mucosa and lateral walls composed of mucosa lining the medial surfaces of the premaxilla, maxilla and palatine bones. Also found laterally in adult mammals are the

Table 8.2. Anatomy of the nasal fossae: terminology and homology

Structure name	Homologue in human anatomy	Synonyms from other authors
Nasoturbinal	*Aggar nasi*	Endoturbinal I (Moore, 1981); ethmoturbinal I (Martin, 1990)
Maxilloturbinal	Inferior nasal conchae	
Ethmoturbinal I (ET I)	Middle nasal conchae	Endoturbinal II (Moore, 1981); ethmoturbinal II (Martin, 1990); anterior lamina of ET I (for some species – Maier, 2000)
Ethmoturbinal II (ET II)	Superior nasal conchae	Endoturbinal III (Moore, 1981); ethmoturbinal III (Martin, 1990); posterior lamina of ET I (for some species – Maier, 2000)
Ethmoturbinal III (ET III)	Supreme nasal conchae (if present)	Endoturbinal IV (Moore, 1981); ethmoturbinal IV (Martin, 1990)
Ethmoturbinal IV (ET IV)	None	endoturbinal V (Moore, 1981); ethmoturbinal V (Martin, 1990)
Ectoturbinal I	Ethmoid bulla	Bulla is considered a product of the fusion of ectoturbinals 1 and 2 by de Beer (1937)
lamina transversalis post.	Ossicula Bertini? (Keith, 1948)	
Olfactory recess	Sphenoethmoidal recess(vestige)	*recessus cupularis* (Rossie, 2006); *recessus ethmoturbinalis* (Maier, 1993)

maxilloturbinal (homologue of inferior nasal concha), and the turbinals of the ethmoid labyrinth — the ethmoturbinals. The 'floor' of each nasal fossa is composed of mucosa lining the palatal processes of the premaxilla, maxilla and palatine bone. The 'roof' of each nasal fossa is formed by the mucosa lining the nasal bones, the ethmoid complex, and, in many primates, a portion of the frontal bone.

The midline nasal septum has an osseous framework composed of the ethmoid superiorly and the vomer inferiorly. A hyaline cartilage septum is attached to the anterior margins of these bones and extends the septum anteriorly to a variable extent. The mucosa that lines the septum includes olfactory, respiratory or stratified epithelia at the surface. In all strepsirrhines, New World monkeys and tarsiers, paired VNOs are found at the base of the nasal septal cartilage, surrounded by scrolls of hyaline cartilage. The VNOs run parallel and inferior or inferolateral to the septal cartilage, but superior to the palatal processes of the maxillae (Smith *et al.* (2001; 2003)). A superiorly displaced VNO occurs in adult humans and chimpanzees, positioned superior to the inferior border of the nasal septal cartilage, with no surrounding cartilage (Smith *et al.*, 2001). In strepsirrhines, tarsiers and New World monkeys, the VNO possesses a neuronal epithelium that expresses olfactory marker protein, an immunohistochemical marker also expressed in mature olfactory receptor neurons (Dennis *et al.* 2004). The VNO has a known role in mediating sociosexual responses in some strepsirrhines (Aujard, 1997), but its postnatal function in New World monkeys and tarsiers is unknown, and doubtful in humans or chimpanzees (Smith *et al.*, 2002; Witt *et al.*, 2002).

From the lateral nasal wall, turbinals invade and subdivide the nasal airways. In morphology, these projections may vary from simple ridges to highly elaborated scrolls. Turbinals are especially complex in strepsirrhines, but no primates have turbinals as elaborate as carnivores (Moore, 1981). In fact, turbinals across different primate taxa appear to exhibit a trend toward reduction and reorientation. Comparison of the turbinals found among primates is complicated by several different schemes of terminology (Table 8.2). Historically, many authors have identified the turbinals closest to the septum as endoturbinals, and those positioned more laterally and deep to the endoturbinals as ectoturbinals, (Moore, 1981; Paulli, 1900). Endoturbinal names are generally based on their anatomical articulation in adults: the maxilloturbinal articulates with the maxilla and premaxilla, the nasoturbinal articulates with the nasal bone (and with the more posterior ethmoid to a variable extent) and the ethmoturbinals arise from the ethmoid. Authors also vary in their treatment of the nasoturbinal, some referring to it as 'endoturbinal or ethmoturbinal I' (Martin, 1990; Moore, 1981; Paulli, 1900), whereas other authors begin with the next

more posterior turbinal as ethmoturbinal I. Thus the total number of ethmoturbinals described by different authors in a given species has varied (e.g. Ankel-Simons (2000); Maier (1991); Martin (1990) regarding *Daubentonia*). These contradictions in terminology, along with some intraspecific variation in ethmoturbinal numbers (Cave & Haines, 1940; Hershkovitz, 1977; Moss-Salentijn, 1991), create a dilemma in comparative studies. Regarding terminology, we prefer to employ a developmental approach to identifying homologous structures in the nasal cavity for reasons elaborated elsewhere (Rossie, 2006). Most of the structures that we are concerned with can be identified with recourse to discrete elements of the cartilaginous nasal capsule as outlined below (see Rossie (2003; 2006) for more detail and citations). This approach yields a terminology similar to that used by Maier (e.g. Maier (1987; 1997)).

In the fetal chondrocranium of most mammals, the lateral walls of the nasal capsule are composed of the pars anterior, pars intermedia and pars posterior — the latter being the lateral portion of the posterior cupula. The pars posterior and pars anterior (or parietotectal cartilage) overlap the pars intermedia medially such that they partially wall-off a recessus lateralis. These projections of the pars posterior and pars anterior into the nasal cavity are the rudiments of the first ethmoturbinal (ET I) and crista semicircularis, respectively (Figure 8.4). The remaining, more posterior or superior ethmoturbinals (variable in number) begin as folds in the mucosa of the pars posterior, and subsequently chondrify. In the anterior portion of the roof of the nasal cavity, the tectal cartilage (medially) and the pars anterior (laterally) join along an anteroposterior line where the edges of both curl inferiorly to project into the nasal capsule

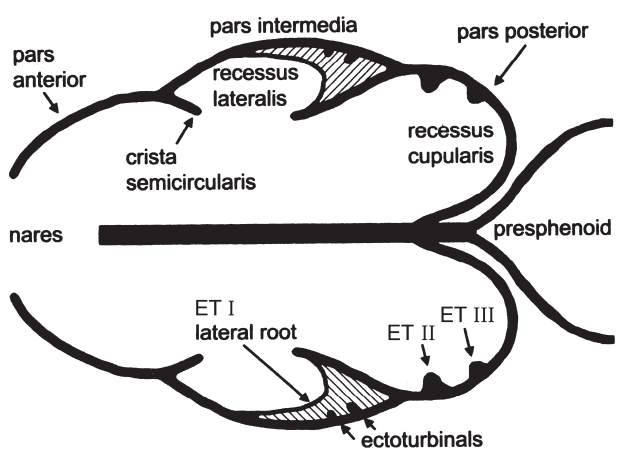

Figure 8.4 Schematic representation of a horizontal slice through the fetal nasal capsule of a strepsirrhine primate. ET I, ET II, ET III, are first through third ethmoturbinals.

below, forming a crest that ossifies as the nasoturbinal. The maxilloturbinal is formed by the inferior edges of the paries anterior and intermedia as they curl medially at the base of the nasal cavity (the wall of the inferior meatus has no cartilaginous precursor). In most mammals, a lateral root of ET I (sometimes called the septum frontomaxillare) projects laterally from its vertical body to anchor on the pars intermedia, partially dividing the recessus lateralis into a recessus frontalis superiorly and a recessus maxillaris inferiorly. In many mammals, the recessus frontalis is further divided by a series of ectoturbinals that develop as folds in the mucosa of the pars intermedia. Finally, the posterior pole of the nasal capsule consists of the concave posterior cupulae. The recess produced by the concavity of the posterior cupula on each side is known as the *recessus cupularis* (Rossie, 2006) or *recessus ethmoturbinalis* (Maier, 1993). In strepsirrhines, this recess is separated from the remainder of the nasal cavity by a horizontal plate of bone, the *lamina transversalis posterior* (Table 8.2). Because this space houses the elaborately scrolled posterior ethmoturbinals and is mostly lined with olfactory epithelium, it is often termed the olfactory recess (Moore, 1981; Table 8.2). In all primates, the nasopharyngeal meatus (found inferior to the *lamina transversalis posterior* in strepsirrhines) has only a respiratory (air conditioning) function.

The anatomical terminology that stems from this ontogenetic approach is simple. The numbering of ethmoturbinals begins with ET I, which is a discrete cartilaginous element. The number of ethmoturbinals following ET I is complicated, as noted above, by the question of whether the ET I of some species comprises two folds. Our own developmental data (sectioned perinatal specimens) suggest that the supposed compound ET I is the product of fusion between two turbinal lamellae that are separate at an early stage of growth. We therefore prefer to recognise only the first fold as ET I in such taxa (making the total number four in most strepsirrhines), but the issue is far from resolved.

The ectoturbinals cannot be confused with ethmoturbinals, since the former develop as folds of the pars intermedia, and the latter as folds of the pars posterior. Hence, ectoturbinals can be found only in the frontal recess, or between the nasoturbinal and ET I, as previously asserted by Allen (1882). The nasoturbinal appears to be the homologue of the human *aggar nasi*, and while the uncinate process is rarely developed in non-human primates, this too is part of the nasoturbinal (Kollmann & Papin, 1925). The recessus maxillaris *might* be considered the homologue of the human infundibulum, but the recessus frontalis is certainly the frontal recess of humans (cf. Keith, 1948).

Mammals possess a number of paranasal sinuses, which emanate from the nasal fossae and excavate the surrounding cranial bones. Sinus development occurs in two stages; primary and secondary pneumatisation.

Primary pneumatisation consists of the formation of the recesses of the nasal cavity (e.g. recessus maxillaris). Secondary pneumatisation occurs after the onset of ossification of the cranial bones, and involves resorption of bone by a front of osteoclasts at the expanding front of the epithelium of each recess. While most mammals possess a full complement of paranasal recesses, many taxa fail to undergo secondary pneumatisation of one or more recesses, resulting in the absence of one or more sinuses in the adult form.

Recognition of homologous sinuses in humans and other mammals has been somewhat challenging, but as with other features of the nasal fossae, the sinuses are easily identified on the basis of their ontogeny. As has long been held, the identity of a sinus is based on the site of its ostium, or its original connection with the nasal cavity (Cave, 1967; Cave & Haines, 1940). However, recent work on non-human primates has revealed that the site of the ostium in *adult* individuals can be a misleading proxy for the site of the original opening. For example, in platyrrhines the cupular recess (formed by the posterior cupula), from which the sphenoid sinus develops, may come to be covered by any number of bones, and hence, the ostium of the adult sphenoid sinus may lie in the ethmoid, frontal or sphenoid bones. As this example illustrates, the key to sinus identity (and homology) is the identity of the paranasal recess from which it develops. Application of this principle reveals that the five sets of sinuses found in humans are found in various combinations in other mammals, including primates. Briefly, the sinuses and the recesses from which they develop are: the sphenoid sinus from the *recessus cupularis*; the maxillary sinus from

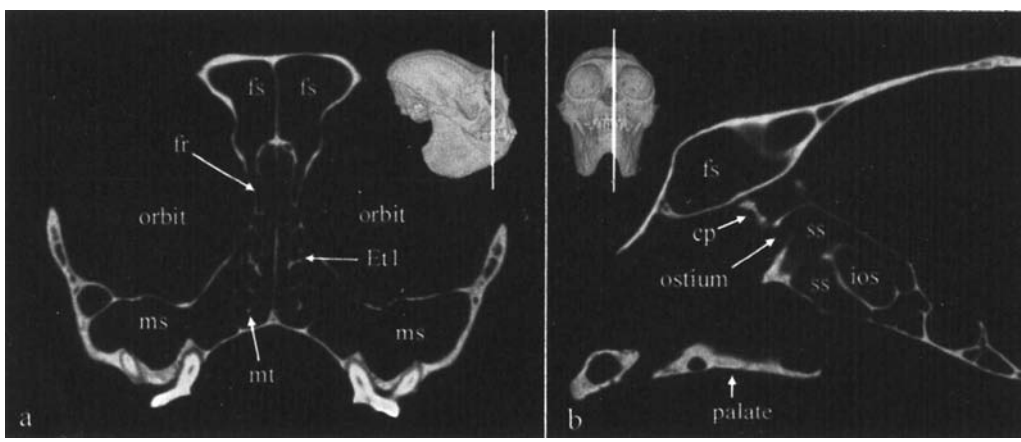

Figure 8.5 Coronal (**a**) and parasagittal (**b**) CT-scans of the platyrrhine *Callicebus* showing maxillary (ms), frontal (fs), and 'sphenoid' sinus (ss). White lines in scout images (insets) indicate plane of each scan. cp, cribriform plate; Et1, first ethmoturbinal; fr, frontal recess; ios, interorbital septum; mt, maxilloturbinal.

the recessus maxillaris; the posterior ethmoid sinuses from the superior and supreme meatuses (the lateral wall of the pars posterior between the first and third ethmoturbinals); the anterior ethmoid sinuses from the recessus frontalis (see Figure 8.5). The frontal or ethmofrontal sinus found in humans is formed by one or more of the anterior ethmoid sinuses and is found in African apes (Cave & Haines, 1940), several platyrrhine monkeys (Rossie, 2006) and reportedly many other mammals including strepsirrhines and carnivores (Paulli, 1900).

Although the function of the paranasal sinuses remains uncertain, many past proposals ascribed some role in olfaction. However, it has been convincingly demonstrated that olfactory epithelium is not found in the paranasal sinuses (although recesses have sometimes been mistaken for sinuses; e.g. Negus, 1958), and that air interchange between the sinuses and nasal cavity is negligible (see Blanton & Biggs, 1968; Witmer, 1997 for discussion). Moreover, the extraordinary diversity of sinus patterns seen in anthropoids shows no signs of correlating with reported differences in olfactory sensitivity (Laska *et al.*, 2004) (see Figure 8.6). In light of these facts, the paranasal sinuses of primates will not be discussed further here.

Comparisons of structures between species

Most strepsirrhine primates exhibit a maxilloturbinal, nasoturbinal and four ethmoturbinals in each nasal fossa (Cave, 1973). A notable exception is the aye-aye (*Daubentonia madagascarensis*), which may have five ethmoturbinals (but see Maier (1991)). One or two small ectoturbinals are found in the frontal recess of most strepsirrhines (Kollmann & Papin, 1925). A similar reduction in ecto- and ethmoturbinals has been noted for tupaiids (Le Gros Clark, 1925; 1926). In this respect, at least, the primate nasal cavity is not uniquely simplified.

The turbinals of haplorhines vary in number. In all haplorhines, paired maxilloturbinals and nasoturbinals are present, though the latter may be quite small (Hershkovitz, 1977). In general, they are simpler in morphology compared to those of strepsirrhines. The maxilloturbinal is single-scrolled in catarrhines, but bilaminar in many platyrrhines. The nasoturbinal is more variable in adults, extending its lamina posteriorly to join the first ethmoturbinal in some taxa (*Papio, Cebus, Lagothrix*), reduced to an anterior vestige in others (e.g. humans), or apparently absent in yet others (some catarrhines). A general trend toward nasoturbinal reduction has been suggested for anthropoids (Maier, 2000).

The ethmoturbinals of haplorhines are reported to range from one to three pairs (Cave, 1973; Hershkovitz, 1977; Maier, 2000). Within cercopithecoids, some of this variation may be due to scaling, with smaller taxa possessing fewer turbinals (Maier, 2000), but *Tarsius* and *Saimiri* are reported to have two

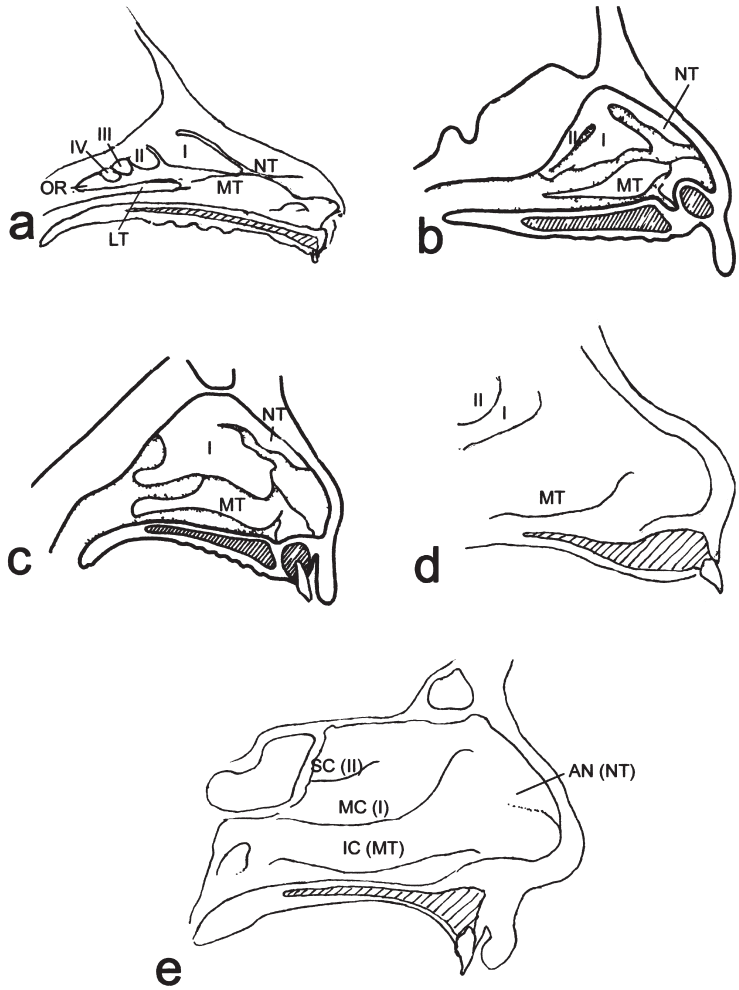

Figure 8.6 Variations in the lateral nasal wall of different primates. (**a**) Lemurs and most other strepsirrhines have 4 ethmoturbinals (indicated anteroposteriorly as I-IV). ET II-IV are found entirely within the "olfactory recess"(OR) and are lined with olfactory mucosa. Note that the ethmoturbinals, nasoturbinal (NT) and maxilloturbinal are oriented in a more vertical arrangement in anthropoids (**b**–**e**), with some variations. Note a reduction in the number of ethmoturbinals and proportionally reduced NT in New World monkeys (**b**, *Saimiri*) and Old World monkeys (**c**, *Macaca*). In the apes, the ETs are more vertically oriented, as shown in the gibbon (**d**, *Hylobates*) and especially in humans (**e**). In some anthropoids, the NT may be absent or extremely reduced, as in the homologous human *aggar nasi* (e, AN). IC, inferior nasal concha (MT homologue); MC, middle nasal concha; SC, superior nasal concha; MT, maxilloturbinal; hard palate (hatched lines). **b** and **c** redrawn from Moore (1981). Specimens drawn to similar sizes, not to scale.

ethmoturbinals (Cave, 1973), while some of the larger platyrrhines (e.g. *Ateles*) have only one (Hershkovitz, 1977). It is also clear that ethmoturbinals show intraspecific variation. A supreme nasal concha (3rd ethmoturbinal homologue) is a relatively common human variant (reported to be present in about 20% of adults and 27% of 14 to 36 week fetuses; Arredondo de Arreola *et al.* (1996); Moore (1981)). Similarly, the varied reports on ethmoturbinal numbers in other anthropoids may reflect actual intraspecific variation, as illustrated in Figure 8.7.

Major evolutionary modifications of the nasal fossae differentiate haplorhines from strepsirrhines and all other mammals. A most salient difference with respect to olfaction is the absence of the olfactory (ethmoturbinal) recess in haplorhines. Rudiments of these fossae do exist in haplorhines (sphenoethmoidal recess, *recessus cupularis posterior*; see Table 8.2 for terminology), but they may or may not be lined with olfactory mucosa and they do not contain the ethmoturbinals that greatly increase olfactory surface area in strepsirrhines and other mammals. The *lamina transversalis posterior* (see Figure 8.3) that separates the recess from the nasopharyngeal meatus is also missing in haplorhines and, as a consequence, the ethmoturbinals are not sequestered from the direct pathway of inspired air.

Regardless of number, the ethmoturbinals of haplorhines are smaller and less elaborately scrolled than in strepsirrhines. In tarsiers, the ethmoturbinals bear some organisational similarity to those of strepsirrhines; i.e. they occur in an

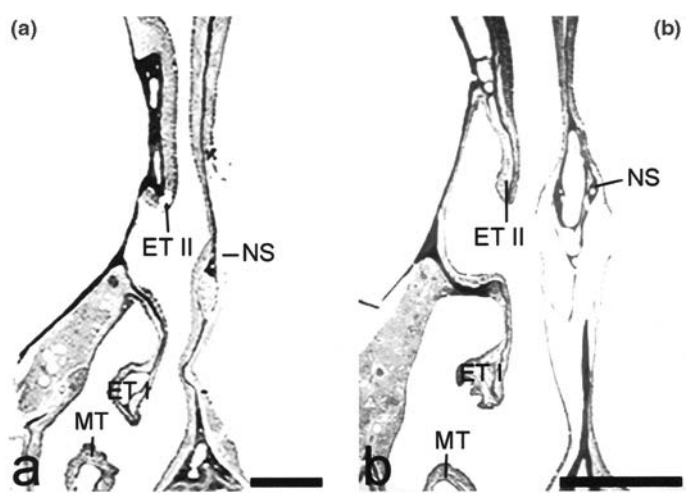

Figure 8.7 Intraspecific variation of turbinal size is shown in adult marmosets (*Callithrix jacchus*), where ethmoturbinal II (ET II) is shown in its largest size coronally. Note in one adult (**a**) it is merely a raised ridge, whereas in a different adult, ET II 'hangs' inferiorly as typical of ET II. Also seen at this sectional level are posterior regions of ethmoturbinal I (ET I) and the maxilloturbinal (MT). NS, nasal septum. Scale bars = 1 mm.

anteroposterior sequence, and their basal lamellae are oriented roughly vertically (Cave, 1973). But in many anthropoids, the turbinals are arranged in a more inferior-to-superior sequence, with a more horizontal orientation of the basal lamellae of ethmoturbinals I and II. This trend is most strongly expressed in hominoids, and culminates in the extreme human condition.

Both the absence of the olfactory recess and the more superoinferior sequencing of the turbinals could be attributed to different facial growth patterns in haplorhines compared to strepsirrhines. Most haplorhines have highly flexed basicrania compared to strepsirrhines (Ross and Ravosa, 1993). In addition, the facial skeleton is rotated inferiorly relative to the anterior cranial base (facial 'kyphosis' – Lieberman *et al.*, 2000) in haplorhines, so that nearly the entire facial skeleton (including orbital cavities) is positioned beneath the level of the cribriform plate (also see Enlow & Hans (1996)). In addition, the snout of most haplorhines is shortened compared to strepsirrhines. The snouts of some species (e.g. baboons, *Alouatta*) appear to have elongated secondarily. However, the additional space within the nasal fossae of such forms appears to be an expansion of the anterior nasal structures, without any elaboration of olfactory mucosa (cf. Maier, 2000).

A final consideration is that the superior regions of the haplorhine nasal fossae are constricted, to a variable degree (more so in smaller haplorhines), by the orbital fossae. This has more to do with orbit position than with their size. In anthropoids, the orbital apertures are oriented more coronally than in strepsirrhines such that the eyes face forward. This is brought about by the combined effect of orbital frontation (vertical orientation of the aperture), and convergence (described above). As a consequence, the interorbital region is greatly reduced in size, and there is often an interorbital septum between the orbits consisting solely of the medial walls of the orbits (composed variably of orbitosphenoid and ethmoid) and the midline septum nasi. In contrast, the orbits are located superolateral and more posterior to the nasal fossae in strepsirrhines, and the interorbital region is largely occupied by the nasal fossae (Ross & Ravosa, 1993; Lieberman *et al.*, 2000). The constriction of the superoposterior portion of the nasal capsule in haplorhines coincides with the loss of the olfactory recess, reduced complexity and number of the ethmoturbinals and the reorientation of the turbinal laminae. It has been suggested that some of these events were actually caused by the changes in orbit position (Cartmill (1970); Cave (1967)).

The scenario developed by Cartmill (1970), and amended by Ross (1995) and others (Kay *et al.*, 1997), theorises that the common ancestor of tarsiers and anthropoids was diurnal, and had descended from a nocturnal ancestor with moderate orbital frontation and convergence (like an omomyoid).

The adoption of diurnality caused a reduction in the relative size of the orbits, which resulted indirectly in the increased orbital convergence seen in anthropoids. Because this increase in orbital convergence occurred in a primate that already had moderate frontation, the orbits became approximated below the olfactory tract (not above it as in lorisids), resulting in the tendency for haplorhines to develop an interorbital septum. This septum essentially occupies the former space of the olfactory recess, which is reduced to a vestige and displaced superiorly along with the cribriform plate. The ethmoturbinal series would need to be reoriented so as to maintain their structural continuity with the cribriform plate, and we believe that this entailed a rotation of the nasal capsule that places the posterior cupulae in a much higher position than in strepsirrhines (see Rossie (2006)), which probably accounts for the inferior to superior arrangement of ethmoturbinals (also see Martin (1990)). The ethmoturbinals no longer reside in an olfactory recess, and due to the rotation of the nasal capsule, they are now above the maxilloturbinal. Subsequent basicranial flexion and frontal lobe expansion caused further increases in orbital frontation, and probably served to displace the nasal fossae farther inferiorly, as seen in hominoids. It therefore appears that a combination of facial shortening, facial kyphosis, basicranial flexion and orbit-related constriction of the nasal fossae have conspired to produce the distinctive haplorhine nasal cavity.

Neural elements and related osteology

Olfactory mucosa and osseous boundaries of the nasal cavity

Human olfactory mucosa is typically described as limited to the posterosuperior nasal fossae, covering part of the superior nasal concha and the facing wall of the septum (e.g. Harkema (1991); but see Menco & Morrison (2003)). Similarly, non-human haplorhines have been described to have olfactory epithelium (OE) limited to the posterosuperior-most ethmoturbinals (e.g. Harkema (1991); Wako *et al.* (1999)). In strepsirrhines, olfactory function has been attributed to all the ethmoturbinals and associated spaces (Moore, 1981). However, recent detailed histological studies have revealed interspecific, intraspecific and age-related variations in the extent of OE anteroposteriorly and inferiorly. For example, OE is distributed more anteriorly in some anthropoids than previously described (Figure 8.8, contra Wako *et al.* (1999)). Importantly, since there is variation in how much of the ethmoturbinals are covered by OE, ethmoturbinal size (however measured) is an unreliable proxy for the amount of OE present, and therefore of olfactory sensitivity (Smith *et al.*, 2004).

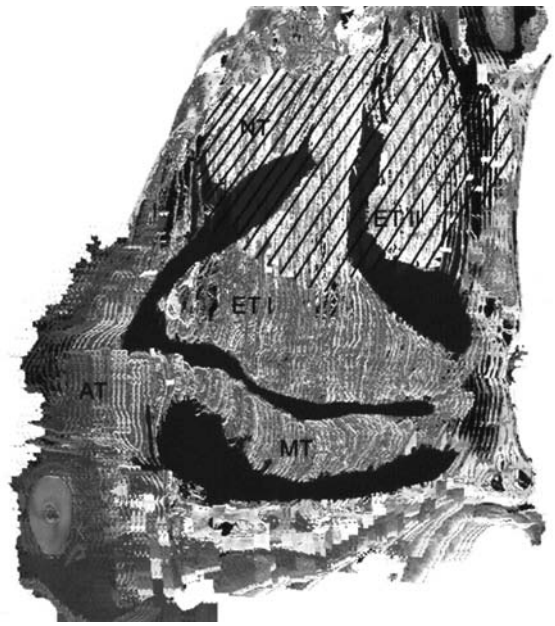

Figure 8.8 A three-dimensional computer reconstruction of the lateral nasal wall (shown slightly obliquely from anterior view) in an adult marmoset (*Callithrix jacchus*), generated from histological sections. The extent of olfactory epithelium (OE) was mapped (oblique, hatched lines) based on direct observation of the epithelium in each section. Note that the OE is not restricted to posterior-superior regions. Instead, OE covers portions of the nasoturbinal (NT), anterior to the ethmoturbinals (ET I, ET II), and covers about the superior one-half of the nasal septum (not shown) and some levels. The anterior aspect is indicated by the atrioturbinal (AT).

Olfactory nerves and cribriform plate

The cribriform plate of the ethmoid bone is pierced by many olfactory foramina that transmit olfactory nerves from the OE to the olfactory bulb (OB). Negus (1958) suggested that these openings 'correlate with the number of (olfactory) nerves' and are 'roughly proportional with the extent of olfactory mucous membrane' in the nasal fossae (p. 55). Such a relationship, between cribriform plate morphology and olfactory function, has rarely been quantitatively analysed in mammals. This is unfortunate, since Bhatnagar and Kallen (1974) were able to demonstrate a strong association between cribriform plate area, OB diameter and the number of openings in the cribriform plate in bats. Furthermore, cribriform plate morphology appeared to vary according to dietary patterns. These findings suggest that this osseous region may be used to draw inferences about mammalian chemosensory abilities in the same way that OB size has been used (see p.152).

Among mammals in general, stark contrasts in cribriform plate size exist between 'macrosmatic' mammals (e.g. deer, fox) and 'microsmatic' mammals (some aquatic mammals and humans) (Negus, 1958). Unfortunately, evolutionary modifications to the nasal fossa of some primate taxa confound such comparisons. In primates where an interorbital septum exists, the cribriform plate becomes separated from the nasal cavity proper, and as a result, the olfactory nerves must travel through a bony canal termed the olfactory tube (Starck, 1984).

Olfactory bulbs and olfactory fossae

Measures of OB volume from fossil endocasts, X-rays, computed tomography (CT) scans, or preserved brain specimens frequently form the basis for inferences of olfactory abilities (Baron *et al.*, 1983; Kay *et al.*, 2004; Takai *et al.*, 2003).

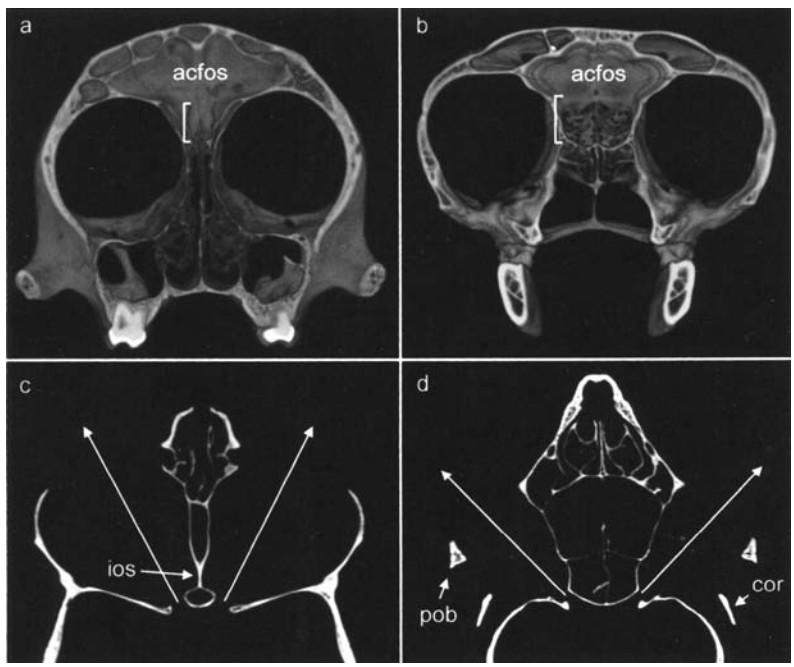

Figure 8.9 Computed tomography of the primate interorbital region. Posterior views of *Cebus* (**a**) and *Eulemur* (**b**), cut at the posterior end of the cribriform plate. White lines in **a** and **b** indicate approximate vertical dimensions of olfactory bulbs. Note that the olfactory fossa is more discretely sequestered in the anthropoid than in the strepsirrhine, but that the frontal lobes overlie the OB in both. Horizontal slices through the level of the optic foramina in *Callicebus* (**c**) and *Eulemur* (**d**). Note the interorbital septum in the small anthropoid *Callicebus*. Unlabelled arrows in **c** and **d** mark the orbital axes (optic foramen to orbital aperture centre). acfos, anterior cranial fossa; cor, coronoid process of mandible; ios, interorbital septum; pob, postorbital bar.

Whether OB volume is measured directly or inferred from osseous morphology, several caveats must be kept in mind. First, methods that reconstruct OB volume on the basis of the size of the olfactory fossa can be complicated by the vague osseous boundaries of the olfactory fossa (Figure 8.9). Second, estimates of gross OB size include the volume of the accessory OB in New World monkeys and tarsiers, but not in catarrhines, which lack the accessory OB (Kay *et al.*, 2004). Lastly, estimates of gross OB size would include the variable size of an inner fluid-filled chamber, the ventricle (Smith & Bhatnagar, 2004). Other problems involving OB volume scaling issues will be discussed below.

Evolution

Fossil evidence of evolutionary modifications

Relatively little can be said about the nasal and paranasal anatomy of early fossil haplorhines, strepsirrhines and plesiadapiformes. This is not so much because of the lack of fossil crania, but because of the difficulty of observing internal morphology. Some CT studies are beginning to resolve this, but much more work remains to be done.

Olfactory bulb size

Plesiadapiformes appear to have very large OBs relative to overall brain size and neocortex size (Kay & Cartmill, 1974; Radinsky, 1977), but this may be an artefact of the small neocortex of these species (cf. Radinsky, 1977). Quantitative data for these taxa are not yet available, but a comparison should

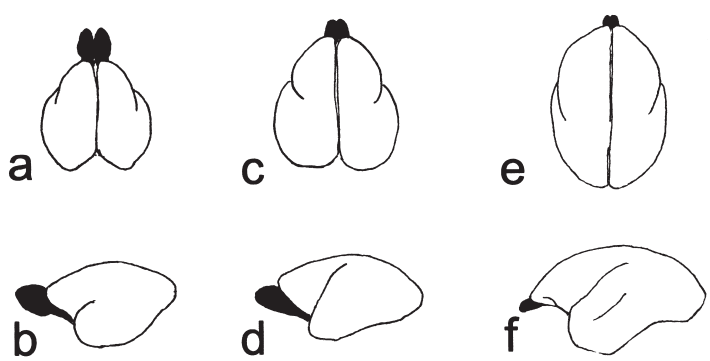

Figure 8.10 A comparison showing the relative size of the cerebral cortex compared to olfactory bulbs (blackened) based on a fossil endocast of the extinct strepsirrhine, *Adapis* (**a, b**) compared to an extant strepsirrhine (**c, d** – *Microcebus murinus*) and haplorhine (**e, f** – *Saguinus oedipus*). Top view, dorsal; bottom view, lateral. **a, b**, redrawn from Le Gros Clark, 1959.

soon be possible using micro-CT scans of *Ignacius* (Silcox, 2003). Data amassed by several different researchers (see Takai *et al.*, 2003) indicate that OB size relative to body size in Eocene adapoids is comparable to that of living strepsirrhines, while the Eocene omomyoids *Necrolemur* and *Tetonius* are intermediate between strepsirrhines and the smaller bulbs of living haplorhines (see Figure 8.10). The early anthropoid *Parapithecus grangeri* (Oligocene of Egypt) has surprisingly large OBs for its body size, again falling between living strepsirrhines and haplorhines (Bush *et al.*, 2004). Data for other Oligocene and Eocene anthropoids are lacking, but the late Oligocene platyrrhine *Tremacebus* has OBs of similar size to diurnal extant anthropoids (Kay *et al.*, in press). It is possible that the proportionately smaller OB of living anthropoids was evolved convergently in platyrrhines and catarrhines from a condition like that in *Parapithecus*, but more data are needed on early members of each group.

Nasal cavity

Ethmoturbinal number is difficult to deduce from fossil crania since most specimens are lacking at least some of the nasal cavity. Although its contents are not well-known, the plesiadapiform nasal cavity is very large (Figure. 8.11a). Ethmoturbinal number is unknown, but the early Eocene genus *Microsyops* had three ectoturbinals in its frontal recess (Szalay, 1969); one more than tupaiids. *Ignacius* possessed a distinct olfactory recess, and an elaborate system of ethmoturbinals of unknown number (J. R. unpublished data).

Nasal anatomy is again poorly known for adapoids, but their rostra are large, and their orbits encroach upon the nasal cavity as much as in living strepsirrhines (Figure. 8.11b). X-rays of *Adapis parisiensis* reveal that a large olfactory recess is present beneath the OBs (Gingerich & Martin, 1981). Overall, the proportions of the rostrum and position of the orbits in adapoids suggest a strepsirrhine level of nasal complexity.

The known crania of omomyids generally resemble tarsiers in exhibiting relatively large orbits that encroach substantially upon the nasal cavity (Rossie *et al.*, 2006). *Shoshonius cooperi*, from the early Eocene of Wyoming, has the largest orbits (Beard *et al.*, 1991), and its nasal cavity has been examined via high-resolution X-ray computed tomography (HRXCT) (Rossie & Beard, 2004). The apical interorbital septum is present in *Shoshonius*, as it is in *Tarsius* and *Necrolemur* (Ross, 1994), taking the place of the olfactory recess. The OBs lie above the nasal cavity as in most haplorhines. Ethmoturbinals in *Shoshonius* cannot be counted, but they appear to be no more complex than in extant anthropoid. So far as it is known, then, the omomyoid nasal cavity appears to herald the onset of nasal regression in haplorhines. Accordingly, further study of the available crania would be of great interest. Of particular interest is the nasal

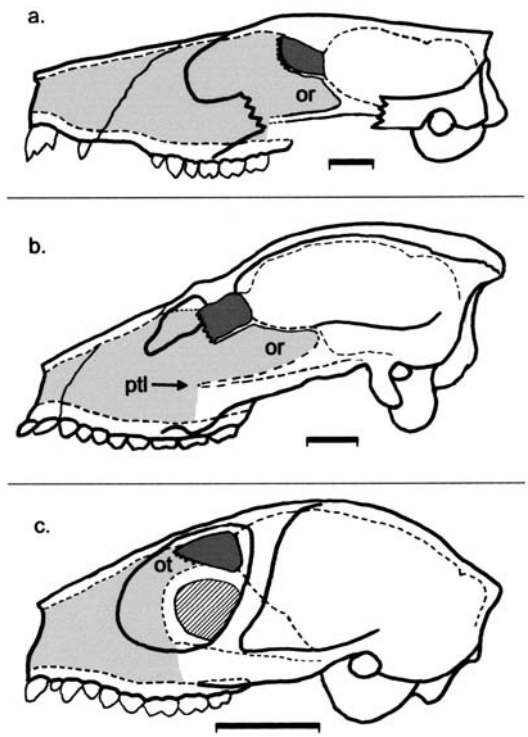

Figure 8.11 Lateral profiles of *Plesiadapis*, *Adapis* and *Necrolemur* showing the extent of the nasal cavity (light grey) and approximate size of the olfactory bulbs (dark grey). Note the interorbital septum (cross-hatched) and olfactory tube (ot) in *Necrolemur*. Anterior extent of posterior transverse lamina in *Plesiadapis* is speculative, and based on data for *Ignacius*. Outlines modified from Szalay & Delson (1979), proportions of neural structures from Radinski (1970) and Gingerich (1976). Scale bar = 1 cm.

morphology of *Rooneyia*, an Oligocene genus that has often been considered an omomyoid. A preliminary study of the nasal cavity of *Rooneyia* found evidence of a distinct olfactory recess floored by a posterior transverse lamina (Seiffert *et al.*, 1999). If *Rooneyia* is retained within the omomyoids, it would have to be viewed as a rather primitive member, but several recent phylogenetic analyses have placed it in the Adapoidea, which is more congruent with its nasal morphology, of which we await more detailed study.

The nasal anatomy of crown anthropoid fossils such as *Paralouatta* (Horovitz & MacPhee, 1999), *Aegyptopithecus* (Rossie, 2005), *Proconsul* (Rossie, 2005), *Sivapithecus* (Ward & Brown, 1986) and *Victoriapithecus* (Rae *et al.*, 2002) generally resembles that of the living members of their respective families, but serves to document a few significant changes. For example, the early to middle Miocene monkey *Victoriapithecus* demonstrates that the absence of

all sinuses is a primitive condition for cercopithecoids. *Proconsul*, *Aegyptopithecus* and *Morotopithecus* show that ethmoid and ethmofrontal sinuses are not unique to African apes and humans, but are more primitive features of catarrhines, and possibly anthropoids (they are also found in several platyrrhines; Rossie, 2006). In the well-preserved faces of the Oligocene catarrhine *Aegyptopithecus*, the maxilloturbinal, nasoturbinal and ET I are found in a typical anthropoid configuration, but the posterior nasal cavity (and any additional ethmoturbinal) is broken away (Rossie, 2005). Unfortunately, none of these taxa shed light on the transition to an anthropoid condition from the ancestral condition, presumably typified by omomyoids (Ross, 1994). Study of stem anthropoids such as *Parapithecus* and *Proteopithecus* is required to address this transition.

External nose

Very little evidence of external nasal morphology can be gleaned from fossil remains, but a few inferences can be made. As described above, the marginoturbinal–atrioturbinal system appears to be functionally linked with the VNO, and although it is lost in crown catarrhines, it is present in some African stem catarrhines such as *Aegyptopithecus*, *Limnopithecus* and *Kalepithecus* (Rossie, 2005), suggesting that the VNO was lost near the Old World monkey/hominoid divergence. Similarly, anatomical haplorhinism appears to be linked to the loss of a gap between the upper central incisors, so the absence of an interincisor gap in fossil taxa may be taken as evidence of haplorhinism (Beard, 1988). This gap persists in all known plesiadapiforms and adapoids, and is intriguingly present in the omomyoids *Rooneyia*, *Macrotarsius* and *Necrolemur* (Beard, 1988). The condition in *Shoshonius* cannot be discerned, but its close relative *Dyseolemur* seems to have had a very small, if any, interincisor gap (Rasmussen *et al.*, 1995). This distribution implies that either the strepsirrhine condition was lost in tarsiers and anthropoids independently, or, more likely, that some omomyoids are stem haplorhines.

In sum, Eocene omomyoids present the earliest evidence of a departure from the primitive mammalian, or at least Euarchontan (tupaiids, Dermopterans and Primates), nasal morphology. At least one omomyoid, *Shoshonius*, possessed a crowded nasal cavity with an interorbital septum and no olfactory recess. Haplorhinism may have developed in some derived omomyoids (*Dyseolemur* and close relatives), but better-preserved specimens are required to document this transition. Relative OB size reduction seems to have begun in omomyoids, but may not have progressed much in stem anthropoids. Early catarrhines most likely possessed intact VNOs, perhaps similar to those of extant platyrrhines. By the time of the divergence of Old World monkeys and hominoids, the VNO may not have been present except as the vestigial structure described in some

extant hominoids (Smith *et al.*, 2001). Further refinement of this loose outline of evolutionary change will require detailed study of Eocene primates via non-destructive methods such as HRXCT.

Olfaction in haplorhines

Relative size of olfactory structures

Based on comparisons of the relative size of olfactory structures, some authors have assigned mammals to different categories of olfactory ability. These categories include highly acute (macrosmatic), diminished (microsmatic) or absent (anosmatic). When the term microsmatic was coined (Turner, 1891), it was used to designate a lesser olfactory ability in humans and apes compared to 'macrosmats' (e.g. carnivores). Aside from anosmia (i.e. complete inability to smell), these categories of olfactory abilities are hardly discrete, and their application to primate taxa has varied. As catarrhine primates completely lack accessory OBs, which are the first central connection of vomeronasal nerves, they may indeed have reduced chemosensory abilities compared to all other primates. New World monkeys have been characterised as hyposmatic by some authors based on turbinal morphology (Wako *et al.*, 1999). However, in light of the variable association of olfactory mucosa with turbinals and other nasal chamber surfaces (Smith *et al.*, 2004), a careful reassessment of this line of evidence is needed.

Trends in neural organisation of primates

A broader view of primate olfaction has emerged from a series of studies based on an immense database on brain structures in primates and other mammals (Stephan *et al.*, 1981). This work has established adaptive characteristics of extant primates compared to other mammals. The sensory modalities of primates are regarded as having a suite of specialisations that reflect ecological adaptations (Dominy *et al.*, 2004). Analyses of brain structures in living primates have suggested that, compared to neural models for ancestral primates:

1. Extant primates are visual specialists, with a greater relative size of neural elements of the visual system compared to extant 'basal insectivores,' which are presumed to resemble ancestral primates. This is especially true of diurnal primates (Barton *et al.*, 1995; Martin, 1990; Stephan *et al.*, 1981).
2. Extant primates have a smaller relative size of the main and accessory OBs compared to 'basal insectivores.' In this regard, there are 'grades' of relative size within the order Primates, with haplorhines having relatively smaller OBs than strepsirrhines (Figure. 8.12), and with diurnal primates having relatively smaller OBs than nocturnal forms (Kay *et al.*, 2004; Martin 1990).

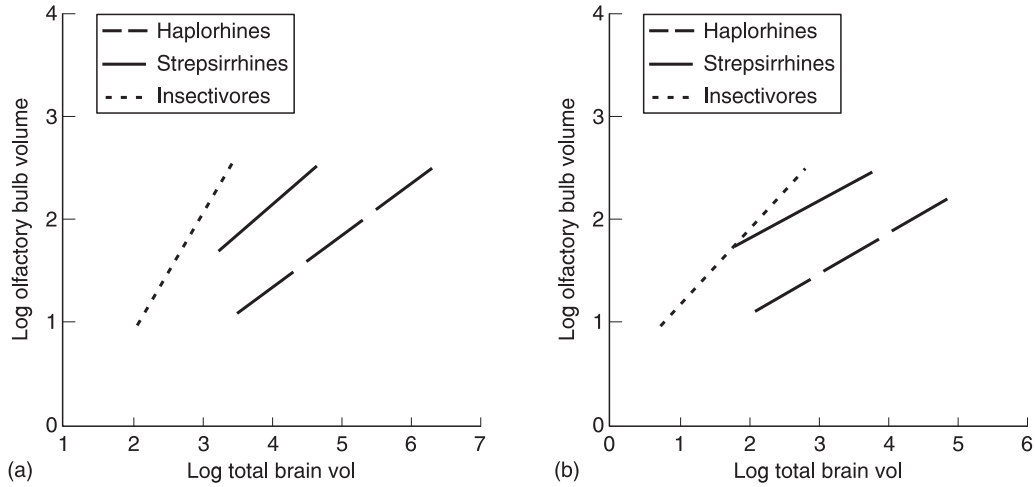

Figure 8.12 Graphs (data from Stephan *et al.* 1981) showing regression lines of log olfactory bulb volume against log total brain volume (**a**) or log body mass (**b**) in primates compared to living neural models of primate ancestors, the 'basal insectivores'. Note the regression lines occur in distinct grades in haplorhines compared to strepsirrhines and insectivores, in each graph. Also note that the regression lines slopes are similar in the two primate suborders, but more vertical (and approximately isometric) in insectivores.

These scaling relationships of special sensory structures in the brain have been supported by numerous studies (Barton *et al.*, 1995; Bush *et al.*, 2004; Frahm, 1985; Kay *et al.*, 2004; Stephan *et al.*, 1981). However, we emphasise that the 'trade-off' is in relative neural size. Within each clade (e.g. haplorhines), extant primates exhibit OB size that increases with brain size, but with negative allometry (Figure 8.12). This OB size increase may well reflect added neural relays as overall brain size increases. Olfactory bulb size increase does not keep pace with overall brain size in primates (especially haplorhines), or with other neural structures, such as the neocortex (Figure 8.13), and the primary visual cortex in particular. Other senses may exhibit similar 'trends'. For example, a recent study illustrates that the total volume of subcortical auditory regions of the brain is smaller relative to overall brain mass in primates compared to other mammals (Glendenning & Masterson, 1998). Yet, no researchers have claimed that there is an evolutionary trade-off between visual and auditory structures.

A case for diminished olfactory abilities might be based on the size of the olfactory bulbs relative to body mass (Figure 8.12). Smith and Bhatnagar (2004) showed that the absolute number of olfactory receptor neurons may be similar in mammals of greatly different body sizes, calling into question the appropriateness of body size scaling in analysis of olfactory abilities (Smith & Bhatnagar,

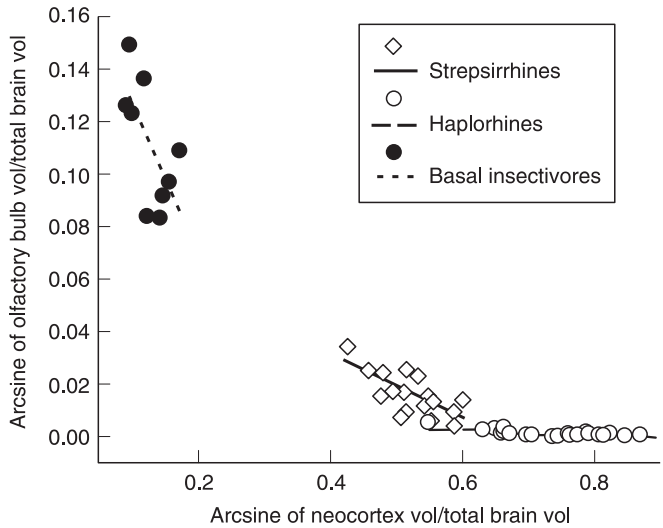

Figure 8.13 When scaled against the total brain volume, which exists in 'graded' sizes among extant primates and living models for their ancestors (largest in haplorhines, smaller in strepsirrhines, smallest in basal insectivores), it appears inevitable that some neural structures will scale with negative allometry. In primates the greatly elaborated neocortex affects the proportional size of other components. Data from Stephan *et al.* (1981).

2004). The small OB/body size ratio in haplorhines requires explanation, but it is not clear that it involved significantly reduced olfactory abilities. Whatever be its cause, existing fossil data (see the section on OB size above) suggest that the dichotomous OB scaling between haplorhines and strepsirrhines developed after the Eocene.

Genetic evidence

Perhaps more convincing evidence for an evolutionary loss of olfactory function derives from data concerning olfactory receptor (OR) pseudogenes and signal transduction pathways for pheromones. Originally described in mice by Buck and Axel (1991), the OR genes have since been described in other mammals, including primates. In a contrast of mice with humans (which have similar quantities of OR genes), humans have a much greater percentage of OR pseudogenes, or OR genes showing sequence disruption (Gilad *et al.*, 2003; Whinnett & Mundy, 2003). But is this accumulation of pseudogenes a characteristic of humans in particular, or of primates in general?

To date, results of OR gene studies on non-human primates are ambiguous in some respects. For example, Rouquier *et al.* (2000) reported that only one of 49 OR genes was a pseudogene among three platyrrhines (marmosets and two squirrel monkey species), yet Whinnett and Mundy (2003) reported

a much higher percentage of pseudogenes for the marmoset (*C. argentata*). A more curious finding, in light of the chemosensory abilities touted for strepsirrhines, is that the strepsirrhines in this study were found to have a greater percentage of OR pseudogenes than any of the monkeys. What has consistently been found is that hominoids (apes and humans) have a greater percentage of pseudogenes than most other primates (Rouquier *et al.*, 2000). Furthermore, Gilad *et al.* (2003; 2004) emphasise that accumulation of pseudogenes is most pronounced in humans (approaching 60% of OR genes), even compared to apes and the rhesus macaque (all near 30% pseudogenes).

Thus, there is genetic evidence that some primates, especially humans, have accumulated more non-functional OR genes than other mammals studied to date. More work to understand apparently contradictory findings is clearly needed. Whinnett and Mundy (2003) cautioned that the functional implications of pseudogene formation are not yet clear.

A final consideration is the vomeronasal system of primates. Among primates, there is ample anatomical (Smith *et al.*, 2001; 2002) and molecular (Liman & Innan, 2003; Zhang & Webb, 2003) evidence for the lack of a functional vomeronasal system in all catarrhines. This finding has recently been interpreted in two ways. Most generally, it is attributed as the result of relaxed selection pressure on primate olfaction and pheromonal detection. However, it has specifically been interpreted as evidence in support of the hypothesis that sociosexual cues are detected via trichromatic colour vision in Old World monkeys, and pheromonal communication is thus largely superfluous (and replaced) in this purpose. However, there is a strong likelihood that some types of pheromonal communication occur in catarrhine primates (Wysocki & Preti, 2004), even in the absence of a functioning vomeronasal system. Thus, functions usually attributed to this system are likely to be taken up by the main olfactory system in humans and other catarrhines. In addition, Gilad *et al.* (2004) emphasise the example of howler monkeys, which possess both trichromatic colour vision and exhibit evidence for a functional VNS. Interestingly, Gilad *et al.* (2004) invoke the olfaction/vision trade-off hypothesis, suggesting that the loss of functional OR genes is related to the acquisition of trichromatic colour vision.

Conclusions

Paleontological and comparative evidence indicate that very little change in anatomy relevant to olfaction occurred in primate evolution until the origin of haplorhine primates. From this point on, there appears to have been little regression of nasal structures until the emergence of the human condition.

However, as noted above, many of the lines of evidence used to infer olfactory sensitivity from gross morphology are suspect. Gross skeletal morphology relates variably to olfactory epithelial distribution among primate species, and measuring olfactory surface area alone may ignore variations in epithelial depth and cellular density (Smith & Bhatnagar, 2004; Smith *et al.*, 2004). The OB size (relative to body size) is smaller in haplorhines than in strepsirrhines, but the functional significance of this is not clear. It remains to be determined whether a haplorhine and a strepsirrhine with olfactory bulbs of the same size, but with different body masses, actually have different olfactory capabilities (Cartmill, 1970; Smith & Bhatnagar, 2004).

Moreover, evidence from OR pseudogenes does not consistently support a function parallel to the gradistic levels of relative OB size, and behavioural studies reveal cases of excellent and specialised olfactory performance in the supposedly 'microsmatic' New and Old World monkeys (Laska, 2000; Laska *et al.*, 2004). Thus, our understanding of comparative olfactory abilities among primates that are most closely related to humans is, at present, confused by conflicting data. The evidence for humans is somewhat clearer. Our species represents an extreme, with indications for small relative and absolute OB size, and genetic evidence suggesting a functionally reduced role of olfaction compared to other primates.

Over three decades ago, Cartmill (1970, p. 356) expressed reservations over assuming a direct correspondence between gross nasal and endocranial morphology and olfactory abilities: 'Given our present ignorance concerning the biochemical mechanisms of olfaction, we have no basis for assessing olfactory acuity on strictly morphological grounds, and few comparative experimental investigations of olfaction in mammals appear to have been undertaken.' We would argue that the results of studies that have been performed in the subsequent years do little to assuage such concerns. We reiterate Cartmill's implicit appeal, and promote revisiting comparative anatomical evidence that assesses actual neuronal populations within the olfactory and vomeronasal systems regarding quantity, connectivity to the rest of the brain and functional characteristics of the neurons themselves.

Acknowledgements

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9

Genetics and family influences on olfaction: a focus in schizophrenia

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Introduction

Family or genetic 'high-risk' studies have described olfactory deficits in asymptomatic or non-fully symptomatic first-degree relatives (siblings, offspring, parents) of individuals diagnosed with a variety of neuropsychiatric diseases, including Alzheimer's disease (Schiffman *et al.*, 2002; Serby *et al.*, 1996), Parkinson's disease (Berendse *et al.*, 2001; Montgomery *et al.*, 1999), Progressive Supranuclear Palsy (Baker & Montgomery, 2001), and schizophrenia (Kopala *et al.*, 1998; 2001; Moberg *et al.*, 1996; Turetsky *et al.*, 2003). The reader is referred to Chapters 13, 14 and 16 for further discussion of olfaction in Parkinsonian disorders and schizophrenia respectively. Such findings tempt a host of questions, which suggest that the assessment of olfaction in studies of persons at risk for illness has the potential to open the 'window to the mind' even wider . . . .

The study of olfaction as a biological marker or risk indicator for illness is in its infancy compared to established strategies such as studies of attention (Cornblatt & Keilp, 1994). However, a number of issues are raised by the presence of olfactory abnormalities in first-degree biological relatives. Does olfactory functioning provide clues to the genetic underpinnings of complex neuropsychiatric diseases? Can it represent a biological marker for a compromised neural system? If so, what role does it play within the relationship between genes, environmental influences and the clinical manifestations of neuropsychiatric illnesses? To begin to answer these questions, we examine the evidence from family or genetic high-risk studies in schizophrenia, an example of

a highly heritable, complex neuropsychiatric disorder for which, despite decades of study, the aetiology and pathophysiology remain elusive. First, a rationale for using family/genetic high-risk studies and the concept of endophenotypes is discussed.

Family, genetic high-risk studies: the concept of endophenotypes

With the exception of Huntington's disease and other disorders that involve major gene effects, most neuropsychiatric disorders do not fit a classic Mendelian model of inheritance in which a single gene locus, or genotype, indicates overt clinical characteristics (the phenotype). Rather, consistent with diathesis-stress models, there are typically multiple pathways involving different combinations of genes and environmental factors, which can result in the development of neuropsychiatric disease. Linking genes, epigenetic or environmental variables and brain regions and networks is an important step in identifying the aetiology and pathophysiology of neuropsychiatric illnesses, and ultimately improving diagnosis and treatment. However, the current diagnostic classification scheme in neuropsychiatry is not based on measures of the underlying genetic or biological pathophysiology of the disorders. Instead, arising both from the lack of knowledge of aetiology and underlying biology, and the need to facilitate communication of clinical descriptors, the diagnostic system was derived from the observation of phenotypes. These phenotypes, such as psychiatric diagnosis per se, may be a rather complex manifestation of the underlying biology that contributes to its clinical expression.

To address this lack of one-to-one correspondence between genetically influenced processes in the brain and the clinical phenomena that define diagnostic categories, and to search for simpler phenotypes, researchers have increasingly relied on family or genetic high-risk studies. Such investigations are valuable for several reasons. Because first-degree relatives share, on average, 50% of their genes with ill, or 'affected' family members, abnormal traits identified in relatives may be linked to their increased genetic risk for the disease. Unlike studies with patient groups, research with unaffected relatives is not confounded by medication treatments, chronic hospitalisations, the potential neurotoxic effects of the disease and other health consequences of serious mental illness. Moreover, characteristic features found in relatives are likely to be more reliable than those found in patients because the patients are more affected by confounds over time. In families with a member who has schizophrenia, other adults over the age of 35 are very unlikely to develop the illness; therefore, any abnormalities would be independent of psychosis, instead suggesting a marker of

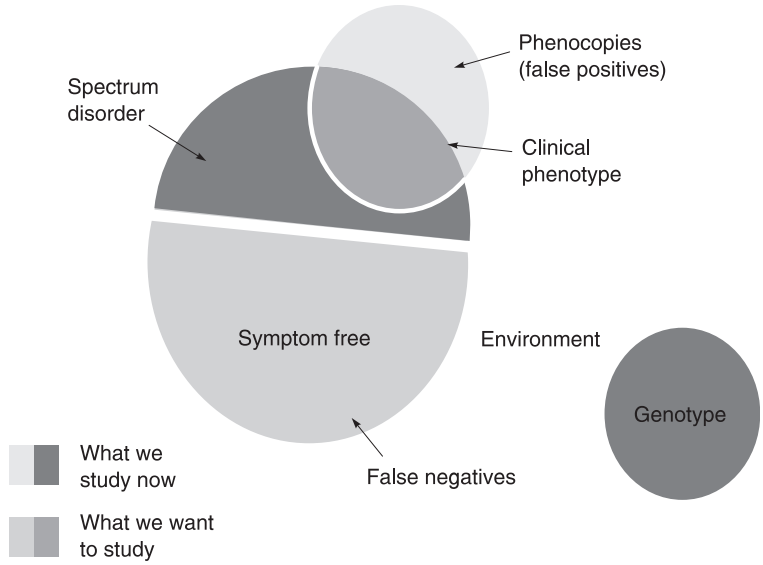

Figure 9.1 (Adapted from Tsuang *et al.*, 1991).

vulnerability without full expression. Additionally, through long-term follow-up of outcome, studies of non-psychotic adolescents or young adults who are at genetic risk for the illness (based on having a sibling or parent with schizophrenia) are also very informative for the prediction of disease and for distinguishing premorbid characteristics associated with vulnerability to illness. Finally, as shown in Figure 9.1, identifying markers of the susceptibility to illness may provide useful phenotypes for future molecular genetic studies.

Over 30 years ago, Gottesman and Shields (1972; 1973) introduced the term 'endophenotype' to the field of psychiatric genetics. They defined endophenotypes as internal measures of brain functioning, which are not apparent to the unaided eye but detected by 'biochemical test or microscopic examination', which reflect abnormalities in brain structure or function related to the genotype. In essence, since the phenotypic, or observable manifestations of neuropsychiatric illnesses are distal indicators of the genotype and associated neurobiologic substrates, endophenotypes may be viewed as intermediary biologic measurements that help to close the gap between phenotype and genotypes. In order to meet complete criteria for an endophenotype, the characteristic must be associated with a candidate gene or gene region, and it must occur in individuals diagnosed with the disease process as well as be found more frequently among their biological relatives than in healthy controls. Moreover, the abnormality must be stable over time and shown to be heritable. Thus, using these criteria, endophenotypes offer suggestive evidence of

genetic links within neuropsychiatric disorders. Carlson *et al.* (2004) further conceptualise endophenotypes as 'subtotals' of the phenotype, which represents the 'grand total' of numerous risk factors. The authors consequently assert that the primary advantage of endophenotypes is their improved signal-to-noise ratio; i.e. the number of genetic and environmental variables influencing each endophenotype is smaller than those affecting the phenotype.

Endophenotypes and schizophrenia

In a recent article, Gottesman and Gould (2003) reviewed advances in the assessment of neuropsychiatric endophenotypes over the past 30 years. Technological progress has considerably broadened the scope of methods and tools available for studying endophenotypes to include biochemical, endocrinological, neuropsychological and neuroanatomical and neurophysiological measures (including advanced neuroimaging techniques). Emphasising applications in schizophrenia research, the authors provide compelling evidence to suggest that further study and identification of endophenotypes hold tremendous promise for clarifying the aetiology and pathophysiology of schizophrenia, and improving its treatment. Members of our research group, along with others, have advanced a multifactorial model of schizophrenia, which posits that 'many of the neurobiological abnormalities (endophenotypes) associated with schizophrenic psychosis will actually turn out to be manifestations of pre-illness neurobiological vulnerability ('schizotaxia') rather than part of the psychotic process per se (Faraone *et al.*, 2001; Gottesman & McGue, 1990; McGue *et al.*, 1983; Tsuang *et al.*, 1999b).' Though the major clinical contributions of this line of research may be decades away, endophenotypes may ultimately lead to an earlier detection of schizophrenia, offering the potential to halt disease progression, reduce relapse rates, increase treatment response and improve long-term outcome. In the long run, the goal is to identify and monitor risk factors and ultimately to prevent the onset of psychosis in those at risk.

Candidate endophenotypes in schizophrenia are varied, and have been reviewed in detail by Seidman and Wencel (2003) and Stone *et al.* (2004). In brief, these endophenotypes, which are shared between patients and biological relatives (some of which demonstrate positive linkage in genetic linkage studies), include: neurophysiological indicators such as sensory gating deficits (Braff *et al.*, 2001; Cadenhead *et al.*, 2000; Clementz *et al.*, 1998; Frangou *et al.*, 1997; Friedman & Squires-Wheeler, 1994; Myles-Worsley, 2002; Siegel *et al.*, 1984; Waldo *et al.*, 1988; 1991; 1995; Young *et al.*, 1996); eye-tracking dysfunction (Arolt *et al.*, 1996; Calkins & Iacono, 2000; Holzman *et al.*, 1974;

Lee & Williams, 2000); numerous cognitive impairments, particularly abnormal prefrontally-mediated cognitive abilities, such as compromised working memory, attention and executive functioning, as well as verbal declarative memory (Cannon *et al.*, 1994; 2000; Cirillo & Seidman, 2003; Conklin *et al.*, 2000; Cornblatt & Keilp, 1994; Faraone *et al.*, 1995; 1996; 1999; 2000; Kremen *et al.*, 1994; 1997; 1998; Lyons *et al.*, 1995; Park *et al.*, 1995; Toomey *et al.*, 1998; Tsuang *et al.*, 1999a); and, clinical symptoms, such as schizotypal and paranoid personality traits (Kendler *et al.*, 1993), flat affect (Tsuang *et al.*, 1991), thought disorder (Shenton *et al.*, 1989), communication disturbance (Docherty, 1995) and neurological signs (Erlenmeyer-Kimling *et al.*, 1982). Moreover, increasing advances in neuroimaging techniques have allowed examination of structural, functional and chemical brain alterations in non-psychotic relatives and high-risk individuals (see Faraone *et al.* (2003) and Seidman & Wencel (2003) for comprehensive reviews), as well as people with schizotypal personality disorder (Dickey *et al.*, 1999).

Results from these candidate endophenotype studies are generally consistent with the hypothesis that increased genetic vulnerability to schizophrenia, independent of the psychotic process itself, affects brain structure and function. The strongest evidence so far, mainly from magnetic resonance imaging (MRI) studies of relatives, indicates altered medial temporal lobe (especially in the hippocampal–amygdala region) and thalamic volumes (Seidman *et al.*, 1999; 2002; 2003), and abnormal brain activity in prefrontal cortical circuitry regulating neurocognitive functions (Callicott *et al.*, 2003; Thermenos *et al.*, 2004). These abnormalities appear to be a subtler version of the findings observed in patients with schizophrenia, and seem to be present to some extent from early childhood.

Olfaction as a candidate endophenotype for schizophrenia

In addition to the endophenotypes listed above, measurement of olfactory functioning is independent of diagnosis and hence provides a feasible approach, both practically and economically, for assessing abnormal brain function and genetic vulnerability to schizophrenia. Olfactory impairments in schizophrenia have been well documented (see Moberg & Turetsky (2003) for a review), including from our research group (Seidman *et al.*, 1991; 1997), and are described in detail in Chapter 16. This is not surprising, as olfactory processing is mediated by structures also implicated in schizophrenia, including the orbitofrontal and entorhinal cortex, the dorsomedial nucleus of the thalamus, and the ventromedial temporal lobe. Recently, Turetsky *et al.* (2000) also reported reduced olfactory bulb volumes in schizophrenia. Moreover, there is a strong genetic

component to the transmission of olfactory functioning (Barinaga, 2001) that is reviewed in Chapter 1. Olfactory deficits in schizophrenia may reflect, at least in part, a heritable vulnerability factor or endophenotype, and provide important insights about the underlying integrity of the orbitofrontal, thalamic and medial temporal brain regions.

A possible genetic contribution to olfactory deficits in schizophrenia was first suggested by Kopala and colleagues (1991) in a report of olfactory agnosia in two members of a family with a partial trisomy of chromosome 5 and schizophrenia. Since then, a number of genetic linkage studies have associated dysfunction of olfactory processing with schizophrenia. The DISC 1 (Disrupted in Schizophrenia 1) gene has been associated with schizophrenia in multiple genetic studies (see Austin *et al.* (2004) for a comprehensive review). In an investigation of Disc1 (the mouse ortholog of DISC 1) expression from embryonic day 14 through adulthood, Austin *et al.* (2004) detected the presence of Disc1 mRNA in olfactory bulbs, among other brain regions, throughout all stages of mouse brain development. Similar findings of Disc1 expression in olfactory bulbs were documented through *in situ* hybridisation in the adult mouse brain (Ma *et al.*, 2002). The DISC 1 mutation in humans may therefore lead to olfactory dysfunction through a failure of development or adult neurogenesis. The GNAL locus at chromosome 18p11 has also been linked both to schizophrenia (Schwab *et al.*, 1998) and the mediation of odorant signal transduction (Jones & Reed, 1989; Wang *et al.*, 1993). Mice deficient for CHL1 show, among other abnormalities, misguidance of olfactory sensory axon projections (Montag-Sallaz *et al.*, 2002). Recently, the potential involvement of altered CHL1 protein in the aetiology of schizophrenia was suggested (Sakurai *et al.*, 2002). Montag-Sallaz *et al.*, (2003) further supported this association to schizophrenia in a gustatory paradigm, in which CHL1 deficient mice showed similar mRNA expression when exposed to familiar or novel tastes, suggesting that these CHL1 deficient mice showed altered information processing comparable to that shown in schizophrenic patients.

To our knowledge, only a limited number of studies have, to date, investigated olfaction in the family members of schizophrenics and high-risk individuals in comparison to healthy controls (see Table 9.1). In the first study of olfaction in first-degree relatives of patients with schizophrenia, Moberg *et al.* (1996) assessed olfactory identification ability, using the University of Pennsylvania Smell Identification Test (UPSIT) (Doty *et al.*, 1984; see also Chapter 13), in 16 schizophrenic probands, 16 non-psychotic siblings, and 32 comparison subjects. Three primary findings emerged from this study: (1) Counterbalanced unirhinal assessment revealed significantly reduced UPSIT scores in schizophrenic patients and siblings, compared to controls, with right nostril

Table 9.1. Genetic and clinical high-risk studies of olfaction in schizophrenia*

Study	Participants	Primary findings
Genetic high-risk studies		
Moberg *et al.*, 1996[1]	16 SZ 16 Non-affected siblings 32 Controls	• Counterbalanced unirhinal UPSIT assessment revealed sig. ↓ scores in SZ and siblings, compared to controls, with *right* nostril presentation only. • In siblings, ↓ UPSIT scores in those who met criteria for SPD compared to those who did not. • In SZ, sig. association between ↑ duration of illness and ↓ UPSIT score in *left* nostril only.
Kopala *et al.*, 1998	12 pairs monozygotic twins discordant for SZ, age: $M = 36.8$, $SD = 5.0$ 12 Controls, age: $M = 37.5$, $SD = 4.6$	• Sig. ↓ UPSIT scores in twin pairs ($M = 35.1$, $SD = 3.8$) compared to controls ($M = 37.7$, $SD = 1.7$). • No sig. difference in scores between affected ($M = 34.1$, $SD = 4.3$) and unaffected twins ($M = 36.1$, $SD = 3.3$).
Kopala *et al.*, 2001	46 First- and second-degree relatives (19 Psychotic, 27 non-psychotic), age: $M = 43.5$, $SD = 10.9$, *range* = 20–64 years, gender: 54% female 43 Controls, age: $M = 42.5$, $SD = 10.9$, gender: 58% female	UPSIT scores in microsmic (impaired) range for 58% of psychotic relatives ($M = 31.8$, $SD = 6.3$), 34% of non-psychotic relatives ($M = 35.3$, $SD = 3.0$), and 9% of controls ($M = 36.8$, $SD = 2.2$).
Turetsky *et al.*, 2003	11 SZ, age: $M = 30.7$, $SD = 11.0$, *range* = 20–53 years, gender: 36% female 19 Non-psychotic first-degree relatives, age: $M = 36.9$, $SD = 14.9$, *range* = 17–54 years, gender: 37% female	• Sig. ↓ right olfactory bulb volumes in SZ and relatives compared to controls. • Sig. ↓ *left* olfactory bulb volumes in SZ compared to relatives and controls.

(continued)

Table 9.1 *(cont.)*

Study	Participants	Primary findings

	20 Controls, age: $M = 36.0$, $SD = 13.4$, *range* = 18–56 years, gender: 40% female	• Sig. ↑ PEA odour detection thresholds in SZ (impaired detection of odours) compared to relatives birhinally and controls in the left nostril only.
		• No sig. difference in UPSIT scores between the 3 groups (20 items administered to each nostril):
		  • Left nostril:SZ: $M = 17.6$, $SD = 3.3$, relatives: $M = 18.1$, $SD = 2.2$, controls: $M = 17.9$, $SD = 1.8$
		  • Right nostril:SZ: $M = 17.7$, $SD = 1.5$, relatives: $M = 17.9$, $SD = 2.2$, controls: $M = 17.8$, $SD = 1.8$

Clinical high-risk studies		
Brewer *et al.*, 2003	81 'Ultra high-risk' [2] adolescents & young adults, age: $M = 20.2$, $SD = 3.7$, *Range* = 14–30 years, gender: 43% female • 27% became psychotic 18 months later (55% diagnosed with SZ; 45% diagnosed with other psychotic illnesses) 31 controls, age: $M = 21.1$, $SD = 3.9$, gender: 29% female	Sig. ↓ UPSIT scores compared to controls ($M = 33.4$, $SD = 1.4$) in high-risk group that later developed SZ only ($M = 29.8$, $SD = 2.2$), not in those high-risk groups that developed other psychotic illnesses ($M = 32.9$, $SD = 2.3$) or who did not become psychotic ($M = 32.2$, $SD = 0.9$).

*All studies include a healthy control group, and age and gender variables are reported when available.

[1] Means and standard deviations for UPSIT scores not reported.

[2] See Brewer *et al.*, (2003) for detailed description of criteria for 'ultra high-risk'.

Sig. = statistically significant difference

↓ = decreased

↑ = increased

SZ = persons diagnosed with Schizophrenia

SPD = schizotypal personality disorder

UPSIT = University of Pennsylvania Smell Identification Test (Doty *et al.*, 1984)

PEA = phenyl ethyl alcohol (see Deems & Doty, 1987, for description of PEA odour detection threshold procedures)

presentation only. The average UPSIT score of the siblings fell midway between the scores of the probands and the control subjects; (2) Within the sibling group, UPSIT scores were worse for those who met criteria for schizotypal personality disorder compared to those who did not, and; (3) Within the schizophrenia group, there was a significant relationship between longer duration of illness and decreased UPSIT score in the left nostril only. Given that the primary olfactory projections are largely ipsilateral, the authors suggested that the right nostril functioning represented a trait component of the deficit, whereas left nostril functioning represented the state component.

Twin studies are particularly powerful methods of examining genetic contributions to phenotypic presentations. Using this technique, Kopala *et al.* (1998) assessed olfactory identification ability (UPSIT) in a group of 12 monozygotic twins discordant for schizophrenia as well as in a group of 12 age- and sex-matched controls. Both twin groups scored significantly below the comparison group. Although the unaffected twins' scores fell between those of the affected twins and those of the control group, the scores of the affected and non-affected twin groups did not significantly differ from each other. Further supporting a genetic role, twin pairs with family histories of serious mental illness had significantly worse olfactory identification ability than did the twin pairs without such family histories.

Kopala and her colleagues (2001) conducted a family study of olfactory identification in 46 first- and second-degree relatives of patients with schizophrenia, 19 of who were psychotic and 27 non-psychotic, and compared them to 43 age- and sex-matched controls. Significant differences in UPSIT scores were observed between the three groups. Scores were in the microsmic (impaired) range for 58% of psychotic relatives, 34% of non-psychotic relatives and 9% of controls. These findings lend additional support to the notion that olfactory deficits aggregate in family members with schizophrenia and may serve as an endophenotype for the illness.

Examining a structural basis for olfactory deficits, Turetsky *et al.* (2003) used MRI to measure olfactory bulbs in 19 non-psychotic first-degree relatives, 11 patients with schizophrenia and 20 age- and sex-matched controls (see also Chapter 16). Consistent with previous findings from this research group (Turetsky *et al.*, 2000), both left and right olfactory bulb volumes were significantly reduced in the patient group compared to controls. However, an intriguing pattern emerged when the relatives' olfactory bulbs were examined. There was a significant difference between relatives and controls in the right olfactory bulb volume only. The left olfactory bulb volumes were comparable between relatives and controls, and significantly greater than those of the schizophrenic patients. The schizophrenic group also showed impaired detection

of odours only in the left nostril compared to controls. These lateralised findings are compatible with those reported by Moberg *et al.* (1996), and similarly suggest that the endophenotypic trait of genetic vulnerability may be localised to right hemisphere olfactory structures, while the phenotypic state component, reflecting the actual presence of the illness, may be localised to left hemisphere olfactory structures. Indeed, left hemispheric deficits appear to be slightly more prominent than right hemispheric deficits in schizophrenia (McCarley *et al.*, 1993; Shenton *et al.*, 1992). This pattern may also generalise to olfactory impairments (Good *et al.*, 1998). Unexpectedly, no corresponding significant differences in UPSIT scores were observed between the three groups. The authors suggest that this discrepancy may be due to reduced power associated with the relatively small sample size and/or the use of unirhinal presentation as opposed to the simultaneous, birhinal presentation typically employed in other studies with the UPSIT, explaining that bilateral presentation may yield additional facilitative mechanisms (Cain, 1977).

The four studies described above use a traditional genetic strategy, which relies on family history alone, for identifying individuals at high-risk for psychosis. Alternatively, the *clinical* high-risk strategy relies on a combination of trait- and state-risk factors by studying individuals during the 'prodromal' stage of psychosis, which includes the earliest symptomatic manifestations of psychosis during the period of time directly preceding the first frank psychotic episode (for a review, see Cornblatt *et al.* (2002)). This strategy has increasingly been viewed as a more efficient way of studying the risk and protective factors that may predict who will develop psychosis. As Cornblatt and colleagues (2002) review, this is largely because of two limitations in genetic high-risk designs: (1) Their low yield – at most, there is a 10–15% conversion rate to schizophrenia, and; (2) The study duration to onset of psychosis may be decades.

Using this clinical high-risk strategy, Brewer *et al.* (2003) recently examined olfactory identification ability in 81 adolescents and young adults at clinical high-risk for developing psychosis compared to 31 age- and sex-matched controls. Eighteen months following olfactory assessment, 27% of the ultra high-risk sample became psychotic; of this psychotic subgroup, 55% were diagnosed with schizophrenia and 45% were diagnosed with other psychotic illnesses. Interestingly, findings revealed that UPSIT scores were significantly reduced only in the subgroup of high-risk subjects who were later diagnosed with schizophrenia. These results were not observed in the high-risk subjects who later developed other psychotic illnesses or who did not become psychotic, or in the healthy comparison subjects. The findings suggest that impairments in olfactory identification are a specific vulnerability marker for schizophrenia rather than psychosis per se.

Summary and conclusions

In this chapter, using schizophrenia as an example, we provide an overview of the evidence suggesting that olfactory deficits may serve as endophenotypes, or genetic vulnerability markers, for neuropsychiatric disorders. The data so far are quite preliminary, as there are only a few published studies, but the results are promising. While we have begun to delve into the role that olfaction plays within the complicated relationship between genes, environmental influences and clinical manifestations of neuropsychiatric illnesses, we still have much to explore.

There are a number of limitations and methodological differences that may account for some of the equivocal findings from the literature so far. For example, as we noted, the mode of administration of the olfactory instrument (unirhinal vs. birhinal) may alter the degree of observable impairment (Cain, 1977). Some studies do not provide healthy comparison groups or adequate demographic data, and type of psychotic disorder (schizophrenia vs. affective psychoses) is sometimes not specified. Due to logistic difficulties associated with obtaining and retaining patient and relative groups, there is often too low a sample size and a related lack of statistical power to detect small group differences, particularly since deficits in relatives may reflect subtle alterations from probands or controls. Because there are no post-mortem studies of non-psychotic relatives, there is no precise correlation of cellular abnormalities with those observed in vivo. Moreover, the current data cannot determine why some relatives that show brain pathology and/or deficits similar to that seen in persons with schizophrenia who do not develop the illness. Further work is needed to determine whether they have less severe pathology, if they have not been exposed to environmental triggers of the illness, or if they have added protective factors. Substantially more research, with larger samples, studying teens or children through the peak ages of risk for schizophrenia, is necessary to determine the robustness, stability and predictive power of the deficits we report. Continued investigations of the olfactory system and related abnormalities, and particularly its role as an endophenotype, may aid in unravelling the mysteries of the molecular and genetic underpinnings of schizophrenia and other complex neuropsychiatric diseases.

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10

Sex differences and olfactory function

Kimberley P. Good and Lili Kopala

Introduction

In the early 1980s, in conjunction with the National Geographic Magazine, Wysocki and Gilbert set out on an ambitious quest. About 10.5 million 'scratch and sniff' surveys were distributed with the magazine in the hope of collecting population-based data on olfactory function. Over 1.4 million completed surveys were returned (Wysocki & Gilbert, 1989). Although limited in its scope, the data served to highlight a number of interesting points. Among those reported was the observation that women outperformed men on all measured aspects of olfactory ability. Moreover, the findings suggested that sex differences in olfactory perception were not uniform across different odorants. Although sex differences in olfactory sensitivity have been anecdotally known for centuries, the data derived from this investigation provided further insight into some of the diverse aspects of olfactory functioning that are differentiated between the two sexes. This monumental study served to spur on subsequent olfactory research, particularly in the realm of sex differences.

This chapter reviews the literature on sex differences in olfactory ability and describes the current state of knowledge on this subject. Moreover, some methodological shortcomings in published reports are outlined. Finally, some hypotheses are offered in order to explain the male/female difference in olfactory function.

Males and females differ in their ability to process odorants

Olfactory findings

Sex differences in olfactory function have been observed on virtually all olfactory measures examined. These include, but are not limited to, detection threshold, sensitivity, discrimination, identification, naming, memory and hedonics[1] (Choudhury *et al.*, 2003; Hulshoff Pol *et al.*, 2000; Koelega & Koster, 1974; Wysocki & Gilbert, 1989). In general, the effect size for these sex differences is modest, but may become more pronounced with age (Ship & Weiffenbach, 1993). Moreover, these differences appear to be consistent across cultures, and as such, are not likely to be solely a consequence of exposure to environmental toxins (Barber, 1997; Doty *et al.*, 1985).

The first objective demonstration of female superiority in olfactory function appeared over a century ago. As reported by Brand & Millot (2001), Toulouse and Vaschides (in 1899) observed that females (young and old alike) had superior odour perception, sensitivity and discrimination ability when compared to similarly aged males. Toulouse and Vaschides failed, however, to replicate an investigation carried out earlier which suggested a male superiority in odour detection ((Bailey & Nichols, 1884; Bailey & Powell, 1885) quoted in Brand & Millot, 2001). The details of the experimental protocol employed by Bailey and colleagues were not reported, making replication difficult. Given the technological imperfections at that time, these discrepant findings are somewhat expected. Predictably, sex differences, as a line of olfactory research, fell silent until the early 1950s whereupon a somewhat more systematic investigation of this topic emerged (Amoore & Venstrom, 1966; Koelega & Koster, 1974; Le Magnen, 1952).

Detection/sensitivity

Detection threshold is defined as the lowest concentration of odorant that is perceptible (see Chapters 1 and 13). No qualitative information is required from the respondent; the subject is asked simply to report the presence or absence of odour. Many different odorants have been examined – most of which are processed by the first (olfactory), rather than the fifth (trigeminal) cranial nerve (Doty *et al.*, 1978). Threshold can be assessed in a variety of ways (single staircase, ascending methods of limits) and allows for an evaluation of more sensory, rather than cognitive aspects of olfactory function.

[1] For a description and definition of the olfactory processes that are referred to in this chapter, please refer to Chapters 1 and 13, this volume.

On odour detection threshold for most odorants, females outperform males. For example, lower thresholds (better sensitivity) have been observed in women for amyl acetate (Corwin *et al.*, 1995; Koelega & Koster, 1974; Wysocki & Gilbert, 1989), phenyl ethyl alcohol (Corwin *et al.*, 1995; Koelega, 1994; but see also Hummel *et al.*, 1991), androstenone and related steroidal odours (Dorries *et al.*, 1989; Koelega & Koster, 1974) and musky odorants (e.g. Exaltolide; Le Magnen, 1952). Additionally, more males than females are unable to detect certain odorants (anosmic) (e.g. androstenone and galaxolide; Wysocki & Gilbert, 1989; for a review, see Bremner *et al.*, 2003).

Sex differences may be difficult to interpret when detection threshold is assessed using a Yes/No paradigm ('Is an odour present?'). Detection appears to be mediated predominantly by peripheral structures (Jones-Gotman & Zatorre, 1988) and thus, top-down processing should not significantly influence performance. Data exist which suggests that females and males differ in their response bias (Messe *et al.*, 1968; Wallach & Kogan, 1959). When faced with a signal detection task and in the presence of an ambiguous situation, males are more likely to guess. In contrast, women tend to respond more cautiously, and only when there is enough information upon which to base their decision. Therefore, the method used to assess olfactory thresholds is of particular importance, especially when assessing potential differences between men and women (Koelega & Koster, 1974). However, in a recent study specifically assessing response bias in odour recognition, Öberg *et al.* (2002) were unable to confirm this contention. Both males and females demonstrated the same neutral response bias. Nevertheless, using a method of limits or staircase procedure minimises this potential confound and thus is more commonly recommended and employed in recent studies.

Discrimination

Sex differences in the ability to *discriminate* or differentiate between odorants have not been extensively investigated. However, in one study, sex differences were observed in performance, again in favour of females (Hulshoff Pol *et al.*, 2000). Male and female subjects were evaluated on their ability to determine the odd odour from a triad (two same, one different). A small but statistically significant difference was noted, with females outperforming males. It is to be noted that when the task duration was increased, the female advantage disappeared. These researchers concluded that the duration of olfactory task may influence the appearance of sex differences and could account for some of the variance seen in the literature pertaining to ageing and olfaction. Increasing test length should, theoretically, improve the reliability of the test,

and as such, it is unclear why women would lose their advantage by virtue of longer test duration.

Identification/naming

According to Dempsey and Stevenson (2002), the ability to name an odorant requires at least two active processes: accurate recognition of the odorant and a search through semantic stores for the appropriate verbal label (see Chapters 1 and 13). Women and men differ in the efficiency by which semantic strategies are employed for performance on odour memory tasks (see next sub-section) (Lehrner, 1993; Rabin & Cain, 1984). This latter sex difference could influence performance of an olfactory identification task regardless of any putative 'biological' difference between men and women in their ability to perceive/recognise odorants.

Early findings from the National Geographic Smell Survey (NGSS) showed that, across all age ranges studied, women correctly identified the six presented odours more accurately than did men. In contrast, when the NGSS was translated into Swedish, no female superiority for olfactory identification for any of the six odours was noted in a Swedish speaking sample (Larsson *et al.*, 2000). The sample size in the latter study ($n = \sim 500$) was smaller than that of the parent study; however, it was sufficiently sized to allow for potentially detecting meaningful differences if they existed. In contrast, sex differences were noted both in a sample of Swedish subjects and a cohort of Finnish participants, using a different olfactory identification test — The Scandinavian Odor Identification Test (SOIT) (Nordin *et al.*, 2002). The normative data collected for the University of Pennsylvania Smell Identification Tests (UPSIT) also demonstrated a distinct female superiority such that separate norms are provided for clinical assessment of both males and females (Doty *et al.*, 1984). This dataset contains evaluations of over 4000 individuals, powering it adequately to detect small effect sizes.

Ship and Weiffenbach (1993) demonstrated that despite consistent sex differences across age, the sex differences in olfactory identification were enhanced during the ageing process. Using a longitudinal research design, men showed a more abrupt deterioration after the age of 55, whereas the decline in performance in females tended to be more linear, at least until approximately the age of 80 years. The results from the SOIT (Nordin *et al.*, 2002) are also consistent with these findings. In contrast, data from the NGSS demonstrated that performance on olfactory identification items did not appear to diverge significantly over the age ranges studied (Wysocki & Gilbert, 1989). However, in this latter study, only a few odorants were assessed and only those subjects who

could detect the odorants (i.e. were not anosmic) were included in their analysis — likely skewing the results.

The ability of humans to assign names or descriptions de novo to odours tends to be uniformly poor. However, performance tends to improve on olfactory tasks in which a list of possible descriptors is provided (e.g. The UPSIT). Despite this potential difficulty, performance on an olfactory free-naming task has also been shown to be distinctly better in women than in men (Öberg *et al.*, 2002).

Odour memory

Not all studies of olfactory memory have reported sex differences in performance (Choudhury *et al.*, 2003; Engen & Ross, 1973; Lehrner, 1993; Oberg *et al.*, 2002). These inconsistent findings may be related to the specific odorants used in each investigation. For example, Öberg *et al.* (2002) demonstrated a female superiority for recall of familiar odours while recall of unfamiliar odours did not result in any significant sex differences. This group maintained that the lack of familiarity with the odorants under study could account for many of the published negative findings. Dempsey and Stevenson (2002) provided evidence in support of this conclusion. In their study, a semantic odour memory task was presented to male and female participants. Novel odours were paired with an arbitrary Swahili name and presented to subjects. After training, no initial sex difference was noted in the subjects' abilities to name the odours. However, after a one-week delay, women significantly outperformed men in their ability to recall the odour names. This latter research group suggested that females were better able to consolidate odour memories, and thus led to enhanced familiarity with the odours. Better performance for these now 'familiar' odours was consequently noted.

Verbal labelling of odours has been shown to augment performance on odour memory tasks (Herz & Engen, 1996; Rabin & Cain, 1984), even if the verbal label is not the veridical (correct) one (Rabin & Cain, 1984). It is likely that women employ semantic strategies more consistently than men in order to encode and consolidate odour memories (Larsson *et al.*, 2003), leading to a more enduring memory trace and better recollection. In support of this hypothesis, Öberg *et al.* (2002) demonstrated that sex differences in olfactory recognition memory disappeared when odour-naming performance was added as a covariate in the statistical analysis.

Functional imaging of the olfactory system

The cost constraints involved in neuroimaging studies pose a limit on sample sizes studied, and as such, examination of sex differences in olfactory function

has often not been economically feasible on a larger scale. The bulk of olfactory neuroimaging studies tend to focus on one sex or the other (usually males). In those investigations that have explicitly sought to examine sex as a variable, inconsistent findings have appeared. For an overview of these studies, the reader is referred to Chapters 1–3.

Olfactory event-related potentials (OERPs) have been assessed in women and men. On average, amplitudes in women tended to be increased relative to men (Becker *et al.*, 1993; Evans *et al.*, 1995), but the latencies were not affected. In both studies, enhanced amplitudes were considered to be consequent to the reported female superiority in olfactory function. However, in one sample (Evans *et al.*, 1995) no sex differences were observed on psychophysical testing, while in the other sample (Becker *et al.*, 1993) the results of olfactory testing were not reported. In a further study examining OERPs, significant latency and amplitude reductions were demonstrated only in older male subjects (Morgan *et al.*, 1997).

Three olfactory neuroimaging investigations in which sex differences were examined have been published. In one such study (Bengtsson *et al.*, 2001), cerebral activation was assessed using $H_2^{(15)}O$ positron emission tomography (PET) in 12 female and 11 male subjects. No differences were observed between the sexes in the location of brain activation when presented (passively) with odorants. An fMRI investigation also did not detect any difference between males and females in the sites of olfactory activations; however, a significant difference was noted in the volume of activation. Females activated 6.4 times greater the number of voxels than did males (Yousem *et al.*, 1999). Interestingly, odorants with a biological significance (see section on 'Are socially relevant odours processed differently than socially irrelevant stimuli?') were associated with sex differences in regional activations patterns. Women were found to demonstrate significant hypothalamic activation in response to androstenone (a derivative of testosterone) while men showed significant hypothalamic activation after smelling oestrogen (Savic *et al.*, 2001).

The consistent behavioural differences between males and females on olfactory psychophysical testing support the argument that it is imperative that 'sex' be taken into account when designing olfactory neuroimaging studies. By ignoring sex differences, the true patterns of brain activation may be obscured or skewed. Finally, if only one sex is evaluated in a particular investigation, the conclusions drawn must be specified by gender, and not generalised broadly across all individuals.

Sex differences are observable early (neonates, pre-school age children)

Doty (1991) suggested that there are innate sex differences in olfactory functioning. Support for this statement came from a study in which male and female

neonates were examined for their preference for cotton gauze pads that had been moistened with the breast odour from their mothers or from an unrelated stranger. Female neonates demonstrated a preference for the odour from their own mothers rather than from a stranger (Makin & Porter, 1989) or that of an artificial odorant (Balogh & Porter, 1986). Male neonates, on the other hand, showed no such preference. In young children (age four years), females were better than males at correctly identifying their playmates based on odour cues (Verron & Gaultier, 1976). Moreover, a sex difference in identifying the odour of preferred acquaintances was observed in prepubescent children, with the performance of girls being superior to boys (Mallet & Schaal, 1998).

When everyday odours were tested using the UPSIT, sex differences were observed in male and female children as young as five years of age (Doty, 1995). This difference was not subjected to a statistical test, but the median olfactory score was two points (out of a possible 40) higher in girls than in boys. Older children and adolescents (age 10 to 19) also demonstrated this same pattern (Doty *et al.*, 1984).

Sex differences are also apparent during puberty

As discussed above, adolescent children perform differently on the UPSIT based on sex. Better performance in females than males have been reported on the UPSIT (median values) (Doty *et al.*, 1984) and on olfactory naming (Stevenson & Repacholi, 2003). No sex differences were detected in olfactory sensitivity in an adolescent sample (Koster & Koelega, 1974). Changes in hormonal status during adolescence may contribute to the female advantage that has been reported (Doty, 1986*)*. However, no study has reported on olfactory test scores in the face of known (quantified) hormonal levels.

In support of Le Magnen's (1952) notion that male sex hormones could impair the ability to detect biologically relevant odours, a change in the ability to perceive androstenone has been reported during this period in a sexually dimorphic fashion (Dorries *et al.*, 1989). Prepubescent boys were able to detect this odour while adolescent boys were less likely to be able to do so. Furthermore, the sensitivity of those males who could still detect androstenone was further reduced relative to females. In females, the changes were not so apparent. No differences in threshold values were obtained over the 9–14, 15–20 and 21+ age bands. Although some young females were shown to become insensitive to androstenone, the percentage of 'non-smellers' was higher in the male than female subjects (Dorries *et al.*, 1989).

Finally, hedonic responses or emotional valence may also change as a function of age and sex during the adolescent period (Stevenson & Repacholi, 2003). When presented with the odour of 'male sweat', young children and adolescent

males disliked the smell equally while adolescent females intensely disliked the odour. However, these researchers favoured the explanation of an acquired social response, rather than a biological sensitivity difference, because when male and female adolescents were told that the odour was 'sweat', the hedonic ratings did not differ between the sexes.

Olfactory function as it relates to endocrine status

Changes in olfactory sensitivity across the phases of the menstrual cycle

There is a widely held belief that women are differentially sensitive to odours over the course of the menstrual cycle (Doty *et al.*, 1981; Gangestad & Thornhill, 1998; Navarrete-Palacios *et al.*, 2003; Vierling & Rock, 1967). The greatest olfactory enhancement (to at least some substances) has been noted mid-cycle or mid-luteal (days 14 to 21 of the menstrual cycle), suggesting that both oestrogen and progesterone play a role in mediating olfactory function (Purdon *et al.*, 2001). Other investigations have provided conflicting results (Amoore *et al.*, 1975; Hummel *et al.*, 1991). Methodological differences along with a lack of objective data to substantiate cycle phase (hormonal assays) may account for these discrepancies. The bulk of the literature suggests that olfactory sensitivity (Doty *et al.*, 1981; Vierling & Rock, 1967), but not olfactory identification (Kopala *et al.*, 1995; Purdon *et al.*, 2001) varies with menstrual phase.

Interestingly, one study that included a sample of young women who were taking oral contraceptive pills (OCP) also demonstrated a mid-cycle enhancement of olfactory sensitivity (Doty *et al.*, 1981). These data suggest that ovarian hormones may only produce a facilitative effect on olfactory function while underlying neural mechanisms (endogenous oscillators) also contribute to the observed effect. However, the sample size examined was exceptionally small ($n = 3$) and information regarding the duration of oral contraceptive use was not provided. In contrast, in a more recent study, Caruso *et al.* (2001) examined this issue in a relatively large sample of women ($n = 60$), both before and after (three months of OCP use). Although a predictable enhancement of olfactory sensitivity was noted at mid-cycle before beginning OCPs, no such fluctuations occurred after beginning treatment. Moreover, olfactory sensitivity was shown to diminish with OCP use. If circulating hormones are hypothesised to contribute to the enhancement of olfactory function, it is unclear why in this study oral contraceptive use was associated with decreased, rather than increased, sensitivity. The data from this investigation suggest that exogenous steroids likely play a role in modulating olfactory function, but the precise mechanisms at various stages of life remain unclear.

Women's olfactory preference also appears to vary across the phases of the menstrual cycle. During ovulation, women have been shown to prefer the scent of 'symmetrical' men (males who are less likely to have experienced developmental aberrations), whereas no such preference was noted during the other phases of the menstrual cycle (Gangestad & Thornhill, 1998). Preferring the scent of men with phenotypic markers of genetic benefits has implications for sexual selection; those with greater reproductive fitness, higher mating success and fecundity could potentially confer a reproductive advantage to the woman.

States of heightened (pregnancy) and diminished (peri- and post-menopausal) oestrogen/progesterone levels

As previously noted, prepubescent females demonstrate superiority over males in their sensitivity to odours. Furthermore, identification performance tends to be superior in young females than in males. These observations do not support the explanation that sex differences in olfactory function are solely accounted for by circulating hormonal effects. Moreover, assessment of women who are post-menopausal does not support the hypothesis of fluctuating levels of sex hormones playing a significant role as specific mediators of olfactory sex differences, as even later in life (e.g. ages 65 to 85) olfactory function is modestly better in women than in men (Ship *et al.*, 1996).

During the peri-menopausal phase, the levels of oestrogen and progesterone begin to diminish. There are data that indicate that a decline in oestradiol levels is associated with cognitive dysfunction, particularly memory, in post-menopausal women (Shaywitz *et al.*, 1999; Sherwin, 1994). Olfactory function (identification and detection threshold), however, does not appear to diminish after menopause in women who are otherwise healthy (Good *et al.* unpublished observations; Kopala *et al.*, 1995). In order to investigate this phenomenon in detail, Deems and colleagues (1991) examined olfactory function in 750 subjects who presented to the University of Pennsylvania Smell and Taste Centre with olfactory complaints. A large percentage of individuals who sought care were post-menopausal women. Of these women, only 4% were current users of hormone replacement therapy (HRT), which suggested that exogenous oestrogens may be protective and preserve olfactory function in post-menopausal women. Moreover, when compared directly, performance on the UPSIT for those who were current HRT users was superior to the non-users ($p < 0.005$); however, detection threshold did not differ between these two groups. These latter findings should be considered in the context that women were included in this study only *if* they attended the Smell and Taste Centre as a consequence of self-reported olfactory complaints. Population-based sampling (i.e. including women without self-reported olfactory deficits) would be more valid.

In this vein, olfactory function was examined in post-menopausal women who were not seeking health care for olfactory problems and who were not current HRT users. Their performance was compared to a cohort of women who had been regular HRT users for at least five years (Hughes *et al.*, 2002). On a number of olfactory tests (detection threshold, identification, quality discrimination etc), no between-group differences were noted. In patients who were HRT users, the data were broken down into those using unopposed oestrogen vs. those who were prescribed opposed oestrogen (with progesterone). The presence or absence of progesterone in the regime also made no difference to olfactory performance. The data from this prospective study does not support prior conclusions that there are benefits of HRT on olfactory function in post-menopausal women. In contrast, olfactory deficits in specific neuropsychiatric disorders such as schizophrenia may be exaggerated by oestrogen depletion (Good *et al.* unpublished observations; Kopala *et al.*, 1995).

During pregnancy, many women report that their sense of smell is distinctly enhanced, particularly during the first trimester (Cantoni *et al.*, 1999). However, psychophysical tests do not support this belief (Kölble *et al.*, 2001; Laska *et al.*, 1996). Rather, women likely misattribute odours during pregnancy, as hedonic ratings tend to shift towards odour aversions during this time (Kölble *et al.*, 2001).

Oestrogen receptors (ER-β) are widely distributed within the brain, including the olfactory bulb, and this distribution is sex specific (Zhang *et al.*, 2002). Oestrogen depletion (oophorectomy) and enhancement are associated with altered levels of ER mRNA in the rat brain (Shima *et al.*, 2003). Oestrogen has been posited to be involved in either modulating the excitability of the olfactory system (Pfaff & Pfaffmann, 1969) and/or controlling the secretion of nasal mucus (to either facilitate or impede odorant diffusion) (Mair *et al.*, 1978). Activating effects of circulating ovarian hormones are likely to contribute to the changes in odorant sensitivity, but are not the sole determinants. The organisational (in utero) effects of steroid hormones cannot be ignored, however, particularly in the development of olfactory sex differences. Chapters 1 and 5 in this book provide further information regarding the development of human brain and olfactory pathways.

Are socially relevant odours processed differently than socially irrelevant stimuli?

Are sex differences more likely when human odours are presented?

In macrosmatic animals (animals who rely heavily on their sense of smell for survival), olfaction is fundamental to a great number of physiological functions,

including foraging for food/prey, predator avoidance and the recognition of sexual receptivity in a potential mating partner. Humans are believed to be more visually oriented and thus may not use olfactory cues for mate selection to the same extent that other species do. This latter assumption has been a long held notion, but has recently been challenged (Herz & Cahill, 1997). Le Magnen (1952) proposed that sex differences should be more likely and prominent for biologically (sexually) relevant odours. Indeed, musk (Galaxolide) and a testosterone derivative (androstenone) are more likely to be detected by women than by men (Wysocki & Gilbert, 1989). Moreover, women tend to perceive these odours as less pleasant and more intense than do men (Wysocki & Gilbert, 1989). Androstenone (5α-androst-16-en-3-one) is produced in boar testes and serves to induce lordosis (sexually receptive posture) in the sow (Pause *et al.*, 1999), and as such has been classified as a putative pheromone. This compound has also been isolated in secretions from human axillae (arm pits) more often in males than in females (Gower *et al.*, 1985), and may serve similar purposes in humans. Emerging data supports the notion that biologically salient odours are processed differently between the sexes.

In the NGSS, more men than women were reportedly anosmic or unable to detect androstenone across all age ranges (Wysocki & Gilbert, 1989). Bremner *et al.* (2003) reported the prevalence of androstenone anosmia ranging from 8 to 24% in females and 13 to 44% in males. Moreover, pleasantness ratings for these odorants appeared to fluctuate across the menstrual cycle, with more unpleasant ratings in the follicular and luteal phases of the cycle and less unpleasant ('neutral') evaluations around the time of ovulation (Hummel *et al.*, 1991). This finding was not replicated in a sample of women who were using oral contraceptives (Grammer, 1993).

Behaviour may be influenced by the presence of androstenone in a sexually dimorphic manner. A sex difference emerged when comparing responses to stimuli of which the participants were unaware. A random chair in a busy dentist's office waiting area was sprayed with androstenone. Seat selection was noted for 840 visiting patients. More women and fewer men chose the androstenone-sprayed chair than would be expected by chance alone (Kirk-Smith & Booth, 1980).

These data suggest that sex hormones may play a role in detection rates and hedonic valence of biological odours and perhaps influence subconscious behaviour (Bremner *et al.*, 2003). However, the effects of sex on odour processing are not limited to sexually relevant odours, as is evidenced by sex differences in odour detection threshold for sexually irrelevant odorants (Wysocki & Gilbert, 1989).

Synchronisation of menstrual cycles—pheromonal effects?

Pheromones (see Chapters 11 and 12) are endogenous compounds that are released by one member of a species and serve to effect behavioural/physiological changes in conspecifics (Karlson & Lüscher, 1959). Although pheromonal effects have been well documented in non-human vertebrates and in invertebrates, the notion that humans are influenced by pheromones remains, to date, unproven and an area of vociferous debate (Doty, 2003). The evidence in support of human pheromonal communication is derived from research on female synchrony of menstrual cycles.

Women who spend much of their time together such as living in dormitories (McClintock, 1971), in extended societies living together (i.e. Bedouin families; Weller & Weller, 1997), cohabitating lesbians (Weller & Weller, 1992; but see also Trevathan *et al.*, 1993; Weller & Weller, 1998), or women who work together (Weller *et al.*, 1999) have been documented to maintain fairly synchronous menstrual cycles. Although there may be social, rather than pheromonal reasons for the timing, such as common food consumed and similar periods of stress (e.g. exams), analyses of control samples argues against this latter explanation. For example, randomly paired subjects within the same dormitory show no greater synchrony than would be expected by chance alone (McClintock, 1971).

This research has been criticised on the basis of retrospective recall of menstrual dates, rather than objective measures of hormonal status. Moreover, the use of oral contraceptives was not always an exclusionary criterion. There tended to be very low response rates of subjects (in those studies in which this variable was reported) and only one menstrual cycle was typically measured (thus ignoring the inherent variability of women's cycles). The results of short-term investigations (four months or less) would suggest that menstrual cycles do appear to converge; however, in those studies in which many important potential confounders were addressed, synchrony has not always been observed (Weller & Weller, 1998). It is possible that long-term menstrual synchrony may not be the most adaptive sexual strategy, and that extended contact may serve to 'dilute' the pheromonal effect (Weller & Weller, 1998).

Female axillary extracts altering timing of ovulation

In rats, two pheromones are thought to mediate synchronisation of ovarian cycles (McClintock, 1984). One of these compounds serves to shorten, while the other appears to lengthen ovarian cycles; they are produced at different times during the oestrous cycle. There is evidence that human females also secrete chemicals that may serve the same purpose. Stern and McClintock (1998)

examined menstrual cycles of 29 regularly cycling young women who did not use oral contraceptives. Nine donor women provided axillary (armpit) secretions during diverse phases of their cycles. These secretions were collected on cotton pads (worn by the donor women) then wiped on the upper lips of the recipient women. In a crossover design, half of the recipient subjects received follicular swabs everyday for two cycles, followed by ovulatory secretions for the following two cycles (again, daily). The other half of the sample received the swabs in reverse order.

In the recipient women, exposure to the follicular compounds induced a shortening of the cycle length. Ovulatory secretions, in contrast, lengthened the cycles. There was no effect for the sequence of compound exposure. These results point to the existence of pheromonal communication in women.

Adaptive strategies for the presence of sex differences in olfactory function

Biological hypotheses

Structural brain differences between men and women are well recognised (Nopoulos *et al.*, 2000). In particular, sexual dimorphisms have been reported in brain regions that are primary or secondary olfactory projection sites (Goldstein *et al.*, 2001). For example, several hypothalamic nuclei show size and total neuronal number differences between men and women (Swaab & Fliers, 1985; Zhou *et al.*, 1995). Moreover, the size of the cerebral hemispheres also shows a sex difference (Goldstein *et al.*, 2001).

The lateralisation of language function has been well documented; yet the existence of sex differences in the degree of lateralisation continues to be debated (Baxter *et al.*, 2003; Shaywitz *et al.*, 1995). Because left hemisphere damage is more likely to produce aphasia in males, McGlone (1977) has suggested that women tend to have language represented in both hemispheres, whereas men are more strongly lateralised. Processing of olfactory information appears to be predominantly controlled by the right hemisphere (Levy *et al.*, 1997; Sobel *et al.*, 1998; Zatorre *et al.*, 1992). Individuals with language function mediated by the right hemisphere may be potentially at an advantage for olfactory tasks that require a verbal component for best performance (e.g. naming, identification, and memory). This potential explanation, however, cannot fully explain the sex differences in olfactory function as performance enhancement on a detection threshold task would not likely be verbally influenced (Lehrner, 1993). However, Herz and von Clef (2001) have described a sex difference in odour intensity ratings that varied as a function of verbal labelling (positive or

negative label), suggesting that top-down processing does indeed influence lower order olfactory processes.

A further biological factor involves the configuration of peripheral structures that could also contribute to the divergent performance between women and men on olfactory acuity measures (Laine-Alava & Minkkinen, 1999). Hornung and Leopold (1999) have proposed that the difference in size of the various compartments within the nasal cavity could account for the female superiority on olfactory testing. In males, the larger capacity of the lateral meatus within the nasal cavity makes it possible that odour molecules will be shunted away from the olfactory epithelium.

Furthermore, the presence of oestrogen receptors in the nasal epithelium may also distinguish males from females, while the differential expression of oestrogen receptors occurring throughout the menstrual cycle may be a factor contributing to increased basal sensitivity to odours (Philpott *et al.*, 2004). In this regard, it has been suggested that differences in nasal mucosal swelling across the menstrual cycle (potentially as a result of changes in oestrogen levels) could contribute to the differences that are observed (Haeggstrom *et al.*, 2000; Philpott *et al.*, 2004; but see also Paulsson *et al.*, 1997). Increased mucosal swelling around the time of ovulation might theoretically diminish, rather than enhance, olfactory sensitivity. Nevertheless, decreased nasal resistance in conjunction with improved olfactory sensitivity has been reported at mid-cycle relative to periods of low sex steroid levels (Grillo *et al.*, 2001).

Evolutionary hypotheses

It is possible that the superiority of female olfactory function is, in part, a learned response. Women typically have been responsible for the gathering and preparing of food and the care of children. Accordingly, women may have had to learn to 'trust their noses' in order to discriminate 'good' from 'bad' food or toxic plants and to be able to identify their own children. A survival advantage would follow for those who could detect, discriminate and recall the odour of a noxious food. Consequently, this enhanced ability would confer a greater likelihood of passing on their genes to the next generation. The difference in olfactory threshold between the sexes could be a result of increased exposure and thus familiarity to different odorants (Brand & Millot, 2001). Increased generalised odour experience could potentially underlie a learned ability for women to attend to the salience of weaker odours.

Genetic diversity is accomplished by virtue of maximising differences in phenotypic markers between mates (see also Chapter 9 for further discussion). As a consequence, the resulting offspring are liable to have enhanced adaptive qualities and immunological competence. Normally ovulating women tend to

rate male body odour as more pleasant when the HLA genotypes are most unlike their own (Wedekind & Furi, 1997). This finding suggests that not only may women be able to detect kin and avoid inbreeding based on olfactory cues, but may be also exploiting a biological need to maximise differences in major histocompatibility complex (MHC) genotypes. In this regard, women rate olfaction as one of the most important characteristics when selecting a sexual partner (Herz & Cahill, 1997).

Furthermore, research findings also indicate that women tend to prefer the odour of 'symmetrical males' or those whose genetic blueprint is less likely to have been damaged by genetic or environmental (developmental) aberrations (Gangestad & Thornhill, 1998). This preference is present during ovulation, but disappears at other times during the menstrual cycle. This fact may serve to increase the likelihood of insemination by a male who will enhance the survival probability of potential offspring.

Summary and conclusions

With the advent of more rigorous and validated psychophysical measures to objectively quantify olfactory performance, the literature supports the findings of sex differences in olfactory ability. Females tend to outperform males on virtually all aspects of olfactory processing and throughout all phases of life (pre-menstrual, menstrual and post-menopausal). Across the menstrual cycle, women tend to become more sensitive to odours during the peri-ovulatory period, relative to phases of the cycle in which both oestrogen and progesterone are low. This latter finding suggests that the salience of odours is enhanced during times of peak fertility, though this is also the case for odours that are not 'sexually relevant'. These two major findings imply that the level of circulating sex steroids is only partially responsible for the observed sex differences in olfactory function. Higher order olfactory processing (processing that involves cognitive input such as naming or memory) is also more accurately performed by females than males, but the evidence for sex steroid enhancement on these tasks is weak. As women tend to be superior to men on general verbal abilities, more accurate verbal labelling may also contribute to the olfactory sex differences. However, again this explanation cannot completely account for the sexually dimorphic patterns of this behaviour.

Clearly, chemical communication occurs in humans. Mother–infant bonding is accomplished predominantly by way of odour cues. Odours appear to carry important information regarding fertility status or genetic make up. In humans, the idea that ovulation is 'concealed' is likely incorrect as olfactory cues appear to be strong motivators for copulation. This fascinating area of

research has sparked the interest of many investigators. The upcoming decades will doubtlessly shed light on numerous unanswered questions.

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11

The role of pheromones and chemistry: lessons from comparative anatomy

D. Michael Stoddart

Introduction

The human sense of smell is as much a product of the evolutionary history of humankind as is every other physical characteristic of our species. Current perspectives view the sense of smell as evolved with the air-breathing, terrestrial vertebrates sometime in the Devonian, more than 300 million years ago. In its essential elements, it remains remarkably similar to that from which it evolved, and in physiological terms it is not much different from the common chemical sense found today in fish, aquatic and even terrestrial invertebrates. What is specific to an air-breathing life is the means whereby chemical molecules reach the olfactory mucosa. To achieve this, chemical molecules are swept into the nasal cavity where the inspired airstream is filtered and humidified. Part of the stream sweeps the molecules upwards and backwards and deposits them on the olfactory mucosa.

As discussed in more detail in Chapter 8, the physical nose and lateral conchae are relatively uncomplicated in humans, lacking the whorls and labyrinths formed by the convoluted filamentous scroll bones frequently found in mammals. The nostrils are simple, intact and directed downwards without the lateral flaps or even trumpet-like projections that often typify the nostrils of other mammals. Furthermore, the rhinarium — the patch of skin at the tip of the nose and surrounding the nostrils — is dry; a characteristic shared by humans only with the higher apes and a few non-primate species such as horses, moose and some desert antelopes. These physical differences are the products of the evolution of a species for which the sense of smell is inferior to the acute,

tricolour vision that evolved sometime in our relatively recent past, perhaps at the time when the great apes were diverging from the New and Old World monkeys and adopting a bipedal locomotor stance (Lowenstein & Zihlman, 1988; Sarich & Wilson, 1985). With the head now lifted up from the ground, odorous signals became less important for information about enemies, or where food might be found; and even the sexual condition of a mate was displayed more with visual than olfactory cues. Since that time, the human sense of smell as the primary source of information about the world has steadily diminished, though in the twenty-first century it is far from extinguished.

This chapter traces the evolution of chemical communication in animals and considers how mammals, and humans in particular, use odours in their daily activities. Pheromones — the chemical messengers that pass between individuals much as hormones pass messages within the individual's body, are briefly examined. Finally, the controversial vomeronasal system, which is the secondary olfactory system, is described.

Evolutionary context

The most primitive of organisms are capable of recognising the presence of an unfamiliar chemical in their immediate environment — a process termed 'chemoreception'. An amoeba in a watch-glass will move sharply away from a drop of vinegar introduced at one side. It recognises that the acidic environment is unfavourable, and undertakes a behavioural change to remove itself from the stimulus. In a single-celled animal such as an amoeba, the entire 'body' responds to the introduced chemical. In the more advanced multi-celled animals, a specialised group of cells takes on the role of sensor, just as other specialised cells adopt roles such as food catching, digestion, locomotion, reproduction and respiration. To begin to understand the evolution of the sense of smell, a basic question is why animals need an ability to respond to their environments.

In the example given above, an amoeba that is able to recognise the change in its environment, and respond accordingly, is more likely to survive than another that does not. Current knowledge accepts that life evolved in the sea — an external milieu that is characterised by remarkably constant physical conditions. The depths of the world's oceans must be among the most constant environments on earth. Here there are living examples of animals, having remained unchanged for over 500 million years, about twice as long as air-breathers have walked the surface of Earth. An example is *Lingula*, a persistent member of a minor zoological phylum. At great depths, the marine environment may be

constant, but it is also relatively devoid of food. The shallower parts of the sea, where sunlight can reach, offer immense advantages to marine animals as there are plants here as a source of food. But this region is subject to rapid change in temperature, salinity, pollution through volcanic ash and dust landing on the ocean, and carbon dioxide tension. Animals exploiting this region gain much from being able to utilise its biological productivity but must be able to detect harmful environmental change, and be able to take some form of evasive action when it changes for the worse. But there is another, and in some ways more fundamental reason why animals must be aware of changes in their environments.

Sexual reproduction arose very early in evolutionary time as a means of enabling offspring to emerge with capabilities not identical to those of their parents. Prior to that, reproduction was asexual and took place by the subdivision of parent organisms producing daughter cells that were identical to themselves. In order for evolution through natural selection to proceed, a large pool of slightly different phenotypes available at any one time is required, with each conferring slightly different advantages to their carriers, although only some will survive to reproduce themselves. In this way, genes that confer advantageous characteristics to the individual will tend to be conserved in the population at the expense of those which do not. Sexual reproduction confers enormous advantages over asexual reproduction and has become the dominant form of reproduction. But there are some practical considerations about how sexual reproduction works.

In the ocean, where environmental conditions are remarkably constant, there are few cues to signal the start of the reproductive season. Close to the surface, where daylight and the lunar cycle can be sensed, reproduction can be easily cued by these phenomena. A dramatic example is the annual spawning of the marine bristleworm *Eunice viridis* (the palolo worm) around Fiji and Samoa, which occurs at the third quarter of the moon in October each year. Spawning is induced by hormonal changes in the worms brought about by the *zeitgeber* of lunar and light changes (Barnes *et al.*, 1988). Palolo worms have such acute light receptors that even the time of day for gamete release is accurately synchronised. The reason for the mass-spawning is to increase the chances of male and female sexual products finding one another, and for fertilisation to occur. It is very much higher if all individuals release their gametes simultaneously. If synchronicity did not occur, many gametes would be swept away by tide and current, and reproduction would be less successful. Most marine animals do not reproduce with such flamboyance, instead constraining their reproductive activities to a longer period of time when others of the same species are doing likewise. Almost all synchronise their reproduction to occur during the season

when their offspring can gain maximum advantage before the onset of the next harsh season. There is nothing remarkable about the phenomenon of synchronised reproduction and it is not restricted to the marine environment. It occurs in all biomes; we are familiar with the song birds vying for breeding territories in suburban backyards in spring, salmon making their mid-summer spawning runs up traditional rivers and beachmaster elephant seals waging bloody battles for possession of the largest harems, all of whom must be impregnated in the space of a few weeks. We now focus on the immobile creatures of the ocean, whence our ancestors arose.

It has long been known that marine organisms are able to recognise metabolites associated with sexual maturation of other individuals. Over 30 years ago, Barksdale (1969) demonstrated that sexual reproduction in the marine fungus *Achyla ambisexualis* was coordinated by the presence of two chemical messengers which he called 'A' and 'B'. Female cells release type 'A' messenger into the water, which stimulates male cells to produce specialised male sex organs. These organs then secrete type 'B' messenger into the water, stimulating the female cells to produce eggs. The male cells then send out hyphal strands towards the eggs, enabling fertilisation to occur. Through the interplay of these two messengers diffusing through the water, much as the vinegar in our earlier example of chemoreception, both sexes of this organism coordinated their reproduction. Sandor and Mehdi (1979) subsequently showed that type 'A' messenger is a C_{29} steroid active at concentrations as low as 6 pg/ml. They have also shown that C_{18} and C_{19} steroid precursors have been found in pre-Cambrian rocks over 3200 million years old, suggesting that this class of compound has been around as bio-regulators for a very long time. What is interesting about these finds is that steroidal molecules coordinate the internal sexual development environment of most present-day animals, and now are known to function quite widely as regulators of sexual reproduction. In a further study, Loumaye *et al.* (1982) demonstrated that a necessary mating factor in common yeast is chemically similar to mammalian gonadotrophin-releasing hormone (GnRH). This GnRH is produced in the mammalian hypothalamus from where it passes via the pituitary portal system to the anterior pituitary where it activates the release of luteinising hormone and follicle stimulating hormone. Release of these hormones into the bloodstream by the pituitary body, and their arrival at the ovary, results in the development and shedding of eggs; an event that is a necessary pre-requisite for sexual reproduction to occur. Thus it appears that, for sexual reproduction to occur, animals need to be able to sense what is happening in their external environments – a statement that holds as true for evolutionarily ancient life-forms as for modern species. Is the integration and coordination of sexual reproduction, then, the primary function for chemoreception in animals?

Lessons from comparative anatomy

To parody the great evolutionary biologist Theodosius Dobzhansky (according to whom, 'Nothing in biology makes sense except in the light of evolution'), 'Nothing in biology makes sense except in the light of comparative anatomy'. Comparative anatomy provides a record of how evolutionary processes have moulded tissues and organs, just as the Antarctic ice core provides a clear record of past climates, or mitochondrial DNA records the evolutionary past of a species. The insignificant sea squirt (Class Ascidiacea; Sub-Phylum Urochordata) sitting on the sea floor would not appear to be an ancestor of the vertebrate animals, but examination of its tadpole-like larva reveals the presence of a notochord, the progenitor of the backbone and a primitive nervous system. It is one of the life forms that illustrates the transition stage between invertebrate and vertebrate. Once the larval sea squirt touches down onto a suitable substratum the tail, notochord and nervous system degenerate and the animal takes the form we readily recognise (Figure 11.1). Adult sea squirts have two siphons. An inlet siphon takes water into a perforated bag called the pharynx from which tiny food particles are sieved. The particles move to the bottom of the pharynx and are transferred to a stomach for digestion. Having passed through the sieve, the filtered water is collected in a membranous outer bag and expelled back into the sea through an exhalent siphon (Figure 11.2).

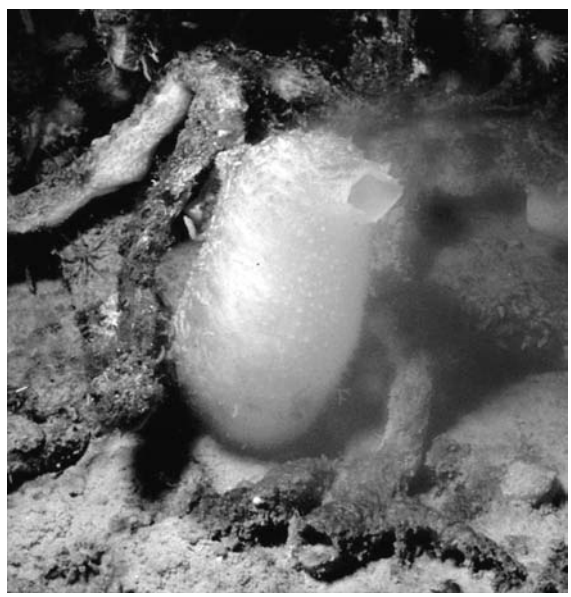

Figure 11.1 A sea squirt *Cnemidocarpa verrucosa* (Photograph by Martin Riddle). For a colour version of this figure please see Plate 2.

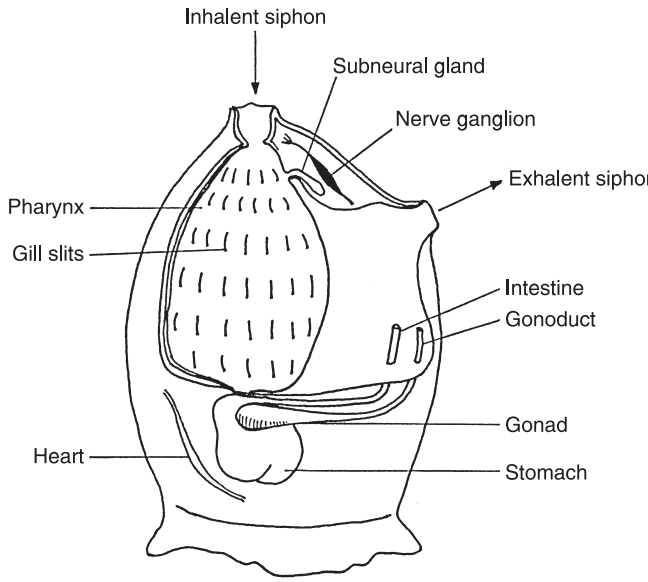

Figure 11.2 Diagram of the internal structure of a sea squirt.

When the nervous system of a larva degenerates, it leaves behind a small piece, called the nerve ganglion, outside the filter basket and high in the body cavity between the inhalent and exhalent siphons. The nerve ganglion has only a few connections to parts of the sea squirt body, including a nerve running to the gonad. Immediately underneath the nerve ganglion lies a small blind-ended arm of the pharynx called the subneural gland, deriving its name from its proximity to the patch of nervous tissue. The subneural gland has long interested comparative anatomists who saw some similarities between it and the anterior pituitary gland, or hypophysis, of mammals (Jefferies, 1986). This is because the gland is derived from the pharynx (as is the anterior pituitary in mammals) and it lies closely attached to the nerve ganglion (the posterior pituitary is derived from the floor of the brain). It is accepted that the mammalian pituitary coordinates the development of sexual maturation and induces the testes and ovaries to secrete the steroid sex hormones testosterone and oestrogen. If the subneural gland/nerve ganglion is homologous with the mammalian pituitary, the complex must play a similar role in sexual reproduction. There is evidence to suggest it does.

Over half a century ago, Carlisle (1951; 1953) demonstrated that if human chorionic gonadotrophin, extracted from the urine of pregnant women, was introduced into the inhalent siphon of a sea squirt, the animal responded by releasing its gametes. After removing the heart and the internal transportation system of the sea squirt, he showed that only gonadotrophin injected very close

to the nerve ganglion elicited the effect, concluding that the subneural gland must be secreting gonadotrophin, or some other chemical messenger with similar effect. The careful introduction of fine particles of carmine dye into the inhalant siphon revealed that some particles were invariably swept up into the subneural gland via a small ciliated funnel at its base. This showed that any eggs or sperm of the same species of sea squirt drawn by the inhalant siphon into the pharynx will trigger the subneural gland to stimulate the nerve ganglion. We can conclude that the subneural gland and its closely associated nerve ganglion are the part of the sea squirt that senses whether other sea squirts are ready to release their gametes, and thus controls synchronous gamete release. It would seem that the subneural gland senses the outside world and passes its information to the sea squirt's somewhat primitive nervous system for action. It acts as though the subneural gland were an aquatic 'nose', confronting the individual's outside world and passing information to the inside world. Figure 11.3a depicts this process diagrammatically.

The science of comparative anatomy of animals teaches important facts about the common origin of the olfactory system and the anterior part of the pituitary. In amphibians the olfactory system and the pituitary are derived from a single patch of embryonic tissue that forms on the surface of the embryo laterally to the tissue that becomes the nervous system (Brunjes & Frazier, 1986; Knouff, 1935). Slightly higher up the evolutionary tree we find exactly the same occurs in the lamprey (*Petromyzon marinus*), a primitive, jawless fish — a remnant of a body form putatively found in the Jurassic, in which the olfactory organ and the anterior pituitary arise from the same plate of embryonic tissue (called the olfactory placode) with the putative nose and pituitary migrating in different directions as the larval fish develops (Woerdeman, 1915). The close association between the olfactory organ and the pituitary body suggests that the precursor of the pituitary was concerned with the coordination and control of reproduction, by sensing the presence in the water of sexual products of another individual and responding by releasing sexual products of the perceiver. As the comparative anatomist Hardistry (1979) states:

> If the pituitary was [originally] concerned with reproductive processes, an association between chemosensory and glandular functions would be hardly surprising.

In humans the anterior pituitary forms from an evagination of the back of the throat (i.e. pharynx) called Rathke's pouch. The tissue it arises from is neural in origin, just as it is in the lamprey and the frog. Quite early in embryonic development (four weeks in humans, Wendell Smith & Williams (1984)), Rathke's pouch starts to migrate upwards to the base of the developing brain, where it fuses with a downwards projection from the floor of the brain to form

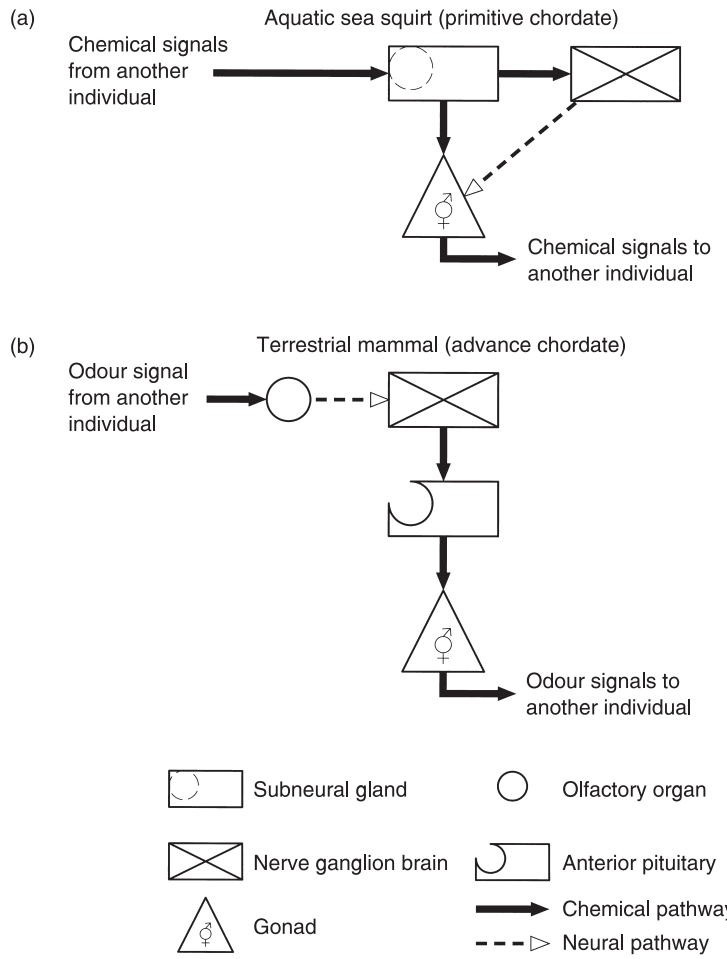

Figure 11.3 Schematic representation of (a) the relationship between the outside world and the sub-neural gland, nerve ganglion and gonad in a sea squirt, and (b) the relationship between the nose, brain and gonad in an air-breathing mammal.

the pituitary body (sometimes called the hypophysis). Its connection with the back of the throat soon atrophies and the pituitary relinquishes all direct contact with the outside world. The mammalian nose becomes relevant here. If the pituitary is to respond to the outside world, then structures need to evolve that will undertake the sensing work and transfer messages back to the glandular tissue.

The pituitary's original role of sensing the outside world for cues about reproduction has been taken over by a specialised structure – the olfactory mucosa of the nose – designed to sense the external chemical world. It is consistent with theories of evolution that the material from which the specialised

structure and the body it stimulates should be fashioned from the same patch of embryonic tissue; evolution works with great parsimony transforming the function of a particular structure through a series of incremental steps. It is not necessary in this case to postulate evolution through convergence — the phenomenon where organs that perform the same function in different types of animals, such as the wings of birds, bats and insects. The olfactory mucosa of the nose can be regarded as a forward functional extension of the pituitary gland designed to sense the external world and to pass its information to the inner world. In air-breathing vertebrates, it communicates directly with the pituitary but via an evolutionarily ancient part of the brain called the rhinencephalon. This structure, sometimes called the 'nose brain', is the dominant part of the brain of the more ancient vertebrates, such as fish. It is retained in the more modern forms, including humans, as the seat of emotion. It is for this evolutionary reason that odours induce such strong emotional responses and why rationality and humanness are no longer olfactory. Figure 11.3b depicts the relationship between the olfactory organ and the gonads, as revealed by the lessons of comparative anatomy.

Mammalian pheromones

Having examined the evolutionary history of the mammalian sense of smell we now review what is known about the mediation of social behaviour and induction of physiological change in mammals through the influence of chemical messengers produced by others. Many years ago two entomologists coined the term 'Pheromone' for a chemical which, when received by an individual other than the one producing it, elicits a stereotypic behavioural or physiological response (Karlson & Lüscher, 1959). Pheromones can be received via olfaction or gustation, that is perception via the sense of smell. *Sensu stricto*, this is not a defining characteristic of what constitutes a pheromone. The defining characteristic is that the perceiver of the chemical signals responds stereotypically and that its behaviour is not overridden by other stimuli. The control of insect pests through the use of olfactorily acting pheromone-baited traps is widely practised in orchards, forests and other environments around the world to great effect and is an example of the use of pheromones to attract one sex (usually the male) to the other for mating.

The pheromonal world of mammals is far less precise. There is no question that mammals utilise odorous and gustatory cues in many aspects of their lives, including the detection of food; the advertisement of social status; the advertisement of sexual status; the detection and induction of oestrus in females

by males; control of behaviours associated with courtship and mating; the imprinting of new-born young upon their mothers; growth of young; physical and psychosexual development; territorial establishment and maintenance; protection from intraspecific attack; and navigation and homing (Stoddart, 1980). Despite this, and half a century after Karlson and Lüscher's defining work, there is still no certainty that the perceiving mammal reacts to the presence of a particular chemical in a stereotypic manner. The pheromonal concept may have little utility in mammalian biology, for exactly this reason (Doty, 2003). This may be irrelevant but it raises another important issue.

Early in the investigation of mammalian olfactory behaviour, pheromones were thought to be of two types (Wilson & Bossert, 1963). 'Releasing' pheromones were thought to be perceived by the olfactory mucosa of the nose in the way commonly associated with olfaction. These pheromones brought about or released a change in behaviour that could be observed. 'Priming' pheromones were thought to consist of molecules that were too heavy to be airborne and were assessed not by the olfactory mucosa but by the chemosensory epithelium lining the structure known as the vomeronasal organ (VNO), a small bone-covered sac lying above the hard palate and opening into the mouth through two fine ducts. Priming pheromones bring about physiological effects that cannot be instantly seen, such as accelerating the onset of sexual maturation in juvenile female mice by the odorous presence of adult male mice (Bronson, 1979), or inducing resorption of embryos when the newly pregnant female is in the presence of the smell of an unfamiliar male (Bruce, 1959). The question is whether humans possess a VNO, and therefore experience the effects of priming pheromones; this matter is addressed below (see Chapter 8 for further details). Before examining the role of the VNO further, a more complete description of how mammals utilise odorous cues in their daily lives is addressed.

Thanks to their use as, arguably, the most important vehicle for medical research, mice have been extremely well studied but it is necessary to note that the extent to which particulars of mouse biology apply more generally is not well known. Mice are prodigious urinators. Urine is used as scent marks and applied at strategic places in an individual's territory. Their urine contains a class of proteins that carry volatile odours to which other mice respond strongly. Bacchini *et al.* (1992) showed urinary proteins act to bind chemical compounds to which other mice respond, and to release them slowly as the scent marks dry. The suite of pheromones they carry brings about a wide range of behavioural and physiological changes in male and female mice, from stimulating the onset of ovulation in juvenile females through the enhancement of luteinising hormone, the enhancement of aggression in adult males through the raising of their testosterone levels, to providing a means for individual recognition

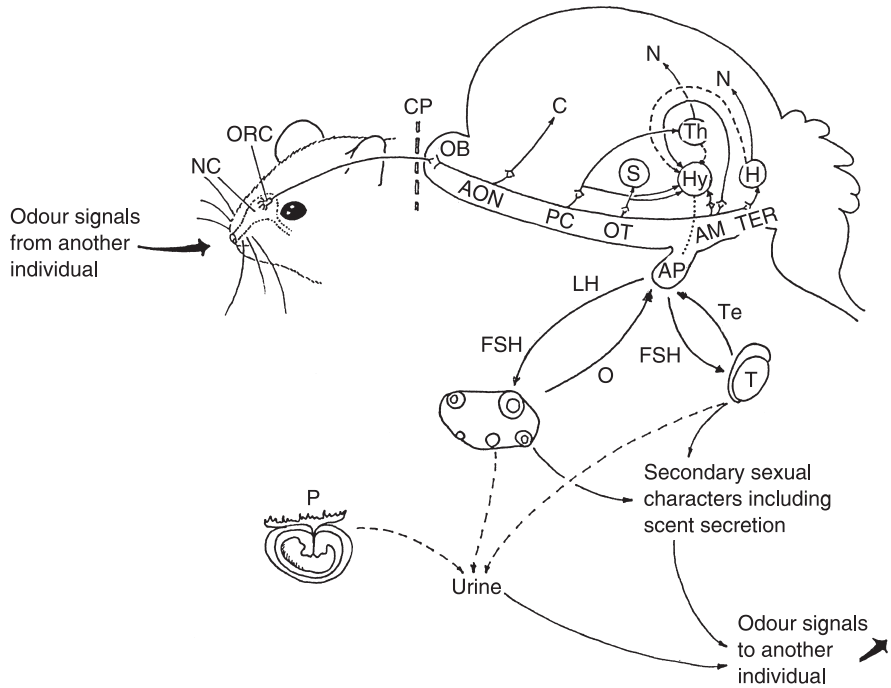

Figure 11.4 The nose–brain–pituitary–gonadal link in mammals.

(Bronson, 1979; Hurst *et al.*, 2001). Whether mice respond stereotypically to these odours, as is required by the strict definition of the term 'pheromone', or not is irrelevant; however, there is overwhelming evidence that chemoreception plays a central role in many aspects of their lives.

Figure 11.4 shows a schematic overview of the pathways in mammals by which odorous information about the external world stimulates the testes and ovaries via the pituitary gland. It should be noted that odours perceived by the nose stimulate various parts of the brain in the thalamo-hypothalamic region of the ancient 'smell-brain', which in turn stimulates the pituitary body. The pituitary body secretes peptide hormones that travel through the bloodstream to the gonads. Under their influence the gonads develop to sexual maturation. The steroid sex hormones produced by the gonads stimulate the development of the many specialised sebaceous scent glands on the skin of mammals whose secretions, together with urinary metabolites from the maturation of eggs and sperm form the odour cues about sexual status that can now be sprayed, dribbled or otherwise applied to the environment, advertising the transmitter's sexual status (Stoddart, 1990).

This brief overview of the complexity of how the nose interacts with the brain and internal milieu of an animal serves to indicate that the olfactory mucosa

of the nose is an organ that stands between the external and internal milieus of an individual. Before examining the function of the vomeronasal organ, some parallels between the nose and the immune system will be made, since both systems function to discriminate between the internal and external milieus of an organism, or to distinguish self from non-self.

The comparison of internal and external milieus

The sense of smell is a system designed such that the external and internal worlds can be compared and their signals analysed to enable consequential activities to be undertaken. As we have seen, comparing self with non-self enabled sexual reproduction to evolve, bringing with it a mixing of genes such that a future generation presents different mixes of adaptations to the forces of natural selection. The choice of a mate plays a crucial role in ensuring a sufficient degree of outbreeding, and is the reason why the marriage of close relatives in humans is outlawed in most human societies. The immune system has evolved to provide the body with a means of recognising alien organisms and destroying them. For the most part the system 'knows' which tissues are part of its own body; this is the key to it being able to recognise invaders. Research on the mouse genome labelled the major histocompatibility complex (MHC) — thought to be responsible for coding the immune system — reveals some interesting observations about how mice are able to detect others that are, in almost every respect, but not totally, identical copies of themselves.

In order to study the MHC, congenic mice need to be bred — these are mice that have identical genetic constitutions except for the genes of the MHC. In a series of experiments in which female mice were allowed to choose which arm of a 'Y' maze they proceeded along and through which flowed air that had passed over the urine of a male of identical MHC constitution as themselves and another male of differing MHC type, the females chose the arm carrying the odour of the different MHC male (Yamazaki *et al.*, 1981). Subsequent research confirmed beyond doubt that the females reacted and responded to odour cues carried in the urine of the males, and that the urinous odour cues owed their origins to the genes governing the immune system (Beauchamp *et al.*, 1985; Yamazaki *et al.*, 2000). In other words, the genes of the MHC advertise themselves through urinary odour cues that enable a female to compare herself with others and to choose non-self on the basis of smell. The mechanism whereby the female 'knows' her own odour and 'knows' not to select an exact copy is not clear, but is of fundamental evolutionary importance. Since the MHC that evolved in response to disease has a high selective value, it is understandable that

MHC genes will be strongly favoured by natural selection. An intriguing notion from Doherty (2004) suggests: 'Is the requirement for immune diversity to counter new pathogens so central to the survival of mammalian species that the olfactory link to MHC Class 1 has been favoured as a further driver of polymorphism?' Perhaps the answer is yes. As the most ancient of the body's sensory systems, it is not surprising that the evolution of the immune system should not have embraced chemosensory communication in its ascendency.

The vomeronasal organ (VNO) and the secondary olfactory system

This final section discusses the priming pheromones and the anatomical apparatus that perceives non-airborne pheromones that are thought to prime the body for future sexual reproduction. The VNO (sometimes known as Jacobson's Organ) was named after its discoverer, the Danish military surgeon Ludwig Levin Jacobson, whose description of it was published in the early nineteenth century (Evans, 2003). Ruysch in 1724 first noted its presence prior to Jacobson, though he made no comment about its internal structure or possible function. The organ is a blind-ended sac that lies close to the hard palate in mammals in the vomer bone and in the vertical structure of the nasal septum. It connects with the mouth via paired ducts that not infrequently lie immediately behind the upper incisors. Jacobson assumed the organ was secretory in nature until the development of electron microscopy revealed that its lumen is lined with olfactory and not secretory mucosa. A VNO occurs in amphibians, reptiles (but not in crocodilians) and mammals, but is absent in birds and fishes (Trotier & Døving, 1998). In the most advanced groups of reptiles, the VNO is the principal route through which information about the outside world passes to the brain. In snakes, the bifid tongue sweeps up molecules from the air and introduces the tips into the large openings of the VNOs in the roof of the mouth, from where they are processed in the VNO (Halpern & Kubie, 1983). The VNO is particularly well developed in mammals, being found in most Orders other than cetaceans (Oelschlager, 1989). It appears to be lacking from adult Old World monkeys and from apes and, for all practical consideration, from humans.

In many Orders of mammals – particularly ungulates, carnivores and marsupials – a specialised behaviour, known by its German name 'flehmen', is displayed as the upper lip is drawn back and an aerosol of inhaled mist is introduced into the exposed entrance to the VNO ducts (Dagg & Taub, 1970). This is often associated with a sharp whistle as air is sucked in during the sharp inspiration. A longitudinal vascular body in the organ increases and decreases in volume, acting as a lumen pump ensuring the inspired aerosol is

drawn deep inside the organ (Mann, 1961). Flehmen is shown more frequently in males than in females and is most commonly observed during the period when the females are in oestrus, though the act of displaying flehmen is neither restricted to males, nor to a particular season of the year (Dagg & Taub, 1970; Verberne, 1976). Flehmen almost always follows nasal sniffing of urine or of the genital area; such stimulation of the primary olfactory system by more volatile molecules appears to be a precursor to VNO stimulation (Evans, 2003).

The developing VNO shares a common embryological site with the olfactory mucosa and the hypophysis – the ventro-medial portion of the olfactory placode (Holtzman & Halpern, 1990). The VNO's neural connections to the brain are distinct and separate from those of the primary olfactory system, passing from the organ to the rhinencephalon and the amygdala region of the limbic system via an accessory olfactory bulb and vomeronasal nerves. The primary and secondary olfactory systems are no longer regarded as being distinct from one another as previously described (Scalia & Winans, 1976), as it has now been shown that the two systems are both able to react to some common chemical compounds (Sipos *et al.*, 1995).

There has been much interest in the possibility that humans possess a functional vomeronasal organ as this might indicate a hitherto little-understood sensory system (Watson, 1999). A sensory system dedicated to sexual awareness would have unfathomable commercial potential. Jacobson, in his original description of the organ in mammals stated '... in the monkeys, it becomes so small that we are prepared to see it vanish completely in man' (Bhatnagar & Smith, 1996). Towards the end of the nineteenth century, Kölliker described the organ in the human fetus and adult, supposing that as the naso-palatine canals leading to the roof of the mouth were so fine that the organ could not sense air and olfactory materials (Bhatnagar & Smith, 1996; 2003). Kölliker was able to determine that the VNO epithelium was well developed and assumed that its function was to produce a secretion to keep the nasal cavity moist. The most recent claims to a functional VNO in adult humans has come from a series of studies carried out in the early 1990s (Monti-Bloch *et al.*, 1998) in which a functional response to putative human pheromones was reported, but these studies have not been confirmed satisfactorily. In a recent treatise on the VNO, Evans (2003) notes that no functional VNO in an adult Old World monkey or in apes or humans has been found, and that a loss of functionality of a secondary olfactory system probably accompanied primate evolution at the end of the late Eocene after the divergence of the New World monkeys. Trotier *et al.* (2000) noted that while an anatomical VNO does sometimes occur in adult humans, this is quite atypical and cannot be taken as evidence for the existence of

a functional secondary olfactory system in humans. Its occasional presence is an example of a once-functional anatomical structure that is now obsolete but the genes for which are still retained within the genome.

Conclusion

This brief account of the evolution of the mammalian sense of smell has endeavoured to demonstrate the close relationship between the olfactory mucosa of the nose and sexual reproduction. Using the techniques of comparative anatomy and homologous function, it has been shown how the part of the brain in air-breathing animals concerned with sexual reproduction communicates with the outside world. It is accepted that, over the course of time, while air-breathing vertebrates have been on dry land, the sense of smell has developed a myriad of functions, quite unrelated to sexual reproduction. Various anatomical structures have evolved to serve precise and accurate food location through stereo-olfactory comparisons of odour plumes (Stoddart, 1979), but in this respect the nose is no different from all other anatomical structures.

Much has been written about sex and the sense of smell, and theories of human well-being have been founded upon them (Stoddart, 1990). Humans are amongst a small minority of mammals that no longer rely upon olfactory information about other individuals and the outside world in the way that most mammals do; instead they rely upon the well-developed visual sense and its speedy connections to the cerebral cortex and logical reasoning. Some individuals have exceptional olfactory ability and can correctly identify a person entering a room, but for most, this remains impossible. Olfactory stimuli may trigger emotions using nervous connections from the olfactory bulb to the limbic system that evolved long before vertebrates first crawled ashore and breathed air. These ancient connections to the emotional centre of our brains allows it to stir long-forgotten memories in a way that sights and sounds cannot. Therapy with aromas may yet offer a powerful avenue for the treatment of psychological and physiological maladies, frequently reported in folklore but still poorly researched by mainstream science.

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12

The impact of olfaction on human social functioning

Dolores Malaspina, Cheryl Corcoran and Nora Goudsmit

Introduction

Social functioning is key to survival and reproduction across species, as it enables the recognition of self, kin, social status, danger and potential mates. For most mammals, social hierarchy and territory are recognised by odour, and smell plays a key role in identifying conspecifics and enemies, and determining safety from danger. The brain circuitry involved in emotional processing and olfactory function is overlapping, and among sensory modalities, olfaction is unique in that it has direct input to the prefrontal cortex as detailed in Chapter 1. This chapter relates the neurobiology of olfactory processing to social functioning in humans, with a focus on schizophrenia to highlight our understanding of compromise of these processes.

In mammals, social functioning is essential for reproduction and survival, and therefore the neural circuitry and hormonal mechanisms underlying social function are likely to be highly conserved across species (see Insel & Fernald, 2004). Although research on the significance of human olfaction and social communication is nascent, smell is known to play a role in mating, parenting, affiliation and prey–predator relationships in other mammals and it is reasonable to expect an association of the olfactory processing system with social functioning in humans as well. Nonetheless, primates in general (and humans in particular) have decreased olfactory acuity compared to rodents and canine species. Over evolution, as humans developed language and other cognitive processes for socialisation, the selective pressure to maintain olfactory genes for survival and social function was reduced and loss-of-function mutations

accumulated in olfactory receptor (OR) genes (Rouquier *et al.*, 2000). However, the evolutionary degradation of OR genes into so called 'pseudogenes' does not preclude a key role for olfactory signaling in organising the fetal brain or in the development or modulation of human social capacities. There is a significant overlap in the neural circuitry that subserves olfaction and social function, and an intimate interplay of these systems with endocrine functioning. Moreover, the neurodevelopment of olfactory and endocrine pathways are interrelated, as the olfactory placode gives rise not only to olfactory receptor cells but also to precursor cells that migrate to the hypothalamus to become the LHRH (luteinising hormone releasing hormone) neurosecretory cells that influence reproductive hormone functioning.

Successful social functioning requires intact recognition of social cues, and hence both sensory and cognitive functions. Social information processing in mammals relies not only on memory formation and motivation, but also the perception of social signals via the main olfactory system and the vomeronasal system.

The emotional processing of diverse stimuli rests on the phylogenetically older limbic circuits that evolved to process odours. They include the entorhinal cortex, a high-level association area. Clearly humans employ vision and hearing for socialisation, particularly observations of behaviour and facial expressions, and perception of language. Yet these associations involve neuronal processing that evolved to link odours to internal mental states, and it is quite possible that these associations may rely on earlier olfactory-based experiences that have conditioned the behavioural states and the endocrine milieu.

The significance of olfaction for social behaviour even in humans is illustrated by the observation that congenitally blind, mute or deaf people normally have intact reproductive–social behaviour, but individuals with congenital anosmia usually do not (Naftolin *et al.*, 1971). Also, in humans, odour conditioning is present in day-old infants (Sullivan *et al.*, 1991), and at two weeks, infants orient more to familiar perfumes (Schleidt & Genzelm, 1990), as well as identify their mothers via smell (Porter & Winberg, 1999; Schaal, 1995). Classic conditioning may link odours to other stimuli in humans through an olfactory-endocrine-neuronal-behavioural sequence, as it does in other mammals. Both conscious and unconscious odour pathways converge at the amygdala (Licht & Meredith, 1987), where odours are identified as aversive or not (Zald & Pardo, 1997), and where odours may be tied to immediate approach or avoidance. Among sensory modalities, only odour information can bypass the thalamus before cortical processing, without intervening connections to more recently evolved cortical areas.

Olfactory systems

As described in more detail in Chapter 1, olfaction may be a sensory modality that evolved early in order to process social information. This sensory modality is comprised of two intricately interwoven olfactory systems in mammals, the accessory and main olfactory systems. The first of these, the accessory system, detects a finite set of pheromones, which are species-specific olfactory signals that convey information relevant for social status and potential reproduction. The second system, the main olfactory system, is able to detect a broad array of odours and is key not only to reproduction and status, but also to the recognition of food and of danger. The importance of the main olfactory system is highlighted by its conservation across species and the potential of olfactory neurons to regenerate (Kandel, 2000). Like other mammals, humans have a thousand highly specific olfactory receptors whose genes constitute more than 1% of the genome (Glusman *et al.*, 2001). Moreover, of all sensory modalities in humans and other species, only olfaction has direct access to the prefrontal cortex, for the fastest route between perception and action. The circuitry by which olfaction can impact social function includes interconnections between the nasal epithelium/olfactory bulb, the ventromedial forebrain, the corticomedial amygdala and the medial septal and preoptic area through to the hypothalamus and median eminence.

Both olfactory systems may also be relevant to social affiliation and reproduction, including through pheromones. Although the role of pheromones and of the accessory olfactory system in humans has been debated, there is substantial evidence that we have behavioural and neuroendocrine responses to unconsciously perceived pheromones. For example, menstrual cycle synchronisation in women is unequivocally due to pheromones (Stern & McClintock, 1998; and see Chapter 10). Women emit one pheromone at ovulation and another in the follicular stage, and these respectively lengthen and shorten the cycles of other women by altering the timing of ovulation, which results from an ovulatory LH surge triggered by increasing oestradiol. Pheromones therefore translate a social environment into differential secretion of LHRH, LH and FSH to coordinate group fertility. Achievement of menstrual synchrony requires adequate androstenol detection (Morofushi *et al.*, 2000). Additionally, pheromones (and their relationship to HLA markers) may underlie preferences by women for odours of particular men. Thus, women rated T-shirt odours of men who differed most in HLA markers as having the most pleasant smell (Wedekind *et al.*, 1995). The reader is referred to Chapters 10 & 11 for further detail on these processes.

As described in Chapter 10, it is possible that humans may detect pheromones with their vomeronasal organ (VNO), as do most mammals, or through the main olfactory system. The VNO are paired organs that are readily visualised in about 10% of adult humans (Moran *et al.*, 1991), although they can be seen with careful study in all adults except those with nasal septum pathology (Garcia-Velasco & Mondragon, 1992; Stensaas *et al.*, 1991). Two families of possible human VNO receptor genes are known, but it is unclear whether they have chemosensory function. But even without a functional VNO, pheromonal communication may occur via olfactory or other receptors. Many animals with intact VNO pathways nonetheless use nasal cells to detect pheromones. Even with VNO lesions, newborn rabbits find their mother's nipples using olfactory cues and sheep recognise their own lambs by odour. About 70% of all odours stimulate the trigeminal nerve (TN) chemoreceptors that innervate both the olfactory and VNO cavities in all vertebrates. Further, although VNO output axons and olfactory bulb axons appear to travel in separate pathways, they converge at the amygdala medial nucleus, bed nucleus stria terminalis (BNST) and medial preoptic area (Swann & Fiber, 1997), which is a critical region in regulating mating.

There is significant overlap between the accessory and main olfactory systems. Both systems are intricately involved in the endocrine system, as cells of the VNO, olfactory receptor cells, and neuronal cells rich in LHRH are all derived from the olfactory placode. In the embryo, precursor cells migrate from the placode (along with terminal and VNO nerves) to the olfactory bulb, thence (via fibres that project to the medial septum and preoptic area) to the hypothalamus (Kjaer & Hansen, 1996). These neurons induce forebrain development and play a key role in endocrine function and behaviour by controlling LHRH release and by modulating sensory function and the autonomic nervous system.

Olfaction and development of sex-specific social function

Olfactory regions and the hypothalamus are central to the circuitry of human emotions. Biologically relevant odours may affect human social and reproductive behaviours and have cardiovascular, endocrine and emotional effects, even when unconsciously perceived. Sexual dimorphism of the LHRH system occurs early in embryological development, prior to gonadal ridge formation, possibly induced by genes on the Y-chromosome (Haqq *et al.*, 1994). More LHRH neurons migrate to the hypothalamus in males than in females (Tobet & Fox, 1989). Prenatal sexual differentiation commences in the olfactory system through

Y-chromosome effects that cause sexual dimorphism in the LHRH secreting cells (Segovia & Guillamon, 1993), effects amplified by differential exposure to prenatal oestrogen or testosterone (Nordeen *et al.*, 1985; Matsumoto & Arai, 1986). Maternal and placental hormones also modulate links between the LHRH and the olfactory systems (Rugarli & Ballabio, 1993). Prenatal sex differences allow immediate postnatal pheromone exposure to amplify brain sexual dimorphism. Neural activity determines patterns of connectivity in fetal life, and this stimulation impacts on neurodevelopment. Thus, fetal diethylstilbestrol exposure affects later behaviour and sexual orientation (Ehrhardt *et al.*, 1985; Meyer-Bahlburg *et al.*, 1985).

During life, olfactory stimuli interact with the genetic substrates (sexual dimorphism) of mammalian behaviour via their influence on steroidogenesis (Kohl, 2001). Odours may change gene transcription in the LHRH secretory preoptic septal cells, which induce anterior pituitary secretion of both LH and FSH (Rubin *et al.*, 1995). This leads to increased levels of testosterone or oestrogen, which in turn alter neuronal survival, synaptic plasticity and secondary sexual characteristics. Well-described odour effects on endocrine function include menstrual synchrony induction, dampening of cycle length irregularities by males, beard growth acceleration from exposure to women, the hastening of puberty for females who reside with unrelated males and the augmentation of male testosterone and sexual behaviour by exposure to vaginal secretions (Grammer & Jutte, 1997). Two steroids secreted from human axillae are implicated in interpersonal relationships (Cowly & Brooksbank, 1991; Gustavson *et al.*, 1987): 5-androstenone, which has a urine-like or sandalwood odour, and 3-androstenol, which has a musk-like or floral odour (Wysocki & Beauchamp, 1984).

Overlapping circuitry of olfaction with motivation and emotion

Motivated behaviour is intertwined with olfactory processing through overlap in neural circuitry, including the limbic system (amygdala and entorhinal cortex), temporal and frontal lobes (specifically the orbital and medial prefrontal cortices) and thalamus. Olfactory bulb axons converge in regions critical for regulation of mating, emotion and fear conditioning, including the amygdala medial nucleus, BNST and medial preoptic area (Swann & Fiber, 1997). Motivational aspects of odours arise from the hypothalamus, deriving from input from the amygdala and midbrain.

Olfactory information is projected from the piriform cortex to the mediodorsal thalamus and then via the entorhinal cortex to the orbital

prefrontal cortex (important for motivation), where it converges with other sensory data. The orbital prefrontal cortex participates in high-level cognitive and emotional processes; it responds to the reward associations of stimuli via reciprocal connections with midbrain dopamine cells and the limbic structures of the amygdala, subiculum and entorhinal cortex, allowing for the integration of stimuli with visceral emotions (Öngür & Price, 2000). The relevance of the orbital prefrontal cortex and amygdala to social functioning is evident from lesion studies in primates, which demonstrate increased aggression (Butter & Snyder, 1972) and loss of position in social hierarchies (Myers *et al.*, 1973). In humans, accidental injury of the orbital frontal cortex can lead to loss of normal social behaviour and insight without intellectual loss – the best-known example being Phineas Gage, the railroad worker who suffered a spike piercing his frontal lobes (Harlow, 1868).

The medial prefrontal cortex (MPFC) is the motor correlate of the sensory integration area of the orbitofrontal cortex, and may be the locus of the 'neural representation of the multifaceted self' (Gusnard *et al.*, 2001). The MPFC has a high resting metabolic activity that decreases with goal-directed behaviour (Gusnard *et al.*, 2001). Both the orbital and medial prefrontal cortices (along with the temperoparietal junction and lateral inferior frontal cortex) appear to be relevant for 'mentalising' (Frith & Frith, 1999), which is the ability to represent internally the mental states of others. Our aptitude to explain and predict the behaviour of others, by attributing independent mental states, such as beliefs and desires, is known as 'Theory of Mind' (Gallagher & Frith, 2003.) It has been argued that human social interaction greatly depends on this ability to mentalise or construct a theory of mind. In other mammals, an odour instantaneously evokes the internal representation of another individual. Ontogenetically, more recently acquired cognitive capacities are often elaborated onto existing neural pathways. Thus, it is not surprising that this circuitry, important for mentalising, is integral to the detection of and response to odour.

Further, output from the MPFC provides information about the internal milieu to the viscera. An inability to make appropriate life decisions has been linked to the absence of visceromotor responses (galvanic skin responses) to disturbing scenes (Bechara *et al.*, 2000; Damasio *et al.*, 1990; Nauta, 1971). It is possible that our visceral responses allow us to label a condition as positive or negative, thence permitting correct perceptions and appropriate life choices (Schachter & Singer, 1962). Failure to generate or perceive bodily information ('gut reactions') could lead to social, emotional and cognitive deficits. Hence, this is another way in which circuitry relevant to olfaction, here the MPFC, is related to social function.

Schizophrenia: compromised olfaction and social affiliation

As described in further detail in Chapter 16, odour identification deficits are robustly described in schizophrenia. One view is that such deficits are just an example of the abnormal sensory processing in this complex disease. Another view is that the neural elements in olfactory pathways are a key disturbance in schizophrenia. Arnold *et al.* (2001) reported aberrant cell lineages in olfactory receptor neurons, which have lifelong neurogenesis, in postmortem schizophrenia epithelial cells. The best-replicated cytoarchitectural abnormalities in schizophrenia occur in olfactory areas, including entorhinal cortex, orbital prefrontal cortex and hippocampus. The neurodevelopment of olfactory and endocrine pathways are also interrelated.

Smell identification deficits (SIDs) in schizophrenia are trait-like abnormalities. They exist irrespective of clinical state and medication treatment and, like social dysfunction, occur across the disorders of the schizophrenia spectrum, including schizoaffective disorder and schizotypal personality disorder; they have also been found in individuals at high risk for schizophrenia (Brewer *et al.*, 1996; 2001; 2003; Coleman *et al.*, 2002; Houlihan *et al.*, 1994; Hurwitz *et al.*, 1988; Kopala *et al.*, 1995; 1997; 2001; Malaspina *et al.*, 1994; 1998; Martzke *et al.*, 1997; Moberg *et al.*, 1999; Purdon *et al.*, 1998; Park & Schoppe, 1997; Striebel *et al.*, 1999). Those studies that have examined the relationship of SID to phenomenology in schizophrenia found that smell identification test (SIT) scores were linked to disorganised and depressive symptoms (Brewer *et al.*, 1996), negative symptoms (Corcoran *et al.*, 2005) and flattened affect (Brewer *et al.*, 2001) and with social behaviour deficits on the Life Skills Profile (Brewer *et al.*, 1996). Studies using the University of Pennsylvania Smell Identification Test (UPSIT; Doty *et al.*, 1984; see Chapter 13), a putative measure of olfactory function, indicates that up to 80% of patients with schizophrenia exhibit deficits in odour identification that are sufficient to interfere with adaptive daily functioning, whereas less than 15% of the general population show such deficits (Moberg *et al.*, 1999).

Social deficits represent a significant component of disease expression in schizophrenia. Social deficits are often present from early in life, preceding the onset of psychosis and further deteriorate as the disease progresses. They comprise the most treatment refractory negative symptoms, particularly for patients with familial schizophrenia (Malaspina *et al.*, 2000). The neurobiology of social dysfunction in schizophrenia is unknown; however, olfactory dysfunction has been well described. Smell identification deficits have been linked with negative symptoms and deficit syndrome schizophrenia, but any specificity of SID for social dysfunction has not been studied.

Deficit syndrome schizophrenia (DS) indicates the presence of enduring primary negative symptoms. To identify and classify DS patients, The Schedule for the Deficit Syndrome (SDS) (Kirkpatrick *et al.*, 1989) is commonly used. It is based upon patient and family interviews, chart reviews and discussions with clinical staff. Restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose and diminished social drive characterise the DS. The DS is rated as present if at least two of these symptoms are determined to be severe, primary and stable.

The DS is hypothesised to constitute a homogeneous subgroup of patients within the schizophrenia spectrum (Carpenter *et al.*, 1988), and Kirkpatrick *et al.* (2001) have estimated the prevalence of DS schizophrenia to be about 15% among first-episode patients and 25–30% among those with chronic schizophrenia. Social drive, at face value, is most closely analogous to social affiliation in other mammals. Lack of engagement in social relationships may provide the context in which emotional experience and expression is dampened, communication is impoverished, sense of purpose in life is attenuated, and interests are stunted. Lack of social interest may be central to the lower education and poor vocational and social adaptation of some schizophrenia patients throughout their lives.

Diminished social drive from the SDS, and impaired volition and lack of spontaneity symptoms, described in the commonly used Positive and Negative Symptom Scale (PANSS), have been found to be related to decrements in smell identification ability and impaired volition (see Malaspina & Coleman, 2003). Volition is the extent to which someone posits, initiates, sustains and/or completes goal-directed activity. Avolition is a contemporary conceptualisation of Kraepelin's 'avolitional syndrome', defined as 'a weakening of those emotional activities which permanently form the mainsprings of volition' resulting in 'emotional dullness, failure of mental activity, loss of mastery over volition, of endeavor and of ability for independent action'. It is one of the three core negative symptoms in the DSM-IV diagnostic criteria for schizophrenia. Kraepelin's definition was operationalised in the DS, and the PANSS 'avolition' item considers the overarching definition of Kraepelin's pathological process as well as a specific manifest symptom. The relationship between aspects of volition (emotional regulation) and psychopathology are explored further in Chapter 6.

Conclusions

In summary, schizophrenia can be used as an archetype for social behaviour in humans, as schizophrenia-linked abnormalities in neural development and

regeneration would be expected to affect primary olfactory cortices preferentially, and consequently result in behavioural deficits in both olfaction and social affiliation. Decrements in social drive and SID could result from a common neurodevelopmental aetiopathology. During childhood and adolescence, both social affiliative behaviour and smell identification ability follow a maturational course that depends upon appropriate neural circuitry laid down during fetal life. In the adult brain, neurogenesis continues to occur exclusively in two privileged regions, namely, the olfactory bulb and entorhinal-hippocampal cortex (Kemperman *et al.*, 2000). Anatomical disarray at the level of synapses or neurons or deficient neurotransmitter levels could account for the random, rather than circumscribed, misidentification of specific odours that are found in people with schizophrenia.

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Section III

Assessment and disorders of olfaction

13

Assessment of olfaction

Richard L. Doty

Introduction

Disorders of the sense of smell, which are responsible for most patients' reports of loss of taste, can profoundly influence quality of life. Among 750 patients presenting to our centre with largely olfactory problems, 68% experienced altered quality of life, 46% described changes in appetite or body weight, and 56% reported influences in daily living or psychological well-being (Deems *et al.*, 1991). In addition to the obvious safety consequences of chemosensory dysfunction (e.g. inability to detect leaking gas, spoiled food, smoke, or such hazards as burning electrical wires or cooking food), smell disturbances often adversely affect nutrition, particularly in the elderly, and can result in depression and the generation of feelings of physical and social vulnerability, as well as of victimisation (Van Toller, 1999). The importance of normal smell function in everyday life is highlighted by the consequences of its loss in those who depend on it for their livelihood (e.g. cooks, homemakers, firefighters, plumbers, wine merchants, chemical plant workers).

Olfactory problems are not uncommon, being present in 1 to 2% of the population under the age of 65 years, and in more than 50% of people older than 65 years (Doty *et al.*, 1984; 1986; Hoffman *et al.*, 1998; Schiffman, 1983). As noted in Chapters 14 and 15 of this volume, decrements in olfactory function are among the first clinical signs of Alzheimer's disease and idiopathic Parkinson's disease, and are commonly present in epilepsy, multiple sclerosis and schizophrenia (for a review, see Doty, (2003a); see also Moberg & Turetsky, Chapter 16). Although some patients initially present with a frank complaint

of a smell disturbance, others are unaware of their dysfunction or are extremely inaccurate in assessing its magnitude (Doty *et al.*, 1987; Landis *et al.*, 2003; Nordin *et al.*, 1995), pointing to the need for routine quantitative olfactory assessment. Indeed, a common error on the part of clinicians is to accept a patient's report of sensory dysfunction at face value and to fail to verify the presence or magnitude of the problem with appropriate testing. Quantitative chemosensory testing is essential to (a) characterise the nature and degree of the problem accurately; (b) establish the validity of the patient's complaint, including the detection of malingering; (c) monitor changes in function over time; (d) establish efficacy of treatment and management programmes; and (e) provide objective data for establishing disability compensation.

Over the last several decades, easy-to-administer clinical tests of smell function have been developed, a number of which are commercially available. Such psychophysical tests, the most widely used of which are discussed in detail later in this chapter, are listed in Table 13.1. Electrophysiological tests are available in some specialized medical centres, including odour event-related potentials (OERPs) and a summated potential recorded from the surface of the olfactory epithelium (the electro-olfactogram or EOG). Such tests may aid in the detection of malingering and, like psychophysical tests, are sensitive to ageing, gender and a number of diseases (for a review, see Kobal (2003)). Unfortunately, few empirical data are available for assessing normality using these measures, although limited normative OERP data have been published (Murphy *et al.*, 2000). Unlike their visual and auditory counterparts, OERPs are presently *unable* to discern where in the olfactory pathway an anomaly exists. This is not the case with EOGs that can, at least theoretically, establish epithelial dysfunction. However, some diseases accompanied by anosmia can have relatively normal EOGs, (e.g., Kallman's syndrome) and others, such as schizophrenia may have exagerated responses. EOGs are somewhat impractical, since many persons cannot tolerate the insertion and maintenance of electrodes within the unanaesthetised nose. Moreover, standardisation of electrode placement is difficult, and it is not clear whether a given recording is representative of the responses of the whole epithelium. This is because the olfactory epithelium is not a uniform structure, exhibiting cumulative age-related damage from metaplasia of islands of respiratory-like epithelium that can influence recordings from specific regions. Given the cost and complexity of electrophysiological tests, and the fact that they add little to clinical assessment based upon psychophysical testing, they are not widely used and are not discussed further in this chapter.

Table 13.1. Clinical tests of smell function

Description	References
Alcohol Sniff Test (AST)	Davidson & Murphy, 1997
Barcelona Smell Test	Cardesin *et al.*, 2006
Brief-Smell Identification Test™ (B-SIT; also known as the Cross-Cultural Smell Identification Test™)	Doty *et al.*, 1996
Combined Olfactory Test	Robson *et al.*, 1996
Jet Stream Olfactometer Test	Ikeda *et al.*, 1999
Odor Confusion Matrix Test	Wright, 1987
Odor Memory Test™ (OMT)	Choudhary, Moberg & Doty, 2003; Doty *et al.*, 1995
Odor Stick Identification Test	Hashimoto *et al.*, 2004
Pocket Smell Test™ (PST)	Duff *et al.*, 2002
Quick Sniff Test™	Gilbert, unpublished
San Diego Odor Identification Test	Anderson *et al.*, 1992
Scandinavian Odor Identification Test (SOIT)	Nordin *et al.*, 1999
Smell Threshold Test™	Doty, 2000
'Sniffin' Sticks' test	Hummel *et al.*, 1997
T&T olfactometer test	Takagi, 1989
The Quick Smell Identification Test™ (Q-SIT)	Jackman & Doty, 2005
University of Pennsylvania Smell Identification Test (UPSIT; known commercially as the Smell Identification Test™ or SIT).	Doty *et al.*, 1984; Doty, 1995
Viennese Olfactory Test Battery (WOTB)	Lehrner & Decke, 1999
Miscellaneous others	e.g. Lecanu *et al.*, 2002; Mosges *et al.*, 1990; Simmen *et al.*, 1999

Threshold measurement procedures

Historically, olfactory threshold measures have been the most common means for assessing smell function quantitatively. This reflects, in part, the early development of threshold methodology, the fact that no physical stimulus dimension analogous to wavelength for colour or frequency for pitch exists for olfaction, and that dilution series of odorants can be easily prepared. A threshold test operationally determines the lowest odorant concentration that can be

detected (the detection threshold), recognised (the recognition threshold) or discerned from another concentration of the same stimulus (the differential threshold). Olfactory threshold values are intuitively acceptable, since they more or less mirror standard procedures used in other sensory sciences, most notably hearing science, for mapping a psychological response to an actual physical entity.[1]

Gustav Fechner formally pioneered the development of modern sensory threshold methodology in his 1860 treatise, *Elemente der Psychophysik* (Fechner, 1860), wherein he described the 'classical' methods for measuring sensory thresholds – the method of limits, the method of constant stimuli and the method of average error. The method of limits and a variant employing a 'staircase' presentation of stimuli are the two most widely used modern olfactory threshold test procedures and are described later in this chapter. Although Fechner is credited as providing the first formal treatise on threshold procedures, workers before him employed, in effect, threshold tests. For example, Weber described differential thresholds in 1834 (Weber, 1834), and Valentin described, in 1848, a procedure in which he mixed a given volume of odorous gas with a volume of air 100 times as large (Valentin, 1848). The resulting dilution was then similarly diluted 100 fold. This process was repeated several times, providing a series of geometrically decreasing concentrations of odorant for sampling.

Today, a number of olfactory threshold tests employing geometric dilution series of odorants are commercially available. Such tests employ liquid diluents, such as water, mineral oil, diethyl phthalate, or propylene glycol, to produce the concentration series. One such test utilises felt tip dispensing agents (Kobal *et al.*, 1996), another glass bottles into which strips of blotter paper are dipped (Yoshida, 1984), and others, plastic squeeze bottles (Amoore & Ollman, 1983; Doty, 2000). One of the more popular of such tests, the Smell Threshold Test™ (STT), is pictured in Figure 13.1. This test employs a single staircase (SS) presentation procedure and 17 dilution steps of the odorant phenyl ethyl alcohol spanning the 10^{-10} to 10^{-2} vol/vol concentration range in half-log steps. Phenyl ethyl alcohol is used because it has little or no ability to stimulate

[1] The concept of threshold, which has ancient origins, was employed in the thinking of Gottfried Wilhelm von Leibniz (1646–1716), the co-discoverer of integral and differential calculus, and Johann Friedrich Herbart (1776–1841), the creator of a so-called mental calculus Herbart (1824). Herbart posited that the mind consists of conscious and unconscious elements and that ideas cross back and forth between the boundary (threshold) of these elements. In his philosophical schemata, some ideas are dominant over others, thereby keeping the other ideas from reaching the threshold of consciousness. Herbart's concepts were employed nearly a century later by Sigmund Freud as a cornerstone of psychoanalytic theory.

Figure 13.1 An example of a commercially-available detection threshold test kit. In this test, standardised forms are used with randomised presentation orders to present stimuli in a single staircase (SS) procedure. Environmental temperature is recorded, and the geometric mean of the last of four staircase procedures serves as the threshold estimate. Photograph courtesy of Sensonics, Inc., Haddon Hts., NJ, USA.

trigeminal nerve (CNV) afferents within the nasal mucosa that may confound the olfactory measure (Doty *et al.*, 1978). Versions of this test have been used at the Smell and Taste Center for over two decades (Betchen & Doty, 1998; Deems & Doty, 1987; Doty *et al.*, 1984; 1987; 1995; Smith *et al.*, 1993).

More sophisticated devices for presenting stimuli of defined concentrations to a subject are available. These devices, known as air-dilution olfactometers, capitalise on advances in airflow control technology (e.g. mass flow controllers) and provide stimuli at known concentrations and flow rates uncontaminated by molecules from a liquid diluent. While somewhat cumbersome and impractical in most settings, these devices provide the temporal stimulus control needed for measuring OERPs accurately. A widely used olfactometer is pictured in Figure 13.2.

As noted earlier, the ascending method of limits (AML) and the single staircase (SS) procedures are the two most commonly used olfactory threshold procedures. In the AML procedure, odorants are presented sequentially from low to high concentrations and the point of transition between detection and no detection is estimated. In the SS method, the concentration of the stimulus is increased following trials where incorrect detection occurs, and decreased following trials where correct detection occurs. Numerous algorithms for making the transitions are now available. Most commonly, the geometric mean of

Figure 13.2 A modern air-dilution olfactometer, the Burghard OMB-4, a device that presents odorants to the nasal chambers at well-defined quantities and durations. Left: Subject being presented with odorants and performing a computerized visual attention task. Right: Data collection module. Center: olfactometer body. Photo courtesy of the University of Pennsylvania Smell and Taste Center, Philadelphia, PA, USA.

a number of the up–down transitions ('reversals') is taken as the threshold value. In both the AML and SS procedures, the direction of initial stimulus presentation is made from weak to strong in an effort to reduce potential adaptation effects of prior stimulation, although recent work suggests that such adaptation is minimal at perithreshold concentrations and that threshold values are little influenced by the direction of stimulus concentration presentation (Doty *et al.*, 2003). The reader is referred elsewhere for a review of these and other stimulus presentation techniques (Doty & Laing, 2003).

'Forced-choice' procedures are usually employed in detection threshold testing. In forced-choice tests, the subject is asked to indicate which of two or more stimuli (i.e. an odorant and one or more blanks) seems strongest, rather than simply to report the presence or absence of a smell. This mitigates the influences of response biases (e.g. conservatism or liberalism in reporting the presence of an odour under uncertain conditions) on the sensitivity measure. Such procedures result in more reliable and lower threshold values than non-forced-choice ones (Doty *et al.*, 1995). It is important to be aware that the nature of the instructions given to the subject in threshold tests are crucial. For example, instructions that ask the subject to report which stimulus produces an odour, rather than which stimulus is stronger, can result in spuriously high

threshold values, since odour quality is usually first apparent only at higher perithreshold concentrations.

It is often said that threshold measures exhibit considerable within- and across-subject variability, and several studies note such variability. Yoshida (1984), for example, using a non-forced-choice single AML threshold procedure, noted inter-subject variation on the order of 16 log units. Stevens *et al.* (1988) collected 60 threshold values over the course of 30 days from three subjects (20 for butanol, 20 for pyridine, and 20 for phenyl-ethylmethylethylcarbinol) using a single forced-choice ascending threshold series. Intrasubject variability across test days was as great as intersubject variability on a given test day, leading to the conclusion that the large inter-individual differences noted by others reflect day-to-day fluctuations in thresholds. However, both of these studies employed a relatively unreliable single AML psychophysical procedure that results in a variable and biased threshold estimate, producing too low a value when the number of trials is less than 15 and too high a value when the number of trials is greater than 15 (Linschoten *et al.*, 2001). In contrast to the AML procedure, the SS procedure does not result in marked day-to-day threshold fluctuations among individual subjects, although obvious influences of age, gender and other between-subject factors are found. As described in detail later in this chapter, the stability or reliability of a threshold measure is predictably related to the number of trials that are presented.

Suprathreshold measurement procedures

Unlike threshold tests, suprathreshold tests employ clearly discernible (i.e. above threshold) stimuli. Among such tests are those of odour identification, recognition, discrimination, memory and attribute scaling; the latter employs, for example, rating scales and magnitude estimation procedures.

Rating scales

Rating scales are the most common procedures used to establish the relative amount of a psychological attribute (e.g. odour intensity or pleasantness) perceived by a subject. Rating scales have been around during much of recorded history. According to McReynolds and Ludwig (1987), Galen employed a rudimentary hot–cold scale that later led to hot and cold body temperature scales employed by physicians as late as the seventeenth century. The use of such scales in medicine became obsolete following the development of the thermometer, although psychological scales denoting subjective sensations of coolness and warmth continue to this day. Christian Thomasius (1655–1728),

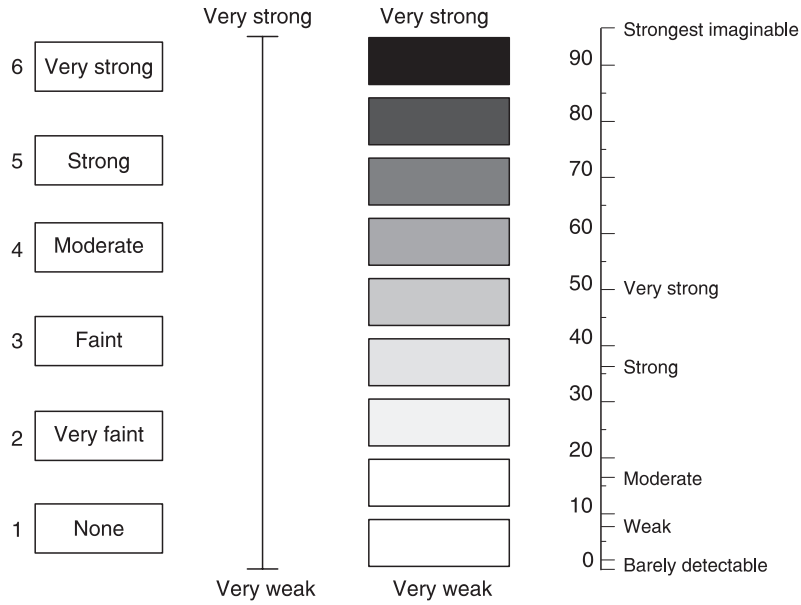

Figure 13.3 Examples of four types of rating scales. From left to right: (a) a standard category scale in which the subject provides answers in discrete categories; (b) a visual analog or graphic scale with anchors (descriptors) at each end; (c) a category scale with logarithmic visual density referents to denote non-linear increasing magnitudes of sensation, with verbal anchors at each end; (d) a labelled magnitude scale with labels or anchors positioned in logarithmic fashion. In these examples, the scales are oriented in a vertical position; in most cases, such scales are presented in a horizontal (left:right) configuration. Copyright © 2002, Richard L. Doty.

the Professor of Jurisprudence at The University of Halle (1694–1724), is credited with having applied attribute scales to quantify such psychological attributes as sensuousness, acquisitiveness and social ambition (McReynolds & Ludwig, 1987). In 1807, the British Navy adopted what was essentially a 12-point rating scale for assessing wind strength (0 = calm, 12 = hurricane), and in 1876, J. W. Osborn and his colleagues rated perceived climatic temperature on a scale of 1 to 20 (1 = unbearably cold, 20 = intolerably hot (McReynolds & Ludwig, 1987)). Rating scales were subsequently employed by Sir Francis Galton (Galton, 1883) and others (e.g. Major, 1895) for assessing a number of sensory and psychological attributes. Apparently rating scales were first introduced to the food industry in the 1950s by Peryam and Pilgrim (see Peryam & Pilgrim, 1957).

Rating scales are intuitive and relatively easy to understand and use. Indeed, nearly all persons in industrialised countries have experienced them at one time

or another. In chemosensory testing, two types of rating scales are commonly used: *category scales*, where the subject indicates the perceived amount of the attribute by indicating which of a series of discrete categories best describes the sensation, and *line scales* (also termed visual analogue or graphic scales), where the degree of the attribute is indicated by the placement of a mark along a line that has descriptors located at its extremes. In some cases, verbal descriptors are located only at the ends of the scales (e.g. very weak, very strong), whereas in other cases multiple descriptors are distributed along the scale. Recently, investigators have explicitly incorporated into their scales logarithmic elements (e.g. descriptors placed at geometrical points along the scale) in attempts to overcome the tendency of subjects to cluster responses in extreme categories and to better approximate the magnitude estimation scales described below (e.g., Green *et al.*, 1996). Discussions of the properties of rating scales, including the influence of category number on their psychometric properties, are available elsewhere (Anderson, 1970; Doty, 1991; Lawless *et al.*, 2000). Examples of various rating scales used in olfactory studies are shown in Figure 13.3.

Magnitude estimation procedures

A popular procedure that overcomes to a large degree the clumping of responses in the extreme ends of category scales is termed magnitude estimation, a form of cross-modal matching. In a common adaptation of this procedure, a subject assigns numbers to stimuli in relation to their relative intensity. For example, if a number of 100 is assigned to the perceived intensity of one odorant concentration, a concentration perceived as smelling four times as strong would be assigned a number of 400. If another concentration is perceived as half as strong as the initial one, it would be assigned the value of 50, etc. When a standard referent and number has been pre-assigned by the experimenter to one of the stimuli, the procedure is termed the 'fixed modulus method.' When the subject is allowed to select his or her own number system, the procedure is termed the 'free modulus method.' The key point is that the numbers are assigned in ratio relations to perceived intensities. While magnitude estimation results, to some degree, in a sensory scale with ruler-like properties (i.e. so-called ratio scales, where the psychological distances along the scale have ratio properties and a true zero point), in fact, judgements of odour intensity are relative. Thus, such judgements are influenced by subject idiosyncrasies and contextual factors (e.g., a moderately intense odour is reported as being more intense when presented with weak comparison stimuli than with strong comparison stimuli). For most practical purposes, however, neither the exact form of the underlying psychophysical function nor the influences of stimulus context are of great concern, as long as standardised test procedures are

employed and the responses reliably differentiate among individuals or groups of interest.

Magnitude estimation data are most commonly plotted on log–log coordinates (log magnitude estimates on the ordinate and log odorant concentrations on the abscissa), and the best fitting line is determined using linear regression. The resulting function, $\psi = n \log \phi + \log k$, where ψ = perceived intensity, k = the Y intercept, ϕ = stimulus concentration and n = the slope, can be represented in its exponential form as a power function, $\psi = k \log \phi^n$, where the exponent n is the slope of the function on a log–log plot. In olfaction, n varies in size from odorant to odorant, but is generally less than 1, reflecting a negatively accelerated function on linear coordinates. As noted elsewhere (Doty, 1991), various modifications have been made in this equation in an attempt to correct for such factors as threshold sensitivity and adaptation (see, for example, Overbosch (1986)).

Although the slope of the function relating odorant concentration to perceived intensity reflects the nature of the build-up in sensation relative to concentration, the Y intercept does not accurately signify information about the absolute intensity of the stimuli. This is because of its dependence on the subject's choice of numbers or the standard assigned by the experimenter. To gain additional information from the ordinate position of the function, the method of magnitude matching has been employed (see Marks (1988) for details). In a common application of this method, judgements of the intensity of sensations from two modalities (e.g. loudness, odour intensity) are made on a common magnitude estimation scale. Under the assumption that subjects experience stimuli on one of the continua (i.e. loudness) in a similar manner, differences among their loudness ratings would be expected to reflect differences in number usage. The odour intensity continuum can then be adjusted accordingly. Such normalisation allows, theoretically, for a direct comparison of scale values across subjects. Thus, if the adjusted odour intensity magnitude value for one subject is 10 and for another subject is 20 at the same odorant concentration level, the second subject is presumed to experience twice the odour intensity as the first.

The technique of magnitude estimation can be applied to odour attributes other than intensity. In one procedure, for example, the degree of pleasantness of a series of odorant concentrations is established using positive numbers in ratio estimates, and the degree of unpleasantness by using negative numbers in a similar manner (Doty, 1975). Zero is applied when the stimulus is perceived as neither pleasant nor unpleasant. An example of data employing such a procedure is presented in Figure 13.4. Note that some odours are perceived as more pleasant as concentration increases, whereas for others, the reverse is the case.

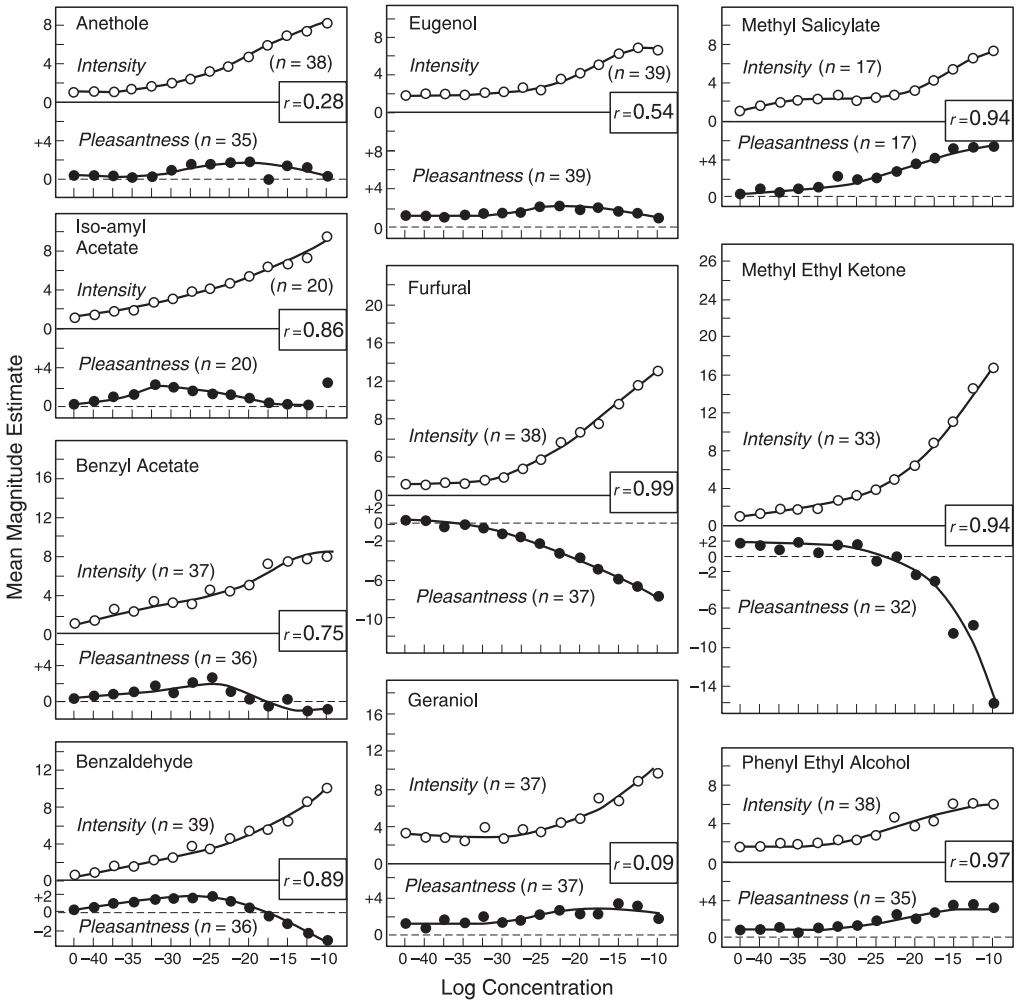

Figure 13.4 Relationship of pleasantness and intensity magnitude estimates to odorant concentration in propylene glycol for 10 odorants. Squares indicate data points not different significantly in intensity from the diluent control, C (t tests, $p < 0.05$). r = Pearson product moment correlation between intensity and pleasantness estimates across data points differing significantly in intensity from control. All correlations significant beyond the 0.01 level with the exception of those for anethole ($p > 0.20$), eugenol ($p > 0.06$) and geraniol ($p > 0.20$). Lines fitted to data points by visual inspection. From Doty *et al.*, 1986.

Some odorants, such as benzaldehyde, are initially more pleasant as concentration increases, but become unpleasant at higher concentrations.

While this procedure for assessing odorant pleasantness/unpleasantness is of considerable value, its scaling relationships can be complicated and can lead

to distortions in the data. Thus, one must be cautious in assuming that accurate ratio relationships between pleasant and unpleasant stimuli are depicted, since (a) the scaling relationships at one end of the continuum (e.g. pleasantness) can be different from those at the other end of the continuum (e.g. unpleasantness) and (b) the direction of the attributes (i.e. greater unpleasantness going in one direction and greater pleasantness going in the other) is reversed on such continua. Moreover, one cannot assume equivalent neutral midpoints for all subjects. One could argue, in fact, that a subject is simply providing, in the same test session, judgements on two separate continua (i.e. pleasantness and unpleasantness) – continua that may not have scale equivalencies. An alternative procedure is first to determine, for a given subject, those odorant concentrations that are perceived as pleasant and those that are perceived as unpleasant, and scale them separately.

Although magnitude estimation has its strengths, other scaling procedures may be more useful in applied applications. In one study, nine-point rating scales, line scales, magnitude estimation, and a hybrid of the category and line scales were comparatively evaluated (Lawless & Malone, 1986a). Specifically, sensations derived from olfactory, visual and tactile stimuli were obtained using each of these methods. In relatively untrained subjects, category and line scales were superior to magnitude estimation and the other procedures in regards to variability, reliability and ease of use. Such factors as mathematical ability, memory and comprehension of directions likely account for this phenomenon, as in a subsequent study of college students and housewives, the inferiority of the magnitude estimation was seen only in the housewives (Lawless & Malone, 1986b).

Odour identification tests

Unlike tests that rely on variations in odorant concentration, odour identification tests exploit a variety of qualitatively distinct odorants and set concentrations of stimuli. The more sophisticated of such tests derive from test measurement theory and focus on the comparative ability of individuals to identify odours. The 40-item University of Pennsylvania Smell Identification Test (UPSIT), known commercially as the Smell Identification Test™, was the first such test to capitalise on this process. This test, which can be self-administered, served as the model for a widely publicised odour survey conducted by the *National Geographic Magazine* in 1987 (Gilbert & Wysocki, 1987). The UPSIT has been translated into numerous languages and has been administered to hundreds of thousands of persons throughout the world. Shorter versions include the 12-odour Brief Smell Identification Test™ (B-SIT; also known as the Cross-Cultural Smell Identification Test™ (Doty *et al.*, 1996; Liu *et al.*, 1995)),

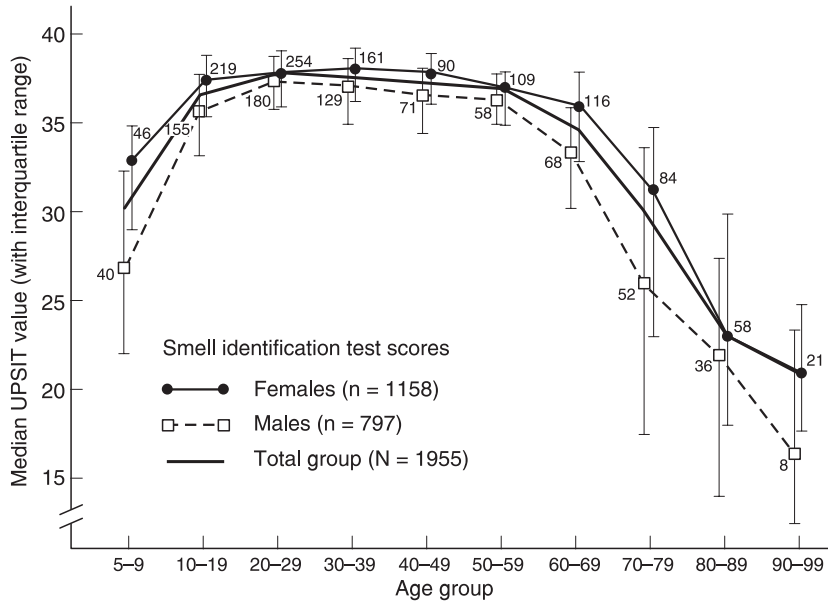

Figure 13.5 Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of age in a large heterogeneous group of 'normal' subjects. Numbers by data points indicate sample sizes. From (Doty *et al.*, 1984).

the 3-odour Pocket Smell Test™ (PST) (Duff *et al.*, 2002) and the 3-odour Quick Smell Identification Test™ (Q-SIT) (Jackman & Doty, 2005).

In all of these tests, the subject smells an odour and then identifies the smell from a list of forced-choice alternatives. This paradigm is surprisingly reliable (e.g. test–retest reliability coefficients for the UPSIT are commonly on the order of 0.95; those for the B-SIT, above 0.70 (Doty *et al.*, 1985)) perhaps because linking an odour to a given object or locale appears to be a quintessential function of the olfactory system. The choice list is critical, as many odours are not readily identifiable without such a list. In the case of the UPSIT, age- and gender-related norms are available, allowing not only for a determination of absolute function (i.e. normosmia, anosmia and mild, moderate or severe microsmia), but also for a percentile rank of the examinee relative to age- and sex-related norms. A determination of malingering can be made, as by chance alone, approximately 25% of the stimuli in a four alternative test should be correctly identified. Malingerers commonly avoid correct answers, thereby exposing their malfeasance. The probabilities of obtaining low numbers of correct responses by chance can be quite low (e.g. obtaining a score of 0 on the UPSIT and not avoiding the correct responses is around 1 in 100,000) (Doty, 1995).

Odour identification testing has contributed significantly to our understanding of human olfaction, both in health and disease. Major findings derived from the UPSIT or one of its variants over the last few decades include the following:

1. Women, on average, have a better sense of smell than men; this superiority is noticeable early in life, does not change at the time of puberty, is culture independent, and is greater in later life (Doty, 1986; Doty *et al.*, 1984; 1985; Liu *et al.*, 1995).
2. Major loss of olfactory function occurs after the age of 65 years, with over half of those between 65 and 80 years of age, and over three-quarters of those 80 years of age and older, having such loss (Figure 13.5) (Doty *et al.*, 1984).
3. There is a substantial genetic influence on the ability to identify odours (Segal & Topolski, 2003) but this influence is not observed in persons over 80 years of age (Christensen *et al.*, upublished).
4. The decrement in olfactory function associated with smoking is present in past smokers and recovery to pre-smoking levels, while possible, can take years, depending upon the duration and amount of past smoking (Frye *et al.*, 1990).
5. Olfactory function is compromised in urban residents and in workers in certain industries, including paper and chemical manufacturing (Corwin *et al.*, 1995; Schwartz *et al.*, 1989; 1990).
6. Odor identification performance decreases with sleep deprivation (Killgore & McBride, 2006)
7. Numerous neurological disorders are differentially associated with smell loss. For example, while Parkinson's disease is strongly associated with such loss, progressive supranuclear palsy — a disorder commonly misdiagnosed as Parkinson's disease — is not (Doty *et al.*, 1988; 1993; see also Hawkes, Chapter 15). Intersetingly, olfactory test scores correlate with the levels of dopamine transporter within the striatum of the brain of patients with early Parkinson's disease (Siderowf *et al.*, 2005).

For a listing of, and a PubMed connection to, the many clinical studies employing the UPSIT and related tests, see the academic publication list at www.smelltest.com.

Odour memory tests

Odour memory tests are more recent introductions than odour threshold or odour identification tests, perhaps because of their complexity and the fact that testing must follow acquisition by some period of time. Relative to most other types of olfactory tests, tests of odour memory appear to have received scant attention, and only one is available commercially for clinical applications

(Bromley & Doty, 1995; Doty, 2003b). However, it is not entirely clear whether such tests, despite their name, are measuring anything more than what is measured by simple match-to-sample discrimination tests or even odour identification tests. Thus, tests of odour memory, detection and identification all exhibit rather robust loadings, in a principal components analysis, on the same principal component (Doty *et al.*, 1994).

While it has been suggested that odours are not forgotten to the same extent as sensory stimuli from other modalities (Engen *et al.*, 1973; Engen & Ross, 1973), this concept appears not to be invariant. Thus, odour memory appears to be influenced by such factors as the stimuli involved and whether testing is performed unilaterally or bilaterally (Bromley & Doty, 1995). As with the case of verbal memory, odour memory appears to be influenced by the richness of the stimulus input, including emotional connotations and associations with semantic and episodic memory systems (Herz, 1998; Larsson & Backman, 1993; 1998; Murphy *et al.*, 1991). Recently, considerable effort has gone into identifying unfamiliar odorants with no or minimal verbal or cognitive referents for research applications (see, for example, Sulmont *et al.* (2002)). This is important because once an odorant is semantically or cognitively labelled, it may be the memory of the label, rather than the odour, that is primarily reflected in the memory score. When this occurs, an odour memory paradigm is conceptually quite different from the paradigm initially employed by Ebbinghaus (1913) and others for memories of nonsense syllables, in which relatively unique entities are put into memory and later recalled without confounding from other associations. The tendency to label odours with cognitive or verbal referents is perhaps not surprising, since odours are largely used to signify and identify environmental animate or inanimate objects, reflected by the fact that nearly all odours are *primarily* classified according to an object referent (e.g. peach, lemon, apple, pizza, strawberry, motor oil, leather, peppermint, faecal matter, medicine-like) or, in cases where such referents are not available, according to hedonic or broad semantic categories (e.g. disgusting, pleasant, unpleasant, fresh, green, lively).[2] The association of odours with concepts or objects may well explain the close correspondence between multidimensional space obtained by using odours alone and that obtained by using concepts of odours (Carrasco & Ridout, 1993).

That being said, odour memory tests may, in some cases, tap mental processes not normally assessed by other types of olfactory tests. For example, we have

[2] The object itself may determine the odour employed in describing it. Morrot *et al.* (2001) showed that odours assigned to wines by experienced wine tasters are largely represented by objects that have a similar colour as the wine. When white wines, which received such descriptors as honey, lemon, grapefruit and peanut, were artificially coloured red, wine tasters switched their descriptions to reflect objects associated with red (e.g. prune, bilberry, cherry, cedar, violet, cinnamon, etc.).

recently found short-term odour memory test scores to be better on the left than the right side of the nose in women but not men (Doty & Kerr, 2005).

Reliability of psychophysical olfactory tests

The stability or reliability of an olfactory test is critical to its validity. Most modern test developers address the issue of reliability, which most commonly is measured as either the correlation between the test or similar forms of the test being administered to the same subjects on two test occasions (test–retest reliability) or as correlations among elements of the same test (intra-test reliability).

In the case of olfactory threshold measures, tests based upon forced-choice procedures are more reliable than those based upon non-forced-choice procedures (Doty *et al.*, 1995). As with educational and psychological tests, the reliability of an olfactory threshold test is generally a function of test length, with greater reliability occurring the more frequently the threshold region is sampled. Koelega (1979) reported test–retest reliability coefficients for a four-alternative forced-choice *n*-amyl acetate threshold test to be 0.65, 0.51 and 0.59 for bilateral, right nostril and left nostril presentations, respectively. Cain and Gent (1991), in a study of 32 subjects ranging in age from 22 to 59 years, found the correlation between single ascending series butanol thresholds determined for the left and right sides of the nose (which they used as a reliability measure) was, at best 0.68 and as low as 0.30 when the butanol threshold was the first in a series of four threshold tests. Heywood and Costanzo (1986) evaluated the test–retest reliability of the ascending butanol threshold procedure in 16 subjects aged 17 to 52 years. The reliability coefficient for the left side of the nose was 0.45 and that for the right, 0.08. Hummel *et al.* (1997) reported the test–retest reliability across 104 subjects on a single ascending butanol threshold component of the 'Sniffin' Sticks' test to be 0.36, a value consistent with other studies employing this odour and threshold procedure. Our group (Doty *et al.*, 1995) found a 0.88 test–retest reliability coefficient for a threshold test that employs a single initially ascending staircase procedure and seven staircase reversals (the last four of which were used as the threshold estimate). When only the first reversal of this test was evaluated for its reliability, the coefficient was within the range of reliability coefficients reported for other thresholds based upon the single ascending series method ($r = 0.45$), emphasising the importance of collecting more than a single reversal in a detection threshold measure. In an empirical assessment of the reliability of threshold tests, it was determined that the number of reversals included in the threshold measure is positively related

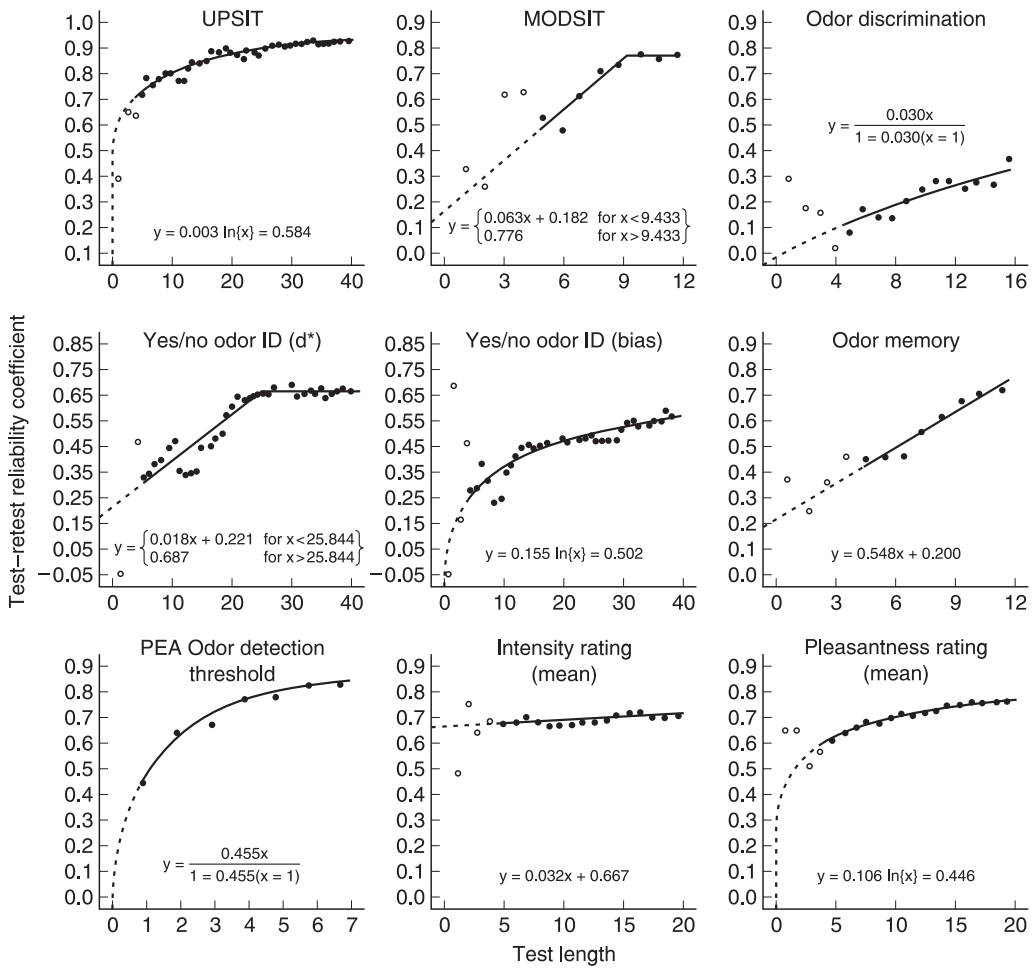

Figure 13.6 Relationship between reliability and olfactory test length for 9 olfactory test measures. Note that in all cases, reliability is clearly correlated with test length. See text for details. From Doty *et al.*, 1995.

to the test's reliability, and reliability is increased as the number of threshold reversals is increased (Doty *et al.*, 1995). The Spearman–Brown Prophesy Formula (Guilford, 1954) provided an excellent fit ($r^2 = 0.98$) to the relationship between the number of reversals included and the reliability coefficient. The relationship between test length and reliability for nine test measures is shown in Figure 13.6.

As in the case of tests of odour threshold, the reliability of odour identification tests depends upon test length. In one study, the reliability coefficient of the 40-item UPSIT was 0.92, whereas the reliability of the one-, two- and

three-booklet fractions of the UPSIT was 0.75, 0.86 and 0.89, respectively (Doty *et al.*, 1989). In another study, the reliability of the 12-item version of the UPSIT (i.e. the Brief Smell Identification Test™) was 0.71, a value similar to a 0.75 value observed in an earlier study of the reliability of a single UPSIT booklet (Doty *et al.*, 1989). More recently, Nordin *et al.* (1998) reported that reliability coefficients for a four-alternative 16-item odour identification test ranged from 0.67 to 0.79, depending upon the subject reference group. A subsequent study of both Swedish and Finnish subjects using this same test found the test–retest reliability to be 0.67 for both nationality groups combined (Nordin *et al.*, 2002). The reliability of the identification component of the 'Sniffin'Sticks' test was reported to be 0.73 (Hummel *et al.*, 1997).

There are few published studies of the reliability of suprathreshold tests other than odour identification tests. In one such study, the test–retest reliability of the mean of suprathreshold ratings given to a range of above-threshold concentrations of amyl acetate was 0.76; the reliability of the slopes of functions fitted to these data was 0.68 (Doty *et al.*, 1995). The reliability of a multiple-target short-term odour memory test (three target odours, six inspection odours) administered to 24 college-age subjects was 0.61 on the left and 0.77 on the right side of the nose. Bilateral testing yielded a reliability coefficient of 0.69. A nine-item single-target odour memory test administered to the same subjects produced reliability coefficients of 0.70 on the left, 0.64 on the right and 0.72 bilaterally. The test–retest interval in these studies was around 7 days. In a subsequent study, a 12-item version of this test was similarly administered twice to 57 subjects on two test occasions separated from one another by two weeks. The reliability coefficient in this case was 0.68.

Relationship between olfactory test measures

To what degree nominally distinct olfactory tests measure independent physiological processes is debatable. In one study, nine olfactory tests, including tests of odour detection, identification, discrimination, memory and suprathreshold intensity and pleasantness perception, were administered to 97 healthy subjects (Doty *et al.*, 1994). A principal components analysis of the correlations among 13 measures derived from these tests revealed four meaningful components. The first comprised strong loadings from a range of measures, including ones from tests of odour identification, detection threshold and memory. The second was made up largely of primary loadings from intensity ratings given to suprathreshold stimuli. The third and fourth components appeared to represent hedonic and response criterion processes, respectively.

This research suggests that conservatism should be exercised in assuming that a test specifically measures an attribute for which it is named. Nearly all tests, for example, require some element of olfactory memory, including forced-choice detection threshold tests. The scores on an odour memory test, for example, are also influenced by factors, other than odour memory such as the ability to encode a distinctly smelling stimulus. Hence one cannot assume simply because the test is called a detection or identification or memory test that it is uniquely tapping one specific attribute of neural process at the exclusion of other neural processes.

Conclusions

It is apparent that olfactory testing can provide reliable and valid assessment of olfactory function useful in a wide range of applications. The reliability and sensitivity of an olfactory test is a function of its length. Thus, while there are a variety of olfactory tests to choose from, shorter tests are comparatively unreliable. Importantly, many olfactory tests, regardless of their name, appear to measure the same underlying neurological processes to one degree or another. These findings suggest that, at least in healthy persons spanning a wide age range, a number of nominally distinct tests of olfactory function measure a common source of variance. Hence, one must be circumspect about inferring from the name of a test its actual physiological referent.

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14

Olfactory impairment in neuropsychiatric disorders

Christos Pantelis and Warrick J. Brewer

Introduction

Being the most evocative of senses, olfaction produces powerful responses in humans and is used as a primitive but potent form of communication among animals. As discussed in Section 1, our understanding of the brain mechanisms underlying olfactory function has improved markedly in recent years, such that brain areas subserving various olfactory abilities have been identified. For example, it has been demonstrated that olfactory function can be broadly divided into acuity, identification ability and olfactory memory, and that each of these are subserved by interrelated cerebral systems. These systems are differentially affected in various neurological and neuropsychiatric disorders. In this chapter we briefly describe the functional neuroanatomical components of olfaction and then summarise the findings in various neurological and psychiatric disorders that are not covered elsewhere (see Chapters 2, 15–18; see also Pantelis *et al.*, 2001).

Neuroanatomical elements of olfactory processing

The functional significance of the components of the olfactory cortex have been determined from experiments in animals, human lesion studies neurological disorders and, more recently from work using newer brain imaging techniques, such as positron emission tomography (PET), and both structural and functional magnetic resonance imaging (fMRI). As described in Chapters 2 and 3, early studies using PET and fMRI indicated that both pleasant and unpleasant odours

activated predicted regions of the entorhinal and orbitofrontal cortices and the amygdala, although odours also activated additional areas in the medial prefrontal cortex including the anterior cingulate gyrus (Levy *et al.*, 1998; Zald *et al.*, 1998). This involvement of areas not traditionally regarded as being part of the olfactory system may reflect engagement of attention and the attachment of meaning to the odours. Interestingly, the act of sniffing in anticipation of any odour also activates piriform cortex in the temporal lobe as well as the medial and posterior aspects of the orbitofrontal gyri (Sobel *et al.*, 1998). This suggests that even the anticipation of odour will activate olfactory processing networks, although it is unclear as to what the intended motor act may contribute here. The same study found that detection of the odour moved the focus of activation in the orbitofrontal cortex (OFC) to the lateral and anterior aspects of the orbitofrontal gyrus. This suggests that sniffing in anticipation of detecting an odour and smelling that odour are represented differently in the frontal cortex. However, cortical activation associated with the detection of odours is part of some supramodal system that attaches meaning to any sensory stimuli, as pleasant smell activated regions in the OFC that were different to those activated by pleasant tastes and pleasant touches (Francis *et al.*, 1999). Interestingly, when patients with hyposmia (who are able to detect but not recognise odours) perform the same olfactory task there is no activation of medial frontal, anterior cingulate, orbitofrontal or temporal lobe areas (Levy *et al.*, 1999). Such studies help to delineate dynamically the neural systems involved in olfaction.

In humans, perhaps, the most informative data regarding olfaction derives from neurological and neuropsychiatric disorders. While knowledge of the pathological processes in neurological disorders has informed our understanding of the olfactory system, one aim of this book, and more specifically this chapter, is to also employ such knowledge to inform our understanding of neuropsychiatric disorders in which pathology is often ill-defined.

Peripheral causes of olfactory deficits

The nasal diseases most frequently responsible for hyposmia and anosmia are those in which hypertrophy and hyperaemia of nasal mucosa block olfactory stimuli from contact with receptor cells; such conditions include allergic, infective or vasomotor rhinitis. In allergic rhinitis, sensory epithelial cells are present, but cilia are shortened and deformed, and hidden under other mucosal cells (Adams & Victor, 1981). Epithelial disorders involving the sensory cells are most often caused by viral infection (influenza—anosmia) or toxic destruction

of the sensory epithelium (solvents or gases) (Huttenbrink, 1995), which can affect acuity. The most common causes of permanent loss of smell are influenza and upper respiratory tract infection. Congestion and swelling of mucous membranes may also result from metabolic and hormonal disorders (Adams & Victor, 1981).

Olfaction in neurology and neuropsychiatry

Independence of function of olfactory abilities has been suggested by studies in neurological patients with lesions in various parts of the olfactory system. Potter and Butters (1980) demonstrated profound olfactory identification (OI) impairments in patients with lesions of the OFC, while odour detection was not impaired. Such dissociation of olfactory function is also observed in Korsakoffs amnestic syndrome (see p. 266, Chronic alcoholism and Korsakoff's phychosis). Potter and Butters (1980) suggest that there is a hierarchical organisation of olfactory processing passing from the medio-dorsal nucleus of the thalamus to the entorhinal cortex, and then to the lateral posterior OFC. They suggest that prefrontal lesions produce more dramatic olfactory impairment than damage to midline structures, such as the thalamus. Further, Jones-Gotman and Zatorre (1988) found that olfactory identification ability was significantly impaired following unilateral excision in the temporal lobe or the OFC on either side, but not after a frontal lobe excision sparing the orbital cortex. Greater deficits in *identification* were associated with the OFC than with lesions of the temporal area. *Thresholds* (measures of acuity) in both groups of lesioned patients were normal. Overall, if the orbital regions are spared, identification ability is maintained, and if they are not, deficits in identification, but not acuity, are found. Projections to the dorsal thalamus and the frontal cortex are the major neocortical representations involved in odour discrimination, and thus involvement of either is inferred in identification deficits (Kopala & Clark, 1990). These principles are discussed in greater detail in Chapters 1 and 2.

Ageing

The available normative data suggest that olfactory functioning decreases with age (Doty, 1989; Kaneda *et al.*, 2000; Knupfer & Speigel, 1986; Schab, 1991; see also Chapter 15). Smell loss occurs with normal ageing due to viral insult, cumulated exposure to toxins, head trauma, and/or calcification of the cribriform plate. Such predominantly peripheral factors impair the ability to detect odours, and consequently higher-order olfactory abilities. While alterations in threshold function may reflect increased peripheral dysfunction

with age, and more complex functions such as discrimination and identification abilities are more likely to reflect central mechanisms (e.g. Koss *et al.*, 1988), such a dichotomy is simplistic (Doty, 1989; see also Chapter 1 and 5). Thus, factors affecting all aspects of olfactory ability involve neurodegenerative processes, genetic factors, personality attributes and environmental factors, albeit differentially. Further confounds in the assessment of olfactory function include the methodological inconsistencies employed in different studies (see Chapter 13).

Larsson *et al.* (2000) examined 532 adults aged between 45 and 87 years and found that both detection and identification were impaired with age. They reported that gender had no effect on detection or identification of odours, and that proficiency in semantic memory, intensity perception and personality style (i.e. neuroticism, impulsivity and lack of assertiveness) were potential predictors for successful odour identification. In a more recent examination of 2491 US subjects aged between 53 and 97 years who participated in a 5-year follow-up, prevalence of identification deficits was 24.5%. The prevalence of dysfunction increased with age, with 62.5% of 80- to 97-year-olds having olfactory impairment, particularly males (Murphy *et al.*, 2002). The most significant association with olfactory impairment in this study was nasal congestion or having an upper respiratory tract infection within the previous week. Other possible aetiological factors for the deficits observed in this study include atrophy of the olfactory bulb and tract (Bhatnagar *et al.*, 1987; Jones & Rog, 1998). These findings are consistent with those from earlier smaller study comparing younger and older males, in which increased task duration was associated with poorer odour discrimination ability (Hulshoff Pol *et al.*, 2000). Structural imaging findings show age-related volume loss in mesial-temporal areas that mediate olfactory sensitivity and discrimination (Jernigan *et al.*, 2001). Moreover, olfactory event-related potentials show longer latencies and smaller amplitudes in older persons (Morgan *et al.*, 1997; Murphy *et al.*, 1994; 2000). In other work, Yousem *et al.* (1997) demonstrated less activation of OFC regions during olfactory stimulation. Interestingly, some evidence suggests that unexplained olfactory identification dysfunction in the presence of one or more APOE-epsilon4 alleles is associated with a high risk of cognitive decline (Graves *et al.*, 1999).

Alzheimer's disease and cortical dementias

Studies in Alzheimer's Disease (AD) have identified impairments in olfaction (Doty, 1991) including difficulties in the ability to identify odours (Royet *et al.*, 2001). This suggests that central mechanisms are involved, although most studies have also found deficits in the ability to *detect* odours (see Harrison

& Pearson, 1989). While the latter finding has often been interpreted as implicating peripheral mechanisms, central mechanisms may also be involved (Doty, 1989). These findings are consistent with neuropathological evidence for typical AD changes in the anterior olfactory nucleus and olfactory bulb, as well as in those olfactory areas described above (amygdala, entorhinal, pyriform cortices and hippocampi) (see Harrison & Pearson, 1989). In keeping with these changes in limbic and paralimbic areas, olfactory memory deficits (OID) may also occur early in the course of AD (Nordin & Murphy, 1996). Furthermore, olfactory identification deficits (OID) may be an early feature of AD, in the presence of intact threshold to detect odours (Koss *et al.*, 1988), though not all studies have confirmed this finding (e.g. Doty *et al.*, 1987; Thompson *et al.*, 1998). Deficits in olfactory function may also discriminate AD from multi-infarct (Knupfer & Spiegel, 1986) or other dementias, though the available reports are inconclusive (Thompson *et al.*, 1998).

In assessing patients with severe cognitive deficits, such as those with advanced AD, it is important to consider how such deficits may affect performance on olfactory tasks. Olfactory deficits are typically assessed by tests of identification ability, discrimination and acuity. As discussed by Peters *et al.* (2003), all these require active co-operation of the subjects and various cognitive functions, including working memory and semantic categorization. In order to address this issue, these authors examined various aspects of olfactory function as well as olfactory event-related potentials in patients with mild AD, patients with mild cognitive impairment (considered preclinical AD patients), compared with age-matched healthy controls. Patients with mild AD and those with mild cognitive impairment were significantly impaired on measures of odour detection threshold, odour discrimination and olfactory identification ability. Significantly more of the patients in both groups also showed no electrophysiological response, indicative of hyposmia and consistent with the neuropathology of the disorder involving medial temporal lobe regions including primary olfactory cortex. While the sample investigated was small, these findings are consistent with those from a larger and more representative cohort of patients with probable AD (Devanand *et al.*, 2000), providing further evidence that such deficits may have clinical utility as an early diagnostic marker for AD.

Subcortical disorders

Parkinson's disease and related disorders

Olfactory function in Parkinson's disease (PD) is reviewed in detail in Chapter 15; here we provide a brief overview. Hawkes *et al.* (1998) found that olfactory identification deficits or abnormal olfactory evoked potentials were

apparent in the majority of patients with established PD, and these patients were more severely impaired than patients with AD, multiple sclerosis (MS) or motor neuron disease. The observed deficits also implicate the involvement of the orbitofrontal cortex (Mayberg *et al.*, 1992). Furthermore, Montgomery *et al.* (1999) demonstrated that a proportion of first-degree relatives of patients with PD demonstrate abnormal olfactory identification ability, suggesting that the University of Pennsylvania Smell Identification Test (UPSIT) (see Chapter 15) may be an early detection tool for the asymptomatic carrier state or risk for PD. Marras *et al.* (2005) investigated 62 male twin pairs discordant for PD and found that OID existed in PD affected twins relative to their unaffected twin, however after a mean interval of 7.3 years, two twins unaffected at baseline had developed PD. Neither had OID at baseline. The presence of cardinal signs of parkinsonism was not associated with lower baseline OI ability, suggesting that OI may not be a sensitive indicator of future PD seven or more years before the development of motor signs, even in a theoretically at-risk population. It has been postulated that the observed OI deficits in PD result from hypodopaminergia, which is the major neurochemical deficit in PD. This may involve dopamine loss in the olfactory tubercle (Quinn *et al.*, 1987) and olfactory bulb (Zucco *et al.*, 1991), or may be associated with depletion of dopamine in some limbic areas (Ward *et al.*, 1983). In contrast, Doty *et al.* (1992) suggest that peripheral mechanisms involving breakdown of the nasal mucosa may be involved.

Katzenschlager and Lees (2004) have considered the issue of specificity in their review of studies of basal ganglia disorders. They concluded that olfactory function is reduced in early PD and in Lewy body dementia, while in progressive supranuclear palsy and corticobasal degeneration there is no impairment of olfactory ability. In multiple system atrophy and in essential tremor the olfactory deficit is mild, as observed in other cerebellar syndromes (see p. 265, degenerative ataxias). These authors consider that impaired olfactory ability may be a useful early marker of PD (for further discussion, the reader is referred to Chapter 15).

Huntington's chorea

Of the few available studies in Huntington's Disease (HD), olfactory deficits have been demonstrated, with identification ability being most impaired. Nordin *et al.* (1995) found a raised threshold for olfactory detection, impaired ability to discriminate smells, and olfactory identification deficits in HD, while odour-recognition memory was intact. Tests of olfaction do not appear to be good indicators of at-risk offspring of HD patients (Moberg & Doty, 1997), or of

asymptomatic gene carriers (Bylsma *et al.*, 1997). However, olfactory dysfunction including impaired olfactory recognition memory may be a reliable early marker of HD after illness onset (Doty, 1991; Moberg *et al.*, 1987). It has been suggested that involvement of frontal-striatal-thalamic circuits, particularly those involving the OFC, caudate and dorsomedial thalamic nucleus may underlie these deficits (Alexander *et al.*, 1986), particularly in identification ability.

Other degenerative disorders

Degenerative ataxias

Connelly *et al.* (2003) administered the UPSIT to patients with ataxias primarily due to cerebellar pathology (spinocerebellar ataxias and related disorders) and to patients with Friedreich ataxia (ataxia associated mainly with loss of afferent cerebellar pathways). Both patient groups had lower UPSIT ability compared to controls, although this was of a lesser degree than observed in other degenerative or neuropsychiatric disorders. The authors suggested that the olfactory dysfunction may be a subtle clinical component of degenerative ataxias, and may be explained by cerebellar degeneration; however, this requires further investigation. Fernandez-Ruiz *et al.* (2003) reached a similar conclusion in their investigation demonstrating olfactory deficits in both basal-ganglia and hereditary ataxia subjects. The role of the cerebellum in olfaction has also been proposed in imaging studies identifying cerebellar activation during olfaction (Sobel *et al.*, 1998).

Human immunodeficiency virus

Deficits in olfactory threshold and identification ability in human immunodeficiency virus (HIV)-infected persons have been consistently reported (see Graham *et al.*, 1995; Razani *et al.*, 1996). Brody *et al.* (1991) reported clinically impaired olfaction in three groups of HIV-infected patients. Asymptomatic patients and patients with clinical evidence of immune compromise showed mild impairments in odour identification ability, whereas dementing patients showed deficits within the moderate range. These authors suggested that mild impairment in olfactory function might be an early indicator of the onset of immune suppression and/or of neurologic disease. While these results received some support from Westervelt and McCaffrey (1997) in their longitudinal study of 'at-risk' HIV negative volunteers, and asymptomatic and symptomatic HIV-infected patients, this study did not identify olfactory deficits in asymptomatic HIV individuals. Further, these studies did not assess olfactory acuity and were not able to exclude the possible contribution of peripheral nerve damage and/or other effects related to treatments, such as AZT (Azidothymidine). Indeed, Hornung *et al.* (1998) identified nasal pathology as the main cause for

variability in olfactory acuity in HIV positive patients, which may partly affect more central olfactory functions. More recently however, Murphy *et al.* (2000) addressed the effects of endoscopic sinus surgery (ESS) on olfactory impairment in HIV positive patients with sinonasal disease before and after surgery utilising a range of measures including nasal cytology, rhinomanometry, nasal endoscopy, olfactory threshold sensitivity and odour identification. They found that significant olfactory sensitivity loss persisted in patients with chronic sinusitis after ESS, suggesting that the impairment in these patients may be due to viral disease rather than inflammation. This receives support from neuropathological studies identifying AIDS virus receptor clusters in limbic system structures, including hippocampus, amygdala and hypothalamus, and in cortical areas including OFC (Ketzler *et al.*, 1990; Pert *et al.*, 1988; Weis *et al.*, 1993), as well as in olfactory nerve fascicles, tracts and bulbs (Lima & Vital, 1994).

Chronic alcoholism and korsakoff's psychosis

Early evidence suggested that individuals with chronic alcohol abuse show deficits in olfactory match-to-sample tests, but not on smell identification (Kesslak *et al.*, 1991). Odour identification was also found to be intact in alcoholic dementia (Serby *et al.*, 1985), while Ditraglia *et al.* (1991) observed olfactory identification deficits in detoxified chronic alcoholics. However, the contribution of general learning and memory deficits to olfactory function in these patients has not been excluded. Rupp *et al.* (2003) demonstrated impaired sensitivity, discrimination and identification ability in non-amnesic and non-demented patients with alcohol dependence (see further discussion of this study in Chapter 7). Korsakoff syndrome patients, in contrast, show relatively intact acuity ability, while identification ability was impaired (Doty *et al.*, 1984a; Jones-Gotman and Zatorre, 1988; Mair *et al.*, 1986; Potter & Butters, 1980). It has been suggested that this may result from the observed degeneration of the dorsomedial thalamic nucleus together with atrophy in the prefrontal areas to which it projects (Jones *et al.*, 1978; Potter & Butters, 1980). Further, volume of the thalamus has been found to be a significant predictor of UPSIT score (Shear *et al.*, 1992). In contrast, in their study of odour detection and discrimination in Korsakoff's patients compared to patients with frontal lobe damage, Hulshoff Pol *et al.* (2002) found that while acuity was unimpaired in either group, odour discrimination was markedly impaired in the frontal lesioned patients rather than in the Korsakoff group. These authors suggested that cortico-cortical rather than thalamo-cortical pathways are involved. However, studies need to examine olfactory identification ability as well as discrimination in Korsakoff patients and in non-demented alcoholic subjects in order to reconcile the discrepancies between the various studies.

Other neurological disorders

Few studies have reported olfactory abnormalities in patients with MS (Doty *et al.*, 1998; Hawkes *et al.*, 1997), and such deficits have been associated with plaque numbers in inferior frontal and temporal lobes (Doty *et al.*, 1998). Zorzon *et al.* (2000) found that MS patients with stable neurological impairment and no recent disease exacerbation exhibited significant relationships between smell loss and lesion load in brain regions (inferior-frontal and temporal lobes) that mediate olfaction. However, as Zivanidov *et al.* (1999) highlight, olfactory identification deficits are also associated with levels of anxiety and depression in MS patients and these confounds need to be addressed in future studies.

Patients with Down's syndrome (DS) demonstrate olfactory deficits related to the onset of Alzheimer-type dementia (Hemdal *et al.*, 1993; McKeown *et al.*, 1996; Warner *et al.*, 1988; see Murphy, 1998 for further discussion).

Solvents and illicit drug use

Mild impairments in odour identification have been reported with low exposure to solvents (Sandmark *et al.*, 1989). Chronic exposure to cadmium fumes impairs odour detection but not identification (Rose *et al.*, 1992). Cacosmia (headaches, nausea and subjective distress when exposed to neutral environmental odours) secondary to organic solvent exposure has been related to impaired verbal learning and visual memory (Ryan *et al.*, 1988). As well as acting on the central nervous system, solvents may act peripherally on nasal mucosa and epithelium to interfere with odour detection (Schwartz *et al.*, 1991). In extreme cases, chemical exposure, usually to a solvent or pesticide, may lead to an extreme sensitised state, diagnosed as multiple chemical sensitivities syndrome (MCSS). This is associated with multiple physical and psychiatric complaints that the sufferer attributes to the chemical substances. To date, however, there is no evidence to suggest that any olfactory mechanism involving fragrance underlies either induction of a sensitised state or the triggering of MCSS symptoms (Ross *et al.*, 1999).

Prolonged use of illicit substances may also have an impact on olfactory function. This may involve direct effects of such substances on olfactory end organs, while the mechanisms underlying addiction may implicate brain regions involved in olfactory ability, such as orbitofrontal areas (Lubman *et al.*, 2004; Yucel *et al.*, 2004; see Chapter 7 for further discussion).

Traumatic brain injury (TBI)

Smell deficits may be found after TBI, particularly when areas involving the olfactory centres are structurally damaged. Doty *et al.* (1997) reported

a high proportion of anosmia (66.8%) in patients with head trauma, though frontal impacts produced less olfactory dysfunction than did posterior or lateral impacts. These post traumatic olfactory deficits generally signify orbitofrontal damage and/or shearing of the olfactory bulbs and are usually permanent. Often, anosmia is caused by damage to the delicate filaments of receptor cells as they pass through the cribriform plate (Adams & Victor, 1981; Lezak, 1983), or from damage to the olfactory bulbs or tracts (Sneider, 1972; in Jones *et al.*, 1975). Deficits in olfactory identification are often associated with lack of awareness of olfactory dysfunction, and are related to injury severity (Callahan & Hinkebein, 2002).

Psychiatric disorders

The discussion in this section is limited to those disorders not examined in detail elsewhere in this book. Schizophrenia is discussed at length in Chapter 16, olfactory hallucinations are covered in Chapter 17, and the olfactory reference syndrome in Chapter 18.

Depression

Results from the few available studies of olfaction in depressed patients are conflicting because of differences in treatment status, use of non-standard odorants or use of irritating odorants (which cause trigeminal nerve activation). See Chapter 16 for further discussion of olfactory dysfunction in affective disorders. Serby *et al.* (1990) found intact olfactory acuity in patients with major depressive disorder (MDD), while Suffin and Gitlin (1986) reported higher olfactory threshold with greater severity of depression. Moberg *et al.* (1986) reported decreased performance in MDD patients on an odour recognition test. Gross-Isseroff *et al.* (1994) demonstrated a significant increase in sensitivity to isoamyl acetate (a traditional odorant used to assess olfactory acuity, which has a low propensity to trigger a trigeminal aversive reaction) after initiation of antidepressant drug therapy in patients with MDD, suggesting that olfactory deficits may be state rather than trait. While Serby *et al.* (1990) found decreased odour identification in MDD, two other studies found no impairment (Amsterdam *et al.*, 1987; Warner *et al.*, 1990). Further, Solomon *et al.* (1998) found intact olfactory identification ability in elderly depressed patients and that presence of olfactory deficits correctly discriminated AD patients from those with MDD. Finally, Postolache *et al.* (1999) reported that, while patients with seasonal affective disorder (SAD) demonstrated no changes in detection or identification ability relative to controls, there was a significant relationship between right nostril UPSIT and depression scores, suggesting that olfaction may be related to fluctuations of right OFC function in this

disorder. Overall, these studies suggest that olfactory deficits are not a prominent feature of depression. This is perhaps not surprising as PET studies in MDD have demonstrated involvement of lateral prefrontal rather than orbitofrontal cortex (Baxter, 1991; Rogers *et al.*, 1998). While the evidence for olfactory identification deficits in depression is not strong, it is a common clinical observation that people who are depressed often report a lowered ability to enjoy odours (see Chapter 3 for further discussion of the neuropathological substrates that may mediate these observations).

Obsessive complusive disorder

Few studies have examined olfactory function in patients with obsessive compulsive disorder (OCD), despite the suggestion that OFC and subcortical nuclei are involved in this condition (Barnett *et al.*, 1999; Rauch *et al.*, 1997). While there are no studies of olfactory memory in OCD, Gross-Isseroff *et al.* (1994) found no impairment in olfactory acuity in 14 patients with OCD, and Hermesh *et al.* (1999) found no difference in olfactory discrimination or acuity in OCD patients compared to controls. In contrast, two other studies have found impaired olfactory identification ability (Barnett *et al.*, 1999; Goldberg *et al.*, 1991) in OCD. Indeed, Barnett *et al.* (1999) in their comparison of 20 patients with OCD with 23 age- and education-matched controls, found that 70% of the OCD patients were microsmic. The findings from these studies suggest a specific impairment of olfactory identification ability, which implicates OFC involvement in this disorder.

Post traumatic stress disorder

In Chapter 6 we described how probes of olfactory function may have utility in mapping disturbances of limbic-prefrontal (especially OFC) pathways and how such compromise may be understood neurodevelopmentally. When exposed to traumatic events, it is possible that a subgroup of those people who develop post traumatic stress disorder (PTSD) may have a higher degree of pre-existing vulnerability to the effects of stress due to deficits in this region with the possibility of increasing sensitisation to the effects of repeated trauma (see Yehuda, 2001 for discussion). Alternatively, the traumatic sequelae of acute stress may trigger compromise of limbic-prefrontal regions. For example, converging evidence from behavioural, neurocognitive and lesion studies suggests that compromise of the OFC and limbic-prefrontal pathways may be implicated in PTSD (Evans *et al.*, 2003; Vasterling *et al.*, 2000; Vermetten & Bremner, (2002)). Vasterling *et al.* (2000) tested the hypothesis that PTSD subjects would exhibit olfactory identification deficits in a sample of Vietnam veterans with PTSD, veterans without PTSD and nonwar zone veterans without PTSD.

Those diagnosed with PTSD performed significantly worse on a task of olfactory identification ability. In contrast, nonwar zone veterans and warzone veterans without PTSD were not impaired, suggesting that the relationship between PTSD and impaired olfactory identification was related to trauma rather than to non-specific aspects of the war experience. This notion also received support in the study by Vasterling *et al.* (2003) who assessed 73 Gulf War Veterans exposed to the warzone on a range of neurocognitive measures, in which no relationship was found between olfactory identification performance and exposure to the warzone or to particular toxins. These findings may provide some evidence for potential OFC compromise prior to the trauma and PTSD onset if lower order compromise of olfactory functioning is considered relatively intact. The study by Vasterling and colleagues (2000) was the first to examine OFC integrity in PTSD using olfactory identification ability as a probe. However, the study was limited, in that the UPSIT was the only measure of OFC functioning, and there were no psychiatric comparison groups or measures of co-morbidity. To date, there are no longitudinal studies to address issues of vulnerability (e.g. in high-risk cohorts), or that examine whether such deficits are related to the severity of the clinical condition.

Developmental disorders

Autism and aspergers syndrome

Recent findings in Autism and the autistic spectrum disorders such as, Aspergers syndrome (AS), implicate compromise of OFC (Bradshaw & Sheppard, 2000; Castelli *et al.*, 2002; Dawson *et al.*, 1998). Given the marked deficits in these disorders in ability to process emotional information, olfactory identification ability as a probe of OFC function would seem an obvious area of enquiry. However, to date there has only been one published study. Suzuki *et al.* (2003) demonstrated that a group of people with AS displayed deficits in odour identification compared with a normal control group. However, this discrepancy may also be attributable to important differences in the age range of the two samples. The clinical group in this study had a mean age of 33 years. Given the known development of the OFC up until early adulthood (Giedd *et al.*, 2001; Sowell *et al.*, 2003), and the concomitant improvement in olfactory identification ability (Doty, 1984b), it is quite possible that the clinical group in this study may 'grow into deficit' as they age.

Brewer *et al.* (manuscript in submission) investigated olfactory identification ability in children with high functioning autism utilising a modified visual analogue of UPSIT in subjects with Autism compared to controls. Fifteen children with high functioning autism (HFA) between the ages of 5 and 9, and fifteen age-, gender- and IQ-matched controls were assessed. The hypothesis

that children with HFA would exhibit impaired olfactory identification ability as measured by the UPSIT in comparison to controls, was not supported. Children in the clinical group demonstrated adequate engagement and capacity to complete the task. However, contrary to that found in the normal population, smell identification ability was not associated with age in the clinical group. The results suggested that some process was disrupting the normal developmental association between olfactory ability and age in the clinical group. Longitudinal studies are needed to further explore these findings further.

Attention deficit hyperactivity disorder (ADHD)

Smell identification in healthy controls appears to depend on increased activation of the right OFC (Good *et al.*, 1998; see also Chapters 2, 3 and 6) and a strong right nostril advantage in smell identification is reported in many studies (e.g. Savage *et al.*, 2002; Zatorre & Jones-Gotman, 1991). Greater impairments in smell identification result from lesions to the right rather than the left hemisphere (Savage *et al.*, 2002). These studies suggest a right hemispheric OFC dominance for normal smell identification.

As right hemisphere OFC deficits have been reported in many studies of children with ADHD (Durston *et al.*, 2004; Stefanatos & Wasserstein, 2001), tests of olfactory identification may also assess the integrity of OFC functioning in children with this disorder. To our knowledge, the UPSIT has been used in only two studies of adults with ADHD. This is surprising considering the weight of evidence implicating OFC dysfunction in ADHD, and the need for early detection and intervention in ADHD with comorbid aggression (Connors *et al.*, 2003; Hartman *et al.*, 2004; Sonuga-Barke *et al.*, 2001). Gansler and colleagues (1998) found that olfactory identification abilities differed between ADHD subgroups. The predominantly inattentive subgroup demonstrated greater impairments on olfactory identification tests compared to the hyperactive group. Murphy and colleagues (2001), however, found that, although olfactory identification was impaired in ADHD adults compared to controls, there was no difference between ADHD subtypes. Only one recent study from our group has examined olfactory identification in children with ADHD (Karsz *et al.*, in submission). We tested the hypothesis that children with ADHD might exhibit OID. As predicted, the children showed poorer olfactory identification abilities overall, but a further prediction of greater OID in aggressive children with ADHD was not supported. These olfactory deficits in ADHD are consistent with reported differences in the underlying neural substrates associated with the disorder, and suggest that OID may be associated with clinical features of this disorder in childhood. Longitudinal studies are needed to examine if these changes are stable features or markers of the illness or whether they

reflect developmental delay in the maturation of such function (see Chapter 6 for further discussion).

Summary

Olfactory deficits are observed in a number of neurological, neurodevelopmental and psychiatric disorders. Such deficits involve different aspects of olfactory function and depend on the nature and extent of neurological involvement. There is evidence to suggest that olfactory functions may be dissociable. The most profound deficits are seen in higher order function involving the ability to identify odours, which implicates OFC integrity. Examination of olfactory disturbances may provide early markers of impending neurological or psychiatric illness and, in some disorders including AD, ADHD and schizophrenia, may be trait markers of the condition.

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15

Olfaction in parkinsonian syndromes

Christopher H. Hawkes

Introduction

Interest in the smell dysfunction of patients with extrapyramidal disorder has increased in recent years with the recognition that most patients with Idiopathic Parkinson's Disease (IPD) are hyposmic and the possibility that olfactory disorder might be an initial event preceding the classical signs of the disease. This has been aided by ^{18}F-dopa positron emission spectroscopy (PET) scan and latterly by the less expensive dopamine transporter scan (DATScan) technique, both of which image cerebral dopamine distribution and raise the possibility of presymptomatic diagnosis. Thus, olfactory disorder can act as a biomarker of a pending disease and may afford the possibility of neuroprotective therapy.

Olfactory testing

Most clinicians do not enquire about olfaction let alone perform any tests of it. At least one-third of the subjects with hyposmia are unaware of their defect (Hawkes *et al.*, 1997) and others complain of loss of taste instead: thus, it is insufficient simply to ask a patient about their sense of smell. Local nasal disease has to be excluded by clinical examination, endoscopy and ideally computed tomography/magnetic resonance imaging (CT/MRI), but a useful clue is that when anosmia is intermittent, the problem is probably conductive i.e. air cannot reach the olfactory neurons in the nose. Conversely, continual anosmia is characteristic of sensorineural loss.

Age has a profound effect on smell function and our recent analysis of smell identification score (Hawkes *et al.*, 2005) showed that ageing effects start

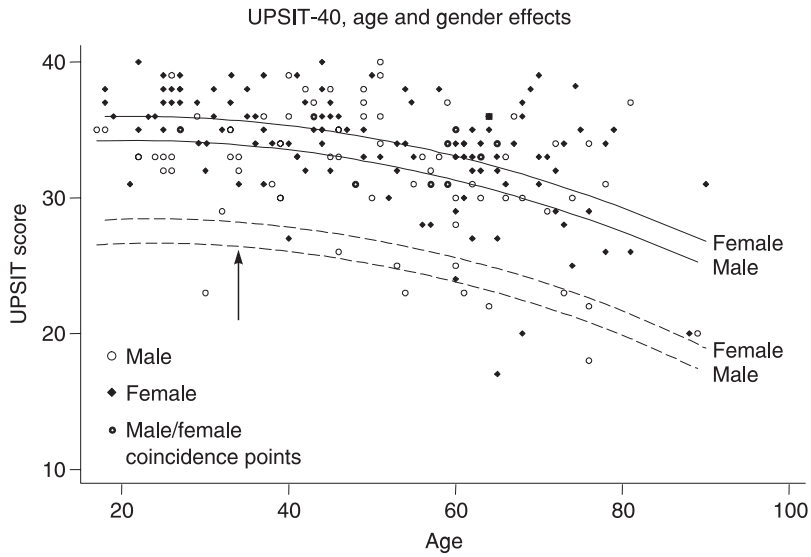

Figure 15.1 Plot of age against UPSIT-40 score in 211 healthy controls. Upper pair of regression lines are mean scores for both sexes and lower dotted pair are 95% limits. Arrow indicates the start of aging process (36 years).

at 36 years (Figure 15.1). There is a gradual decline in both sexes that becomes steeper with age, especially after 65 years, but females always perform better than males irrespective of age. Note should be made of smoking habit. In general, smoking causes a slight impairment in smell sense (Frye *et al.*, 1990), in part, related to nasal congestion. Only a minority of patients with IPD smoke (Tanner *et al.*, 2002), and in the later stages, disability even for the ardent nicotine addict makes the habit increasingly difficult. For these reasons, smoking will have relatively little impact on smell tests provided the nasal passages are clear.

Sniffing enhances smell detection, and apart from redirection of airflow to the olfactory neuroepithelium, functional MRI studies have shown that it activates the pyriform and orbitofrontal cortices (Sobel *et al.*, 1998; see also Chapter 2). In a further meticulous study of sniffing in patients with IPD, Sobel and colleagues (2001) showed that sniffing was impaired in IPD and this caused a slight reduction in their performance on identification and detection threshold tests. This equates to a mean reduction of around 2–3 points on the 40-odour University of Pennsylvania Smell Identification Test (UPSIT-40) (see Chapter 13). Increasing sniff vigour improved the olfactory scores. Studies that have not allowed for this effect (which includes the majority) may tend to exaggerate slightly the severity of any smell defect, especially where bulbar

function is involved. This factor is probably of no relevance in mildly affected individuals, but in the later stages of parkinsonism – especially conditions such as progressive supranuclear palsy – there may be significant problems with bulbar function which in turn will affect sniffing.

Simple bedside tests of smell appreciation are of four types: detection threshold, discrimination, odour memory and identification (see Chapter 13 for further details). Identification tests are rapid and simple to perform and correlate well with threshold and discrimination scores, and for this reason most workers have preferred identification tests unless there is a possibility of cognitive impairment. Many assessments have involved small groups of subjects and test odours have had significant trigeminal (irritant) effects (Mesholam *et al.*, 1998). Prior assessment of cognitive function is clearly important for tests of smell identification and memory. Mild depression and use of antidepressant drugs probably have no important effect on smell identification ability (Amsterdam *et al.*, 1987), but not all agree with this (Serby *et al.*, 1990), and it is better to screen out depressed patients in any research programme. A popular identification procedure for research work is the UPSIT-40 (Doty *et al.*, 1984). This uses microencapsulated odorants that are released on scratching an impregnated strip with a pencil. There are 40 different odours, and a forced choice is made from four answers. Possible answers include the smell of skunk, root beer and pumpkin pie – substances with which non-Americans may be unfamiliar. Undertaking a large local control sample so that cultural differences will be balanced out best circumvents this. Local control data are essential research prerequisites in any event. Another strategy is to employ the smaller International UPSIT-12 kit which has a good cultural cross-platform; inevitably it is less sensitive for research work because of the large variance associated with just 12 test samples. An alternative method of assessing olfaction is by 'Sniffin' Sticks'. This consists of a collection of felt-tip pens impregnated with various odours. Published normative data are available for over 1000 German citizens (Kobel *et al.*, 2000) and assessment may be expressed as a threshold, discrimination and identification score ('TDI index'). 'Sniffin' sticks' will be more time consuming to use if the TDI score is required, but in the long run they are inexpensive. For a more complete description of the assessment of olfaction, the reader is referred to Chapter 13.

This chapter focuses mainly on IPD and familial parkinsonism, as well as the known variants – Guam PD–dementia complex; Lewy body disease (LBD); multiple system atrophy (MSA), Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Drug Induced PD (DIPD), Vascular parkinsonism (VP) and X-linked dystonia-Parkinsonism ('Lubag').

Idiopathic parkinson's disease

Impairment of smell sense in IPD was first documented in 1975 by Ansari and Johnson (1975). The majority of olfactory studies in IPD, have used clinical diagnostic criteria; this is of considerable relevance as the diagnostic error rate of neurologists contrasted with autopsy diagnosis is anything from 10 to 26% (Hughes *et al.*, 1992; 2001). Despite this, it is very likely that patients with IPD have a profound disorder of olfactory function (Doty *et al.*, 1988; Hawkes *et al.*, 1997). This observation is based on pathological abnormality, psychophysical tests and evoked potential studies.

Pathology

Dystrophic neurites but no Lewy bodies were found at autopsy of the olfactory neuroepithelium in two of three patients with IPD, but several patients displayed accumulation of amyloid precursor protein fragments which would not allow distinction from Alzheimer's disease (Crino *et al.*, 1995). All three varieties of synuclein (α, β, γ) are expressed in olfactory neuroepithelium, particularly α-synuclein. This is of potential relevance as a mutation in the gene coding for α-synuclein has been found in a few families of Italian–Greek descent (Polymeropoulos *et al.*, 1997). Unfortunately the expression of α-synuclein was found to be no different from other degenerative diseases (Lewy body disease, Alzheimer's disease, MSA) and seemingly healthy controls (Duda *et al.*, 1999).

In a preliminary study, we examined 'blind' to clinical information, olfactory bulbs and tracts from formalin-fixed brains of eight controls and eight patients with a clinical and pathological diagnosis of IPD taken from the UK Parkinson's Disease Brain Bank (Daniel & Hawkes, 1992). By inspecting the olfactory bulb and tract, all eight cases were correctly diagnosed 'probable PD'. Cortical type Lewy bodies were most numerous in the anterior olfactory nucleus but they were also found in mitral cells. It was subsequently shown that loss of anterior olfactory neurons correlated with disease duration (Pearce *et al.*, 1995).

Braak and colleagues (2003) performed detailed analyses of pathology in IPD in 125 cases. PD-related lesions were identified by immunoreaction to α-synuclein, a protein specific to PD, which is found in Lewy neurites and Lewy bodies. They demonstrated that the pathological process advances in a predictable sequence, but the earliest changes (even before the motor components were present in life) were found in the dorsal motor nuclei of the glossopharyngeal and vagal nerves and the anterior olfactory nucleus. This is a pivotal study as it clearly identifies the dorsal medulla and olfactory bulb as the starting points for IPD.

There have been few studies of the olfactory bulb beyond anatomical description, but it is clear that there is considerable cell loss in the bulb.

The glomerular apparatus seems to vanish in IPD (H. Braak, personal communication). A recent report (Huisman *et al.*, 2004) suggests that expression of tyrosine hydroxylase in the olfactory bulb is increased 100-fold in IPD, and that this might explain the hyposmia of IPD. It is also suggested that increased levels of dopamine in the bulb may explain the lack of response to levodopa. In mouse MPTP models of PD, there is an approximate 4-fold increase of dopamine neurogenesis in the olfactory bulb (Yamada *et al.*, 2004) that probably relates to the migration of dopamine secreting cells from the subventricular zone — the so-called rostral migratory stream (see Chapter 2). This experiment infers that ongoing compensation is taking place and only when the process fails, do the symptoms of disease become apparent.

Psychophysical tests

The first case-control study (Ansari & Johnson, 1975) examined 22 patients with a clinical diagnosis of IPD by detection threshold to amyl acetate. There was a correlation with average olfactory threshold and more rapid disease progression. There appeared to be no influence from medication (levodopa, anticholinergics) or smoking habit. A subsequent larger study in IPD (Quinn *et al.*, 1987) also used detection threshold tests to various concentrations of amyl acetate in 78 subjects and 40 controls. Thresholds were reduced, but no correlation was found with age, sex or use of levodopa. Unlike the first study, there was no correlation with disease duration. The next sizeable olfactory studies (Doty *et al.*, 1988; 1992b) using the UPSIT-40 showed that age-matched olfactory dysfunction did not relate to odour type; it was independent of disease duration and did not correlate with motor function, tremor or cognition. These studies also demonstrated that the deficit was of the same magnitude in both nostrils, and not influenced by anti-Parkinsonian medication. Further evaluation in sub-types of presumed IPD showed that females with mild disability and tremor dominant disease had a significantly higher age-matched UPSIT-40 score than males with moderate to severe disability and little or no tremor; age at disease onset was not relevant (Stern *et al.*, 1994). A comparable survey (Hawkes *et al.*, 1997) was undertaken using the UPSIT-40 in 155 non-depressed, cognitively intact IPD patients aged 34 to 84 years, and 156 age-matched controls (Figure 15.1). The age-matched UPSIT scores for PD patients were significantly lower than for controls (Figure 15.2). Only 19% (30/155) of the PD patients had a score within the level expected for age-matched healthy controls, and 65 (42%) were anosmic. There was no correlation between disease duration and UPSIT score ($r = 0.074$) (Hawkes *et al.*, 1997). Analysis of the 40 individual odours in the UPSIT showed that identification of pizza for age-matched patients was the single most difficult odour and that the combination of pizza and wintergreen

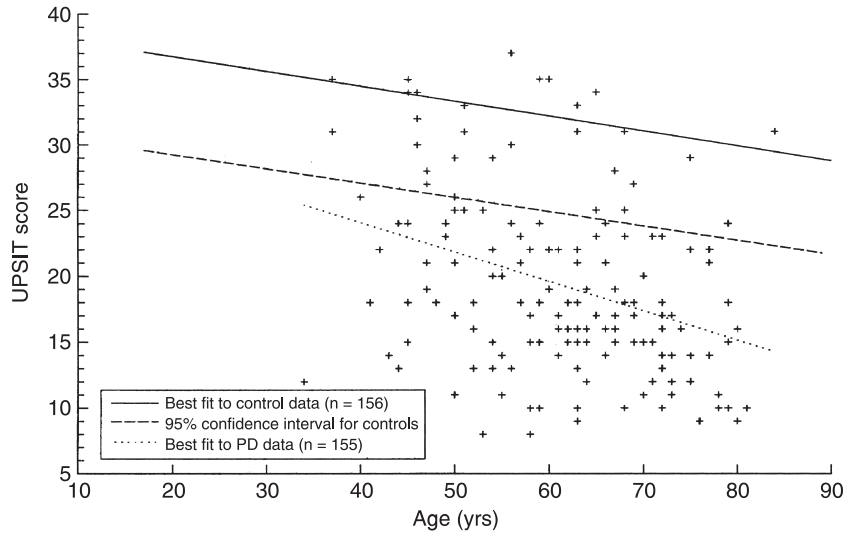

Figure 15.2 UPSIT-40 score vs. age in (IPD) (156 patients). Continuous line is regression line for control mean. Long dotted line is 95% limits for controls and short dotted line is regression line for patients. The + signs represent individual patient scores. See Hawkes *et al.* (1997).

was the best discriminator, with a sensitivity of 90% and specificity of 86% (Hawkes & Shephard, 1993). A degree of selective loss has been found in another series using the 12-odorant UPSIT (Double *et al.*, 2003). Impairment of smell sense has also been documented in IPD patients using Sniffin' Sticks (Daum *et al.*, 2000). According to the most recent study (Tissingh *et al.*, 2001), there was a significant negative correlation between odour discrimination and disease severity, suggesting that as psychophysical tests go, and in contrast with earlier observations, there is some correlation between olfaction and disease severity.

Neurophysiological tests

One of the most informative validated and objective measurements of smell sense is the olfactory (chemosensory) evoked response (OEP) pioneered by Kobal and Plattig (1978). We tested 73 patients with IPD by OEP recording (Hawkes *et al.*, 1997) and compared them to 47 controls of similar age and sex (Figures 15.3 and 15.4). None were depressed, all were cognitively intact and all had a clinical diagnosis of IPD. In 36 patients (49%), responses were either absent or unsatisfactory for technical reasons. Regression analysis on the 37 with a measurable trace showed that for hydrogen sulphide (H_2S) a highly significant latency difference existed between diagnostic groups (i.e. control or PD). Assuming that those who had no detectable OEP were abnormal, and combining

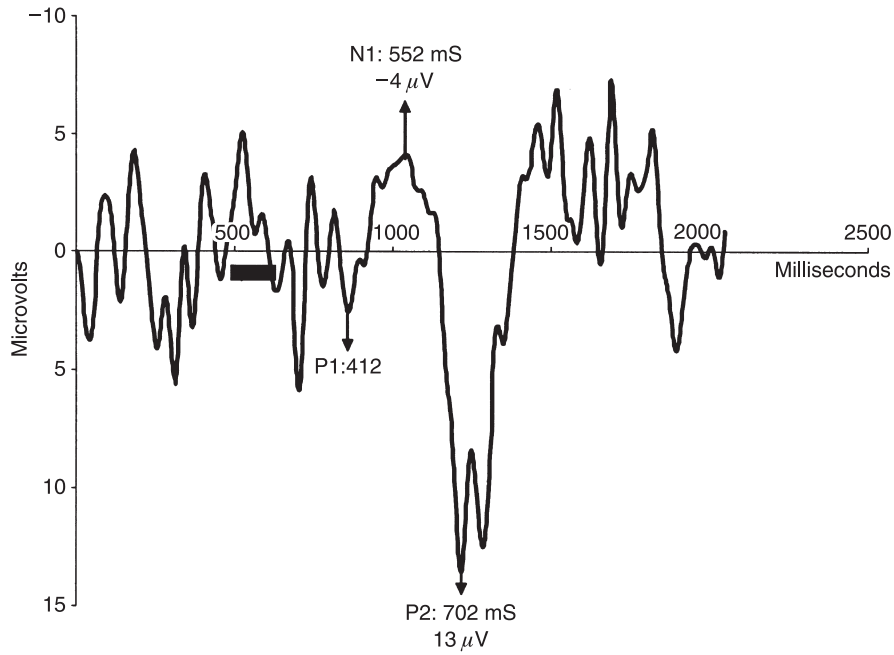

Figure 15.3 Healthy control subject: Olfactory evoked response to hydrogen sulphide (2 ppm) recorded from PZ. The black bar is the 200 mS stimulus. The main response P2 occurs at 720 mS amplitude, 13 μV.

this with the abnormal 12/37 (32%), then 81% showed a deficit on OEP which is the same as for UPSIT measurements. In 10 patients with normal UPSIT-40 scores, there was one with H_2S responses absent and three with significantly prolonged latency to H_2S suggesting that the prevalence of olfactory disorder may be higher still. We used only one odour whereas the UPSIT employs 40. If a large number of different gases were used, the sensitivity of OEP might well increase. Similar results were obtained in 31 patients with clinically diagnosed IPD tested by OEP to vanillin and H_2S (Barz *et al.*, 1997). Responses were found to both stimulants in *all* patients, which is remarkable given that many would be anosmic. Prolonged latencies were seen in the PD patients whether they were taking medication for the disease or not. More marked changes were seen in those on treatment, possibly because they had greater disability. The same group demonstrated a correlation between disability (as measured by Webster score) and latency to the H_2S-OEP. This observation complements the recent findings of others mentioned above (Tissingh *et al.*, 2001). To date, the issue of correlation of clinical status and olfactory test score is not resolved, but it would appear that the original suspicion of poor correlation is not correct.

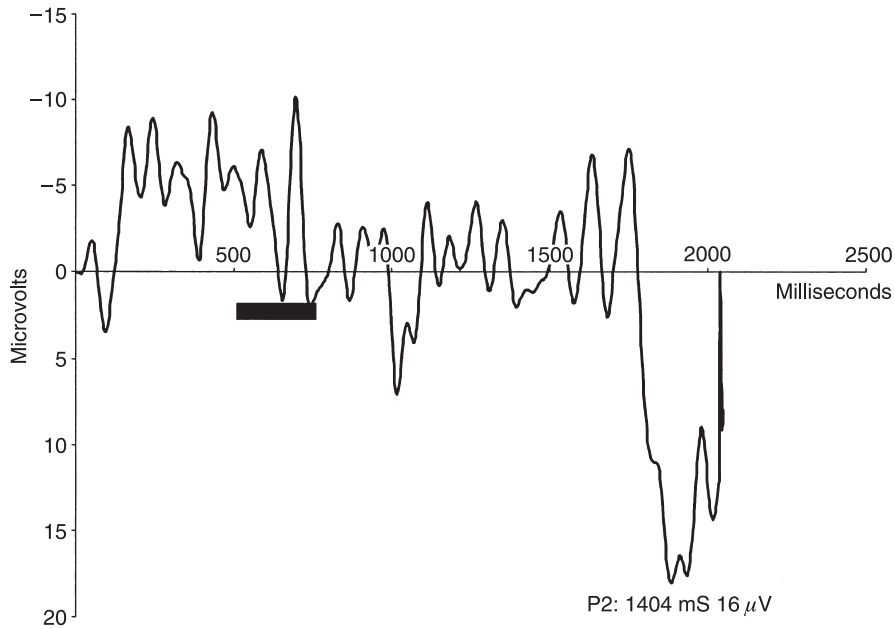

Figure 15.4 Patient with Parkinson's disease: Olfactory evoked response to hydrogen sulphide (2 ppm) recorded from PZ. The black bar is the 200 mS stimulus. The main response P2 occurs at 1404 mS amplitude, 16 μV which is markedly delayed.

Familial and presymptomatic parkinson's disease

In an initial study of familial parkinsonism (Markopoulou *et al.*, 1997), the UPSIT-40 was applied in six kindreds of which three had typical PD and three had a 'parkinsonism-plus' syndrome. In the typical families, there were four apparently healthy individuals at 50% risk of whom three were microsmic. In the PD-plus families there were eight at risk and two had abnormal UPSIT scores. Clearly this situation opens the potential for premorbid disease detection. A follow-up study has not yet been published, so the findings must be regarded as provisional. Others (Montgomery *et al.*, 1999) administered a test battery to first-degree relatives of IPD patients. The battery included tests of motor function, olfaction (UPSIT-40) and mood. There were significant differences in first-degree relatives (both sons and daughters), particularly where the affected parent was the father. Another group (Berendse *et al.*, 2001) examined asymptomatic IPD patients' relatives who were hyposmic. The DATScan revealed abnormal binding in 4/25 hyposmic relatives — two of whom subsequently developed IPD. None of the 23 normosmic relatives developed IPD. These authors suggested that olfactory dysfunction preceded clinical motor signs of the disease.

There are 10 known or suspected mutations that are related to parkinsonism, but in this category only one small study on olfaction has been published (Khan *et al.*, 2004). This was on *PARK2* ('Parkin'), a rare autosomal recessive form of juvenile parkinsonism. The authors used a culturally modified form of the UPSIT-40 and found a slightly reduced mean score in 17 *PARK2* subjects, which was no different from their control group; however it was significantly higher than the IPD group and the *PARK2* negative group. It is suggested that smell testing may help differentiate parkin disease from other varieties, but at least four parkin patients had low scores suggesting considerable overlap. It raises the possibility that some patients with apparent IPD and normal UPSIT scores (approximately 20%) may have a similar mutation.

The question of olfaction and its relation to the basic aetiology of PD is discussed in depth elsewhere (Hawkes *et al.*, 1999). It remains possible that the olfactory system is the site of initial damage in IPD, along with the dorsal medulla, and that the motor component is a late manifestation of what is a primary olfactory disorder. The results of large ongoing prospective studies in relatives of PD patients may resolve this issue.

Guam PD-dementia complex (PDC)

This is typified by parkinsonism which may coexist with Alzheimer-type dementia or amyotrophic lateral sclerosis (ALS). Pathologically the presence of neurofibrillary tangles and the absence of Lewy bodies place this disorder well apart from IPD. In a study (Ahlskog *et al.*, 1988) of 60 patients using a culturally modified form of the UPSIT, marked olfactory deficit was seen in all four syndromes — ALS, pure Parkinsonism, pure dementia and PDC. Another group (Doty *et al.*, 1991) administered the Picture Identification Test (to lessen cognitive confounding) and the UPSIT-40 to 24 patients with PDC and likewise found severe impairment of olfactory function of a magnitude comparable to that seen in IPD.

Lewy body disease (LBD)

In comparison to IPD, LBD is characterised by a more rapid course, early onset of confusion, hallucinations, drug sensitivity and dementia. Many consider that the pathology differs only quantitatively from typical PD. In a detailed analysis (Tsuboi *et al.*, 2003) of the olfactory bulb in LBD, tau pathology was found in the anterior olfactory nucleus (AON) of 9/10 cases, but not in subjects with PSP or corticobasal degeneration. This is consistent with the clinical olfactory findings described later in this paragraph. Alpha-synuclein pathology was demonstrated in the AON in most cases of LBD and frequently associated with tau pathology, suggesting that a common pathogenesis influences accumulation

of both molecules. In one study of clinically defined LBD, severe impairment of olfactory identification and detection threshold was observed and test scores were independent of disease stage and duration (Liberini *et al.*, 1999; 2000). In another study (McShane *et al.*, 2001) simple smell perception of one odour (lavender water) was examined in 92 patients with autopsy-confirmed dementia of whom 22 had LBD and 43 had Alzheimer's disease. They were compared with 94 age-matched controls. The main finding was of impaired smell perception in the LBD group and little or no defect in the Alzheimer patients. Although just one somewhat unsatisfactory odorant was used for perception tests, this study confirms clinically based conclusions (Liberini *et al.*, 1999; 2000) that impairment of smell is significant in LBD. Those who consider LBD to be no more than severe IPD would not be surprised by this observation. The suggestion of normal olfaction in Alzheimer's probably reflects the poor choice of the single stimulant used (lavender water).

Multiple system atrophy (MSA)

This is likewise a rapidly progressive form of Parkinsonism in which autonomic dysfunction predominates, particularly affecting bladder and orthostatic blood pressure control. Pathological change characteristic of MSA can be seen in olfactory bulbs — as well as those typifying Alzheimer's and Pick's disease (Daniel & Hawkes, 1992). In a detailed study of olfactory bulb pathology (Kovacs *et al.*, 2003), glial fibrillary inclusions, the hallmark of MSA, were found in oligodendrocytes of the olfactory tract and to a lesser extent in the olfactory bulb. Significant neuronal loss was found in the anterior olfactory nucleus. Alpha-synuclein was more sensitive in detecting pathological change than ubiquitin and it was concluded that these changes could aid diagnosis.

In an early study (Wenning *et al.*, 1993) of smell identification in 29 patients with a clinical diagnosis of MSA, mild impairment of UPSIT-40 score was demonstrated with a mean score of 26.7 compared to the control mean of 33.5. A subsequent examination of eight MSA patients using 'Sniffin' Sticks showed a TDI score in the hyposmic range for seven of eight patients (Muller *et al.*, 2002).

Cortico-basal degeneration (CBD)

In CBD, Parkinsonian features are supplemented by limb dystonia, ideomotor apraxia and myoclonus. In a study of seven patients with clinically suspected CBD, smell identification scores (UPSIT-40) were in the low normal range with a mean of 27.1 (Wenning *et al.*, 1995) — a value not significantly different from their age-matched controls.

Progressive supranuclear palsy (PSP)

In this variety, there is failure of voluntary vertical gaze, rapid course, marked imbalance and dementia. In a large study of olfactory bulbs (Tsuboi *et al.*, 2003), tau and α-synuclein pathology was found in only nine of 27 bulbs. The bulbs which showed tau pathology also had coexisting AD or LBD, implying that pure PSP is not a tauopathy.

Normal smell identification values have been found in two studies (Bonnuccelli *et al.*, 1991; Wenning *et al.*, 1995). In another study (Doty *et al.*, 1993) there was likewise no difference in age-matched UPSIT-40 score, and threshold tests to phenylethylalcohol were not significantly different from control values ($p = 0.085$), but there was a trend to higher threshold values which may have failed to reach significance because of the relatively small numbers of patients. In all instances the diagnosis once more has been clinically, not autopsy based. A more complex picture was found in relatives of patients with PSP (Baker & Montgomery, 2001). A test battery consisting of measurement of motor function, olfaction and mood was administered to 27 first-degree relatives of whom nine scored in the abnormal range. This confused picture overall emphasises the major need for studies in pathologically confirmed cases.

Drug induced parkinson's disease

In MPTP-induced PD, six subjects were tested and found to be normal for UPSIT-40 and detection threshold (Doty *et al.*, 1992a). Although this is a small series, it implies that MPTP-PD is an unrepresentative model of its idiopathic counterpart. We undertook a small study of drug-induced PD in 10 cognitively normal patients (Hensiek *et al.*, 2000). Each had experienced Parkinsonism in response to a variety of phenothiazine drugs that had been administered for at least two weeks. Of the 10 patients, five had abnormal age-matched UPSIT-40 scores and none made a complete recovery, whereas all but one of those who did recover had a normal UPSIT score. The interpretation is difficult but it implies that patients with drug-induced PD may be those who are genetically predisposed to develop IPD.

Vascular parkinsonism

Some patients with extensive cerebrovascular disease that involves the basal ganglia (particularly putamen) may develop a syndrome that mimics IPD but the response to levodopa is variable. The distinction of VP from IPD is based primarily on clinical criteria supplemented by MRI or DATScan. A recent study (Katzenschlager *et al.*, 2002) of the UPSIT-40 in 13 patients fulfilling strictly

defined criteria for VP showed no significant difference compared to age-matched controls (25.5 in VP and 27.5 in controls), suggesting that identification tests may aid differentiation from IPD.

X-linked dystonia-parkinsonism ('Lubag')

This is an X-linked disorder affecting Filipino male adults with maternal roots from the Philippine Island of Panay. A single study of 20 affected males using the UPSIT-40 showed that olfaction is moderately impaired in Lubag even early on in the disorder and that it is independent of phenotype (i.e. degree of dystonia or rigidity), severity or duration of disease (Evidente *et al.*, 2002).

Essential tremor

Essential tremor is included in this chapter because it is often confused (at least by non-neurologists) with IPD. There are particular difficulties when tremor appears to be dystonic or when there is co-existing rigidity that may occur in up to 30% otherwise typical patients. Distinction from benign tremulous Parkinson's disease can be difficult. In the first study of olfactory identification in 15 subjects with benign essential tremor, all performed normally (Busenbark *et al.*, 1992). A subsequent analysis (Louis *et al.*, 2002) claimed significant abnormalities in ET as measured by the UPSIT-40 and suggested that hyposmia might be related to cerebellar dysfunction. The sample size in this study was adequate (37 patients) and all cases were carefully defined. However, it is unclear how carefully the authors allowed for the effects of ageing and no confirmatory imaging (e.g. DAT or PET Scan) was undertaken. In a recent investigation (Hawkes *et al.*, 2003), we examined 50 patients with ET with the UPSIT-40 and evoked potential studies to H_2S. No abnormal UPSIT or OEP response was found in any of the ET subjects, although some older patients had borderline values. Exclusion of those patients without a family history eliminated the borderline values and suggests that the diagnosis of pure ET requires the presence of a family history. If it is correct that patients with ET have normal smell sense, this might allow the distinction of essential tremor from Parkinsonian tremor — although females with tremor-dominant IPD are thought to be less likely to have olfactory impairment (Stern *et al.*, 1994).

Conclusion

The olfactory system is damaged to varying degree in the presence of clinically evident Parkinsonism (Table 15.1). The most severe changes are seen in

Table 15.1. Relative olfactory dysfunction in neurodegenerative conditions*

Disease	Severity of smell loss
IPD	++++
LBD	++++
PDC	++++
Familial Parkinsonism: affected/at risk	+++/+
MSA	++
Drug-induced PD	++
X-linked dystonia-Parkinsonism (Lubag)	++
PSP	0/+
MPTP Parkinsonism	0?
Cortico-basal degeneration, Vascular parkinsonism, Parkin disease	0?
Essential tremor	0?

*Relative degree of olfactory dysfunction in various conditions on an arbitrary scale. Most of the values are provisional as they are based on relatively small patient numbers except for IPD and essential tremor. See text for references. ++++ marked damage; + mild; 0 normal.

the Idiopathic, Guamanian and LBD varieties. Least involvement would be expected in CBD, PSP, VP and intermediate damage in MSA. These differences could aid diagnosis. For example, if a patient is suspected to have IPD, the presence of normal olfaction on psychophysical tests should prompt review of the diagnosis, especially in the akinetic rigid variety. Anosmia in CBD or PSP would also be unexpected. In a patient with tremor it may be difficult to know whether this is tremor-dominant IPD or the benign essential variety. Normal olfaction would favour essential tremor with the proviso that females with tremor-dominant IPD might also have a normal result. Degenerative syndromes with smell impairment may be split into two major categories i.e. IPD, LBD, MSA where there is disorder of α-synuclein (alpha-synucleinopathy) and those with more normal olfaction i.e. Alzheimer's disease, CBD and PSP where there is disorder of tau protein (tauopathy). There is probably too much pathological overlap for this to be clinically useful, and it is dubious that AD patients have normal smell function. There is the possibility that olfactory testing in families with IPD may allow identification of patients at risk of subsequently expressed disease. Prospective studies of families with Parkinsonism that contain substantial members at 50% risk will help solve this problem, and a large study of 'premotor' Parkinson's disease is in progress (Wolters *et al.*, 2000).

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16

Olfaction in psychosis

Paul Moberg and Bruce Turetsky

Introduction

Neuropsychological, structural and functional imaging studies converge in finding that patients with schizophrenia have selective impairments in the areas of memory, attention and executive function, and have neuroanatomic and physiologic abnormalities in the temporal and frontal lobe areas underlying these cognitive domains (Saykin *et al.*, 1991; 1994; Turetsky *et al.*, 1995). Efforts to precisely characterise these fronto-temporal deficits and their clinical correlates have employed a variety of methods and an array of neurobehavioural probes, including physiological assessments of declarative memory, working memory, executive function and vigilance (Berman *et al.*, 1986; Bernstein *et al.*, 1990; Calev, 1984; Weinberger *et al.*, 1992). Little use has been made of olfactory probes, despite the fact that these may be ideal tools to assess limbic pathophysiology.

As outlined in Chapter 1, the olfactory system is unique among the sensory modalities, in that it does not utilise the thalamus as a central relay station (Price, 1987). Primary olfactory neurons arising in the nasal epithelium project unmyelinated afferent fibres through the cribriform plate into the brain cavity, where they terminate on mitral and tufted cells whose dendrites are clustered in glomeruli in the ipsilateral olfactory bulb (OB). Axons from these second order OB neurons form the olfactory tracts, which project directly to the ipsilateral pyriform and entorhinal cortices, the ventral striatum and the ventromedial hypothalamus, with essentially no crossover to the contralateral hemisphere (Eslinger *et al.*, 1982). Olfactory information passes, in turn, from these primary recipient zones to the amygdala, hippocampus, thalamus

and orbitofrontal cortex (Tanabe *et al.*, 1975). While these secondary projections remain predominantly ipsilateral, a small percentage of fibres cross over to the contralateral hemisphere via the anterior commissure. With only two synapses between olfactory receptors and secondary cortical and subcortical targets (Eslinger *et al.*, 1982), the olfactory system provides the most direct environmental access to several structures that have been implicated in schizophrenia.

The olfactory system is also unique in that it retains its plasticity and exhibits robust neurodevelopment throughout life. The olfactory epithelium regenerates approximately every three months (Takagi, 1969). Basal stem cells divide to give rise to new immature neurons that migrate towards the epithelial surface. These neurons differentiate into mature olfactory receptor neurons (ORN) that project new axons back to reinnervate the glomeruli of the olfactory bulb and form new synapses with target neurons. The olfactory system thus offers an unparalleled opportunity to observe the developmental processes of neurogenesis, axon guidance and synapse formation that are no longer evident, to any significant extent, in other adult brain areas. Given the growing clinical and post-mortem evidence implicating abnormal neurodevelopment in the pathogenesis of schizophrenia, and the evidence, detailed below, of olfactory deficits associated with the illness, physiological probes of the olfactory system may hold special promise for understanding neurodevelopmental contributions to schizophrenia pathophysiology.

Developmental neurobiology of olfaction

Morphological differentiation of the human olfactory system occurs early in embryonic development (Farbman, 1991). The nasal placodes begin to invaginate to form nasal pits at about the 6th week of gestation, and the nasal cavities are fully sculpted by week 11 (Larsen, 2001). The ORN axons reach the bulb by the end of the first trimester and there is evidence of mitral cell synapse formation by the 17th week of gestation. The olfactory system is believed to be functional towards the end of the third trimester, and newborns can discriminate between a wide variety of odorants. Consistent with its early development, the olfactory system is vulnerable to disruption, in utero, by physical and chemical teratogens including X-rays and alcohol (Farbman, 1991). There is clear evidence that abnormalities in brain development also play a role in the pathophysiology of schizophrenia. As detailed in Chapter 5, history of gestational or perinatal complications, including second trimester influenza infection (Mednick *et al.*, 1988), rhesus and ABO blood-type incompatibility (Hollister *et al.*, 1996), and perinatal anoxic birth injury (Cannon *et al.*, 2000), all increase the risk of illness.

A neurodevelopmental aetiology is also supported by findings of reduced cranial size (Gur *et al.*, 1994) and, in particular, minor midline physical anomalies (e.g. reduced palate height, cleft palate) that arise from the same embryologic process that produces the olfactory structures, and is often associated with abnormal central nervous system (CNS) development (O'Callaghan *et al.*, 1991). Cytoarchitectural and neuronal morphometric investigations have described abnormal arrangements of neurons in limbic cortices and abnormalities in neuron size, shape, orientation and packing density in various limbic and association cortices and subcortical nuclei (Arnold *et al.*, 1996). It is plausible, therefore, that early developmental abnormalities in the structure, growth or functioning of olfactory neurons would not only result in the olfactory deficits seen in schizophrenia, but would also be representative of neurodevelopmental disturbances that were extant throughout the brain during gestation (see also Chapter 5).

Dr. Steven Arnold recently conducted a post-mortem study designed to exploit the persistence of neurodevelopment in the olfactory epithelium. By staining neurons for different protein markers expressed at different stages of development, he was able to quantitatively characterise the neurodevelopmental process in patients and controls. There was an abnormal increase in the number of immature ORNs in the olfactory epithelium of patients (Arnold *et al.*, 2001). This was interpreted as dysregulation of the ORN developmental lineage, arising either from disturbances of the factors controlling differentiation or the inability of these developing neurons to gain trophic support from their axonal targets in the OB. The latter interpretation is further supported by data from the OBs themselves. Patients with schizophrenia had reduced levels of glomerular expression of the pre-synaptic protein SNAP25 and the post-synaptic protein MAP2. This is consistent with the hypothesis of impaired neurotransmission at the level of the synapse in the OB (Arnold *et al.*, 2001).

Psychophysical assessments of olfaction in patients with schizophrenia

Since the pioneering psychophysical studies of odour recognition memory in patients with schizophrenia by Australian researchers Campbell and Gregson (1972), a number of investigators have reported that schizophrenia patients exhibit olfactory dysfunction (see Moberg *et al.* (1999) for a review). In an early study, Bradley (1984) reported that psychotic patients, most notably males with schizophrenia, were hypersensitive to the odorant 5-16-androsten-3-one. However, more recent studies have not confirmed this hypersensitivity, with

some studies finding intact olfactory sensitivity (Kopala *et al.*, 1989; 1993), and others demonstrating decreased sensitivity (Serby *et al.*, 1990a). With only one exception (Warner *et al.*, 1990a,b), deficits in odour identification (Brewer *et al.*, 1996; Hurwitz *et al.*, 1988; Kopala *et al.*, 1989; 1993; 1994; 1995; Malaspina *et al.*, 1994; Moberg *et al.*, 1997; Seidman *et al.*, 1992; Serby *et al.*, 1990a,b; Wu *et al.*, 1993), odour detection threshold sensitivity (Serby *et al.*, 1990a), and odour memory (Campbell & Gregson, 1972; Dunn & Weller, 1989; Wu *et al.*, 1993), have all been reported. Notably, in the case of odour identification, a number of studies have suggested that men with schizophrenia evidence greater olfactory impairment than women (Kopala *et al.*, 1989; Kopala & Clark, 1990), possibly reflecting a neuroprotective effect of oestrogen (Kopala *et al.*, 1997).

Despite the increasing interest in olfactory abnormalities in patients with schizophrenia, very few studies have explored the relative severity of different olfactory deficits (i.e. identification, threshold, memory, intensity/hedonics). Given the presumed differences in neuroanatomic loci for these different olfactory domains as described in Chapters 1–3 and 6, it may be expected that they would be differentially impaired in the disorder. In addition, the effects of potential moderator variables, such as gender, medication and smoking history, have not been consistently assessed across studies. Results of a comprehensive meta-analytic review of the English language literature pertaining to psychophysical olfactory function in schizophrenia (Moberg *et al.*, 1999) revealed that: (1) comparable deficits are seen for all psychophysical measures (odour detection, identification and memory); (2) no differences exist between male and female patients, except in the domain of odour hedonics; (3) there are no significant effects of antipsychotic medications on olfactory performance; and (4) patient deficits persist after accounting for the effects of smoking.

Assessment of hedonic odour processing

Olfaction has long been associated with emotions and emotionally laden memory (Jones-Gotman & Zatorre, 1993), in both popular and scientific literature. There is ample evidence that olfaction and emotion utilise many of the same limbic system structures, and similar right hemisphere dominance has been proposed for both olfactory (Clark *et al.*, 1991; Zatorre & Jones-Gotman, 1990; Zatorre *et al.*, 1992) and emotional (Gainotti, 1989; Malloy *et al.*, 1993; Sackeim *et al.*, 1982) stimulus processing. This has led several investigators to posit a direct link between the two (Jones-Gotman & Zatorre, 1993; Malloy *et al.*, 1993; Seidman *et al.*, 1992). Given the configuration and relevance of the underlying neural substrate, olfactory probes are ideal for illuminating limbic system dysfunction, which may be responsible for the well-known deficits in

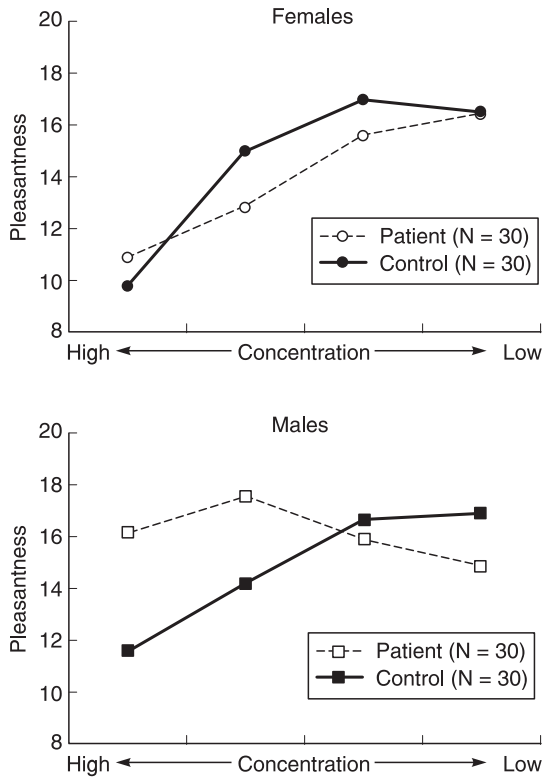

Figure 16.1 Rating of hedonic valence of odours.

emotional reactivity, emotion recognition and anhedonia seen in patients with schizophrenia. We presented a sample of 30 patients and 30 controls with four different concentrations of amyl acetate (banana odour) and asked each subject to rate both the intensity and the pleasantness of each concentration (Moberg *et al.*, 2003). An interesting characteristic of many odours, including amyl acetate, is that they are subjectively experienced as increasingly unpleasant as their concentration increases. Patients and control subjects were both able to detect the increased intensity of the higher concentrations, without any notable differences. However, male patients, who typically experience greater anhedonia and clinical disturbances of emotional expression and processing, were unable to appreciate the change in hedonic character of the stimuli. In fact, they tended to rate the high odorant concentrations as more pleasant, rather than less (see Figure 16.1). This suggests that there may be a gender-selective disruption of the circuitry mediating olfactory inputs to emotion-processing areas in schizophrenia. This may be related to our previous finding (Gur *et al.*, 2000) that male, but not female, patients had smaller amygdala volumes

compared to gender-matched controls. Increased blood flow in the amygdala has been associated with responses to unpleasant odours in normal controls (Zald & Pardo, 1997).

Family and 'at-risk' studies of olfaction in schizophrenia

The olfactory system is, among all the sensory systems, the most highly genetically predetermined. (For a more detailed discussion, see Chapter 9.) Responses to odorants often appear to be instinctual, and highly consistent responses are observed across individuals within a species. This is thought to reflect the fact that the olfactory system is genetically 'hard-wired' and relatively immune to modification by individual experience (Barinaga, 2001). So, it is reasonable to consider whether the olfactory abnormalities observed in schizophrenia might also be genetically mediated. There have now been a few olfactory psychophysical studies of unaffected family members of patients (Kopala *et al.*, 1998; 2001; Moberg *et al.*, 1996). Although results have been inconsistent, some deficits have been found. In the most compelling study to date, Kopala and colleagues (2001) examined 19 probands, 27 nonpsychotic family members and 43 healthy controls using the University of Pennsylvania Smell Identification Test (UPSIT) and an ascending staircase odour detection threshold test. They found that the UPSIT performance of the nonpsychotic family members was intermediate to that of the patient probands and the healthy controls. Fifty-eight percent of the probands and 34% of the nonpsychotic family members performed in the microsmic range, compared to nine percent of healthy comparison subjects. Recent work from our lab has substantially expanded on these early efforts. We have found significant impairments in odour identification in a large sample of healthy family members. Moreover, our neurobiological studies have documented robust physiological and structural abnormalities in the olfactory system in these unaffected first-degree relatives (Turetsky *et al.*, 2003a,b). These latter findings, in particular, provide strong evidence that olfactory disturbances aggregate in the families of people with schizophrenia. They are therefore likely to represent genetic markers of vulnerability to the illness, rather than manifestations of the disease itself.

Consistent with this, olfactory performance deficits have also been found in individuals with schizotypal personality disorder (Park & Schoppe, 1997) who are thought to share the same genetic vulnerability as patients with schizophrenia. Studies of 'psychosis-prone' individuals, who do not meet criteria for any disorder but score high on measures of perceptual aberration, physical anhedonia and magical ideation, have shown that these sub-clinical symptoms

are correlated with increases in deviant olfactory experiences (e.g. misperceptions, hallucinations) (Mohr *et al.*, 2001; 2002) and with abnormal olfactory event-related potentials (ERPS) (Becker *et al.*, 1993). The relationship between olfaction and aberrant cognitive and perceptual experiences extends beyond mere correlation. In a 10-year longitudinal study (Kwapil *et al.*, 1996), the presence of such deviant olfactory experiences was found to significantly predict the development of future psychosis. More importantly, a similar investigation (Brewer *et al.*, 2003) examining psychophysical olfactory deficits, as opposed to aberrant olfactory experiences, found that odour identification performance was significantly impaired in those 'high-risk' individuals who subsequently developed schizophrenia, but not in those who went on to develop affective psychoses or remained symptom-free.

Diagnostic specificity of olfactory dysfunction

The causes of olfactory impairments are numerous, including chemical, infectious, traumatic, metabolic and hormonal disturbances. Within the realm of neuropsychiatry, several neurodegenerative disorders have been shown to compromise olfaction, including Alzheimer's disease, Down's syndrome, Huntington's disease, Parkinson's disease and multiple sclerosis (Doty, 1991). Among these, the relationship of olfaction to Alzheimer's disease is perhaps of greatest interest, since the anterior medial temporal lobe areas that receive afferents from the OB are among the earliest to exhibit the characteristic neuropathology of that disorder. It has therefore been suggested that olfactory deficits may be an early indicator of disease onset, prior to the development of clinically observable memory loss (see Chapters 14 and 15). The question of diagnostic specificity, or lack thereof, is much less certain with respect to the major psychiatric disorders. For reasons that are not clear, there have been only a few studies of olfaction in affective illnesses, and the data that do exist are inconsistent. Patients with major depression or seasonal affective disorder have variously been reported to exhibit increased (Gross-Isseroff *et al.*, 1994; Postolache *et al.*, 2002), decreased (Pause *et al.*, 2001) and normal (Amsterdam *et al.*, 1987) olfactory acuity, as well as normal (Kopala *et al.*, 1994; Warner *et al.*, 1990a,b) and reduced (Serby *et al.*, 1990a) olfactory identification ability.

There is even less information concerning bipolar affective disorder (BPD) patients. One early study (Hurwitz *et al.*, 1988) found no impairments in either acuity or identification among BPD patients being treated with antipsychotic medications. A subsequent investigation (Striebel *et al.*, 1999) found that

affective disorder patients were indistinguishable from schizophrenia patients on olfactory identification performance. However, those affective patients with psychotic symptoms also performed significantly worse than those without evidence of psychosis. Most recently, a study of heterogeneous first-episode psychosis patients (Brewer *et al.*, 2001) reported no difference, across the diagnostic subgroups, in the level of odour identification impairment. The authors concluded that olfactory deficits exist at the onset of psychotic illness, but they are not specific to schizophrenia or schizophreniform disorder. The accumulating evidence from these studies, and from the 'high-risk' studies cited above, indicate that olfactory deficits are relatively specific to psychotic disorders, as distinct from nonpsychotic psychiatric conditions. However, the specificity to schizophrenia, as opposed to BPD with psychosis, is less clear. The finding cited above (Brewer *et al.*, 2003) that olfactory impairments during the prodromal phase significantly predict a subsequent diagnosis of schizophrenia, supports the idea of a disease-specific vulnerability marker. This has now been replicated by another group of independent investigators (Malaspina *et al.*, personal communication).

It is important to emphasise that all of these investigations were based solely on behavioural performance measures. These types of measures depend upon a subject's cooperation, motivation, attention and cognitive capacity to ensure accurate assessment. Few prior studies have included physiological or structural assessments of the integrity of the olfactory system. Such structural and functional measures, which do not rely on nonspecific factors such as motivation or attention, are likely to be more sensitive to differential deficits across patient groups.

Neuroimaging studies of olfaction in schizophrenia

Recent years have brought rapid expansion of structural and functional imaging technologies, including high-resolution structural magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission tomography (SPECT) and ERP. These have been extensively applied to the study of schizophrenia. However, there has been limited application of these research tools to the study of olfactory function (Doty *et al.*, 1997), especially as it relates to schizophrenia.

Structural MRI

There have been a vast number of quantitative MRI studies in schizophrenia (see review by Shenton *et al.* (2001); see also Chapter 2). Areas of the temporal

lobe, including the superior temporal gyrus, hippocampus and amygdala, have been among the most extensively studied. Interest in these particular regions stems from their association with the verbal, cognitive memory and affective symptoms that are prominent in the disorder. In contrast, primary olfactory brain regions have been virtually ignored. To our knowledge, only two prior studies have examined the entorhinal cortex (Nasrallah *et al.*, 1997; Pearlson *et al.*, 1996) which functions as a critical relay between the hippocampus and cortical association areas and which also receives direct OB inputs. Patient decrements were identified in one of these two. No studies specifically assessed the perirhinal cortex, which receives the bulk of these bulbar afferents, or more peripheral elements of the olfactory system.

Olfactory cortex

Based on the importance of the biological substrate, we extended this approach by applying it to those anterior ventromedial temporal lobe (AVMT) areas that are directly engaged in olfactory sensory stimulus processing (Turetsky *et al.*, 2003). As noted, the AVMT has been relatively ignored in the schizophrenia literature up to now. A possible explanation is the problem of selecting appropriate MRI landmarks to guide region-of-interest (ROI) identification in this area. Boundaries between AVMT subregions are based on cytoarchitectural distinctions, rather than gross anatomical features. Cytoarchitecturally, the AVMT may be subdivided into temporopolar (Brodmann area 38), perirhinal (Brodmann areas 35 and 36) and entorhinal (Brodmann area 28) cortices (Insausti *et al.*, 1998), with the piriform cortex included as part of the perirhinal cortex. The perirhinal and entorhinal cortices are considered part of the limbic cortex, and have been implicated in both olfaction and memory. The temporopolar cortex, however, is generally considered to be developmentally and functionally distinct. Although it connects to the amygdala, hippocampus and basal forebrain, it does not receive direct olfactory afferents. In this investigation, we used transitional landmarks derived from a histological analysis (Turetsky *et al.*, 2003) to parse the AVMT into discrete temporopolar, perirhinal and entorhinal cortices. We then quantified the cortical grey matter volume in each of these cytoarchitecturally distinct regions.

We found significant diagnosis-by-cranial volume interactions for the perirhinal and entorhinal cortices, but not for the temporopolar cortex. Relative to cranial volume, patients had smaller than expected regional volumes, but only for those regions that receive direct OB afferents. We also found a direct structure–function relationship between decreased olfactory threshold detection sensitivity and decreased perirhinal grey matter volume (Figure 16.2).

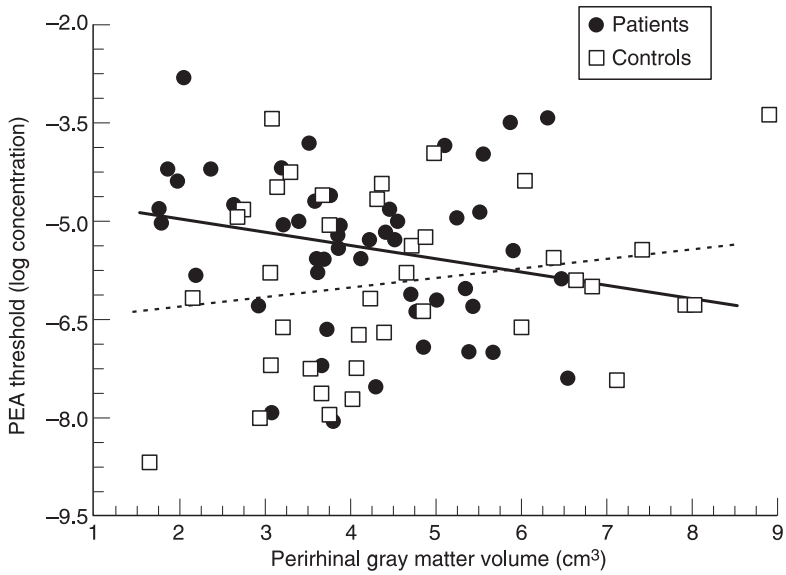

Figure 16.2 Relationship between perirhinal cortex volume and olfactory threshold sensitivity.

This makes sense, given that the perirhinal region receives the vast majority of bulbar afferents. The relationship to olfactory acuity was also quite specific. Patients were markedly impaired on tests of memory, as well as olfaction. However, there were no associations between memory performance and volume for any of the AVMT regions, even though the entorhinal cortex, in particular, is known to be involved in hippocampal-mediated memory processing. This study offers the first evidence that behavioural olfactory deficits are related to cortical brain abnormalities in the regions underlying primary olfactory sensory processing.

Olfactory bulbs

The olfaction-specific findings in the AVMT raise the question of whether structural abnormalities also exist in more peripheral elements of the olfactory system in people with psychotic disorders. Using a high-resolution scanning protocol that allowed us to acquire localised coronal images of the OB (Yousem *et al.*, 1997a), in which trained operators were able to identify and outline the structures with intra- and inter-rater reliability exceeding 0.9, we conducted volumetric analyses of the OB. Our initial study (Turetsky *et al.*, 2000) examined the OB in a sample 26 schizophrenia patients and 22 healthy control subjects. Figure 16.3 demonstrates the appearance of the OBs on the MRI

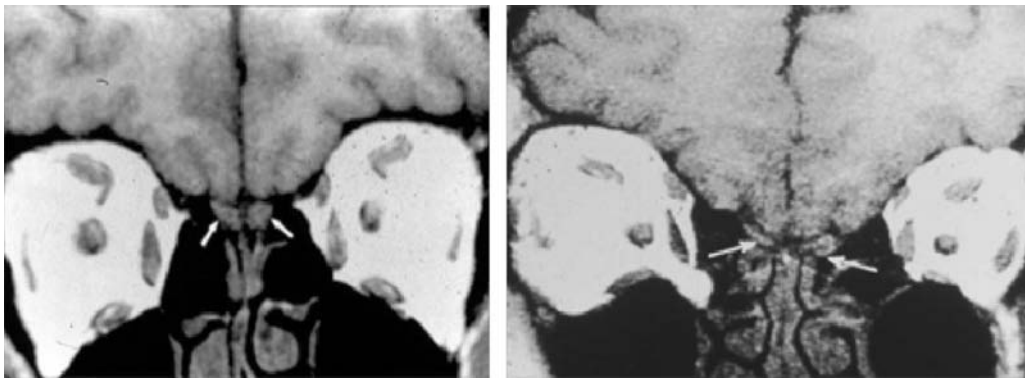

Figure 16.3 OB: left side = control, right side = patient.

scans. They can be clearly visualised along with, in this individual case, an obvious patient abnormality.

Statistical analysis revealed significant bilateral reductions in patients, with no effects of either gender or smoking. Mean patient volume was 23% smaller than controls, which greatly exceeds the 5–10% reductions typically seen in terms of cortical volume reduction in schizophrenia patients. There was a strong association between OB volume and odour threshold sensitivity in healthy individuals [$r = 0.86$], with larger bulb size correlating with better odour detection threshold sensitivity. However, this was not observed in patients [$r = 0.30$]. These findings indicate that structural abnormalities of the olfactory system are not limited to the olfactory cortex, but extend peripherally to the site of the initial synapse. Whether these abnormalities reflect neurodevelopmental or neurodegenerative processes cannot be determined from these data. However, there are reasons to believe this is a developmental abnormality. As discussed in Chapter 5, the OB, unlike most other brain regions, remains highly plastic, with synaptogenesis continuing throughout adult life (Arnold, 1998). It is, therefore, relatively resistant to degenerative processes that affect other areas of the brain. Also, developmental abnormalities of other midline structures have been previously reported in schizophrenia (Scott *et al.*, 1993) and, histopathologically, central olfactory pathways exhibit cytoarchitectural, morphometric and cytoskeletal protein abnormalities that are consistent with aberrant development rather than degeneration (Arnold, 1998; Arnold *et al.*, 1998). The reader is referred to Chapter 5 for a more detailed discussion of neurodevelopmental aspects of schizophrenia.

To further assess the possibility of a genetically mediated developmental aetiology for this bulb abnormality, we acquired comparable MRI data from 19 first-degree relatives of schizophrenia patients, and compared their OB

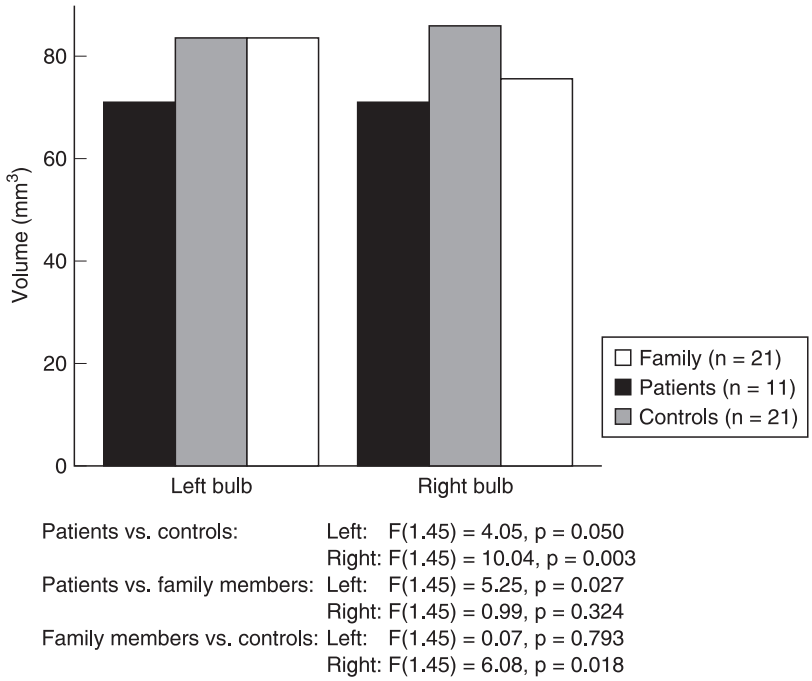

Figure 16.4 OB volumes for patients, relatives and controls.

volumes to those of their respective probands and to age and gender-matched control subjects (Turetsky *et al.*, 2003a). Patients, again, exhibited bilateral reductions in bulb volume relative to controls. The family members had selective volume reductions only for the right OB. Their left OBs were normal. Consistent with this, patients had smaller left OBs than their relatives, but these two groups were indistinguishable on the right side (Figure 16.4).

The presence of a bulb abnormality in the family members provides strong evidence to support the hypothesis of a genetically mediated vulnerability factor that affects primary sensory components of the olfactory system. These two studies are the first demonstration of any such basic peripheral deficit, for any sensory modality, in either schizophrenia patients or their family members. The restriction of the deficit to the right bulb in relatives is consistent with what we observed for the psychophysical measures. This makes it less likely to be artifactual, and strengthens the suggestion that right-sided olfactory deficits may be endophenotypic markers of an inherited neuronal abnormality that conveys risk for the development of schizophrenia. It is well established that the right hemisphere is better adapted to processing olfactory inputs than the left (Doty *et al.*, 1997), and this functional asymmetry presumably extends to the level of the bulb. Recent studies have demonstrated larger right OBs, as a consequence

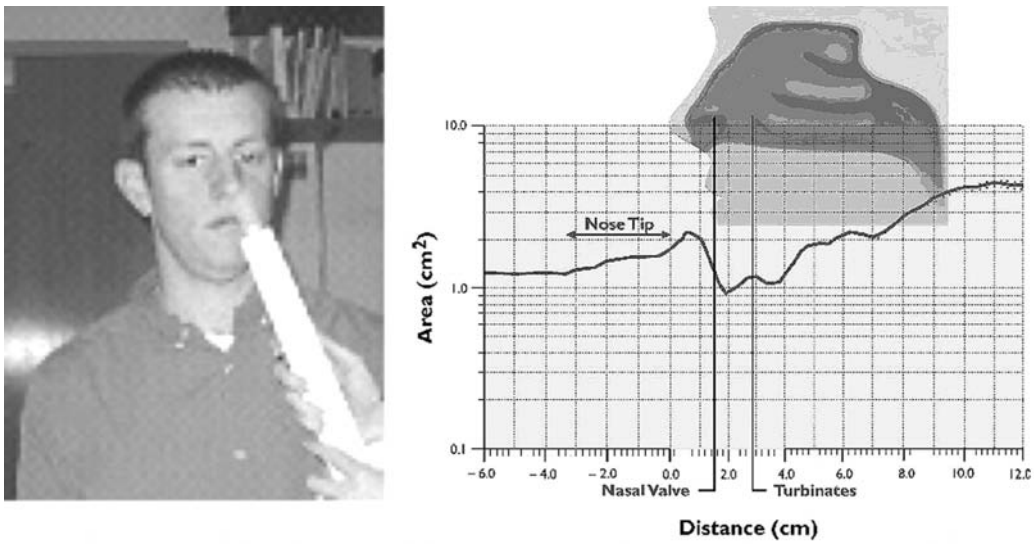

Figure 16.5 Acoustic rhinometry instrumentation and data readout. For a colour version of this figure please see Plate 3.

of normal development, in diverse species (Heine & Galaburda, 1986; Prasada & Finger, 1984). There is also evidence that the two bulbs contain different levels of both modulating neurotransmitters (Dluzen & Kreutzberg, 1996) and the enzymes involved in their synthesis (Rodriguez-Gomez *et al.*, 2000). It is reasonable, therefore, that a neurobiological deficit might manifest itself preferentially in only one bulb.

Nasal cavity volume

A macroscopic examination of the structures underlying olfaction can, of course, be extended even more peripherally to include an evaluation of the nasal cavities. We have employed an acoustic rhinometer, which is essentially a type of ultrasound device, to determine the volumes of the left and right nasal cavities. This methodology yields measures of the cross-sectional area of the cavity from the tip of the nose posteriorly towards the nasopharynx (see Figure 16.5).

Auxiliary measures include the minimum cross-sectional area and air-flow resistance. These allow us to distinguish reduced volumes secondary to mucosal engorgement, which would compromise airflow, from deformities of the underlying cartilaginous structure. We recently conducted an investigation of nasal volumes in 40 male schizophrenia patients and 24 healthy male comparison subjects, all of whom were screened for symptoms of nasal congestion, nasal trauma and septal deviation (Moberg *et al.*, 2004). Results revealed no significant main or interaction effects of diagnosis on air-flow resistance,

minimum cross-sectional area, or location of the minimum cross section. There was, however, a significant main effect of diagnosis on nasal volume (patients < controls), but no effect of race and no interaction between diagnosis and race. There was a significant interaction between diagnosis and nasal compartment. *Post hoc* contrasts indicated that patients had smaller posterior nasal volumes than controls, but did not differ in anterior nasal volume. The posterior volume difference was present for both left and right nostrils. On a percentage basis, posterior nasal volume was 31% smaller in patients, compared to an 11% reduction in anterior volume. Importantly, it is this posterior compartment that contains virtually all of the ORNs. These latter findings indicate that this is a focal developmental craniofacial abnormality. Embryologically, the nasal cavities develop through invagination of the nasal placodes that are derived from neural crest tissue. This occurs between the 6th and 11th weeks of development, in conjunction with palatal and nasal septal fusion. While subsequent development results in overall enlargement, there is no substantial reshaping of the cavities (Larsen, 2001). Consequently, these data directly implicate a perturbation during first-trimester development in the aeotiology of schizophrenia, at least in males. Whether this disturbance is genetically or environmentally mediated is unclear; further study in healthy family members of patients will be crucial in this regard.

Functional imaging (PET, SPECT, ERP)

A small, but increasing, number of studies have examined brain activity in response to odour stimuli in healthy control subjects (Anderson *et al.*, 2003; Gottfried *et al.*, 2002; Yousem *et al.*, 1997b; Zald & Pardo, 1997; Zatorre *et al.*, 1992). Most have reported increased haemodynamic activity in the orbitofrontal regions (right > left) following olfactory stimulation, with some also noting activation in the amygdala and/or perirhinal (piriform) cortex. Recent studies (Anderson *et al.*, 2003; Gottfried *et al.*, 2002) have attempted to identify specific brain regions responsible for different elements of olfactory information processing (see also Chapters 1 and 2). The results suggest: that (1) areas of the piriform cortex are activated nonspecifically by all odour stimuli; (2) amygdala activity is associated with odour intensity, not odour valence; (3) orbital frontal activity is responsible for processing the affective valence or hedonic qualities of odorants.

Direct olfactory activation studies of patients with schizophrenia have been extremely rare. Several studies, however, have evaluated metabolic activity in olfactory-related regions in the absence of odour stimulation. In an early study, Clark and colleagues (1991) examined regional cerebral glucose metabolism in 16 male schizophrenia patients and eight healthy male controls. Eight of the patients

had normal olfactory function and eight were microsmic, as determined by scores on the UPSIT. Overall, the schizophrenia patients had lower rates of frontal metabolism than the normal controls. However, the microsmic schizophrenia patients had lower right basal ganglia and thalamic metabolism than the normosmic patients, suggesting dysfunction in subcortical brain regions associated with olfaction. While limited in sample size and design, this study argues for a relative decrement in the right hemisphere brain activity and an increased activity in the contralateral left hemisphere regions in olfactory-deficient schizophrenia patients. Wu *et al.* (1993) examined odour memory and identification ability in 28 healthy controls and 20 neuroleptic-naive schizophrenia patients, some of whom underwent concurrent PET scanning. Among the patients, significant positive correlations were observed between UPSIT scores and frontal lobe metabolism, especially in the left middle frontal and left inferior frontal gyri. The left frontal/occipital ratio was also positively related to UPSIT performance. However, the results of this study are confounded by the use of a continuous performance task as the probe stimulus during PET, rather than olfactory stimuli. Bertollo and colleagues (1996) examined resting cerebral metabolic rate in two olfactory cortical projection areas in eight men with schizophrenia and eight controls. The patients exhibited hypometabolism in the right lateroposterior quadrant of the orbitofrontal cortex, which receives primarily uncrossed projections from the OBs bulb via the pyriform and entorhinal cortices. A smaller but more symmetric degree of hypometabolism was also seen in the medial anterior aspect of the orbitofrontal cortex, which receives crossed afferents from the limbic system. While the authors did not obtain psychophysical measures of olfactory function or clinically define olfactory dysfunction in these subjects, these data are generally consistent with the notion that the olfactory deficit in schizophrenia reflects a rhinencephalic deficit that is more pronounced in the right hemisphere.

In one of only two olfactory activation studies, Malaspina and colleagues (1996) examined six male schizophrenia patients and seven age- and sex-matched controls using SPECT. Subjects sniffed UPSIT test items simultaneously through both nostrils, to activate the olfactory system during scanning. Controls, but not schizophrenia patients, had significantly increased regional cerebral blood flow (rCBF) in the right hippocampus, right medial temporal, left occipital and left medial temporal lobes following olfactory activation. This experiment suggests deficient activation of the tertiary cortical and medial temporal lobe olfactory areas in patients with schizophrenia. More recently, Crespo-Facorro and colleagues (2001) compared the haemodynamic response to a pleasant odorant with the response to an unpleasant odorant, while subjects evaluated the emotional valence and intensity of the stimulus. They found that

schizophrenia patients subjectively experienced an unpleasant odour in a manner similar to healthy volunteers but demonstrated impairment in the experience of a pleasant odour. Analysis of the rCBF data revealed a failure to activate limbic/paralimbic regions during the experience of unpleasant odours, with recruitment of a compensatory set of frontal cortical regions instead. These two studies provide very preliminary evidence supporting the hypothesis of functional olfactory impairments in patients with schizophrenia. However, their data must be viewed with caution, as they relied on relatively crude procedures and devices to deliver odours in the imaging environment. These methods are susceptible to marked variability in the quality and quantity of the odour stimulus, and to uncontrolled air pressure and thermal artifacts.

Event-related potentials

The ERPs, with their exquisite sensitivity to issues of timing, have had limited utility in olfactory research, due to the technical difficulties associated with precise odour stimulus delivery. Recent advances in olfactometry equipment (e.g. Olfactometer OM4/B, Heinrich Burghart GmbH, Wedel, Germany) have alleviated this problem and have given rise to a growing body of chemosensory ERP research. This multi-odorant dynamic air dilution olfactometer allows for precisely timed pulses of odorants to be embedded in a constantly flowing air stream with specified temperature and humidity (36.5°C; 80% relative humidity) without transient pressure artifacts (Figure 16.6).

Initial studies employing this methodology confirmed the chemosensory specificity of the method and the absence of cross-modal contamination.

Figure 16.6 Olfactometer for odour delivery during ERP studies. For a colour version of this figure please see Plate 4.

Subjects with congenital anosmia had intact ERP responses to chemosensory agents that stimulate the trigeminal nerve, while responses to pure olfactory stimulants were absent (Doty & Kobal, 1995). Olfactory ERPs (OERPs) were also found to be sensitive to the functional decline in olfactory abilities that occurs with normal ageing. ERP amplitudes were diminished in older healthy individuals, relative to younger subjects. These reductions were, as expected, greater in men than women (Evans *et al.*, 1995). The question of differential processing of odorants with different hedonic valences has also received some attention. Kobal and Hummel (1991) reported that an unpleasant odour (hydrogen sulphide) elicited larger amplitude responses following the right nostril stimulation, while responses to a pleasant odour (vanillin) were larger when presented to the left side. This is consistent with more general hypotheses concerning hemispheric specialisation for the processing of pleasant (left) and unpleasant (right) emotions (Davidson, 1984).

Although there have now been a few studies examining other clinical patient populations (Barz *et al.*, 1997; Hummel *et al.*, 1995), there has been little use of this methodology to study patients with schizophrenia. In the only previous related investigation, healthy subjects considered to be 'psychosis prone' were studied using pleasant (vanillin) and unpleasant (hydrogen sulphide) odours as physiologic-probes (Becker *et al.*, 1993). Results indicated that psychosis-prone subjects who scored high on 'physical anhedonia' showed higher OERP amplitudes in response to vanillin, whereas subjects who scored high on 'perceptual aberration' showed smaller OERPs to hydrogen sulphide. This is consistent with the psychophysical data, noted above, indicating that subjects at risk for psychosis may have aberrant physiologic responses to olfactory stimuli, suggesting the presence of an olfactory risk factor or marker for psychosis.

Neurophysiological studies

A dose-response olfactory ERP study in schizophrenia patients

Previous studies of olfactory dysfunction were limited to behavioural psychophysical measures of olfactory ability. To characterise more directly the functional status of the olfactory system, we have employed ERPs to assess the physiological brain response to odour stimuli. Using the sophisticated air dilution olfactometer described above, our research group characterised the physiological ERP response to three different concentrations of hydrogen sulphide in 21 patients with schizophrenia and 20 healthy controls (Turetsky *et al.*, 2003c). Figure 16.7 illustrates the characteristic biphasic OERP waveform. Note that the N1 and P2 components seen here are delayed by 200 to 300 ms, relative to typical auditory or visual ERP waveforms. This reflects the additional

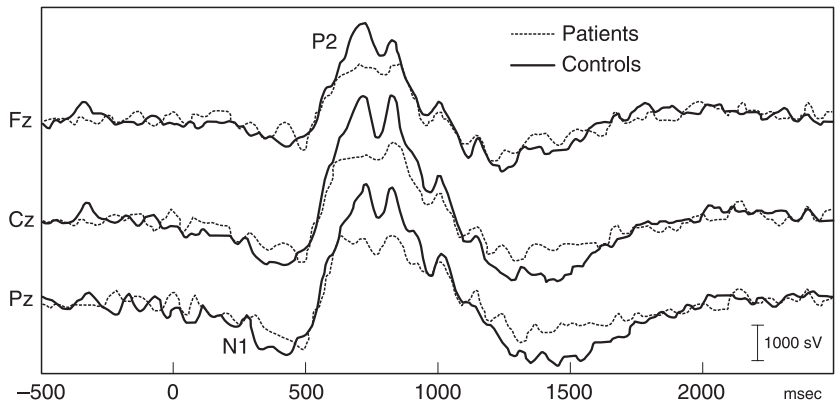

Figure 16.7 Olfactory Event-Related Potentials(OERPs).

time required in olfaction, compared to audition or vision, for molecules of the odorant to bind to chemoreceptors in the olfactory epithelium.

We found that patients had dose-dependent reductions in the amplitudes of both N1 and P2, with associated P2 latency prolongation. The patient deficits were more prominent with increasing odour concentration, with the magnitude of the cortical response exhibiting an abnormal ceiling effect. It appeared that the olfactory systems of these patients were 'overwhelmed' by the stronger stimuli, becoming more dysfunctional as they tried to respond to the increased stimulus demand. These physiological measures were directly related to psychophysical performance measures: N1 amplitude, which specifically denotes primary olfactory cortex activity (Kettenmann *et al.*, 1997), was related to impaired odour detection threshold sensitivity; P2 amplitude, which reflects secondary sensory integrative processes, was related to impaired odour identification. These data provide the first direct evidence for a physiological impairment in the olfactory cortex in patients with schizophrenia. It is important to emphasise that this abnormality reflects an obligate physiologic response elicited by repetitive stimulation of the first cranial nerve, in the absence of any attentional or cognitive processing demands. Although odour concentration varied, the stimuli were neither qualitatively distinctive nor task-salient. It is unlikely, therefore, that this reflects other nonspecific factors that might alter brain function. It is not clear, at this point, whether this cortical deficit is primary, or secondary to more peripheral abnormalities.

A dose-response OERP study in first-degree relatives

To assess the possible role of a genetic vulnerability factor in this physiological ERP deficit, we conducted the identical study in a sample of 15 healthy family

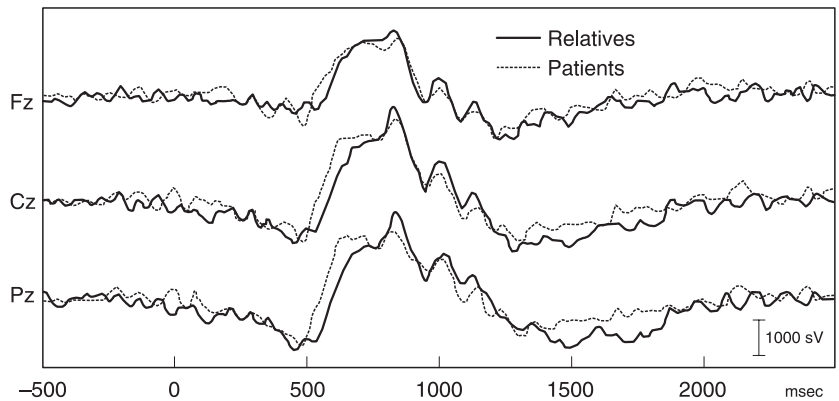

Figure 16.8 Olfactory ERPs in family members of patients.

members and matched controls. We found a profile of abnormalities in the family members that precisely matched what we observed in patients. That is, there were dose-dependent deficits in N1 amplitude, P2 amplitude and P2 latency. There are two important features to note, concerning this physiological deficit. First, similar to the results of the OB study, this subgroup of family members was not impaired on psychophysical tests of olfactory ability. This likely reflects a threshold phenomenon. That is, behavioural impairments may not be observed until the substrate abnormality rises above some critical threshold. Such structure–function relationships are well established in many organ systems. This confirms our expectation that these physiological studies are more sensitive to detecting subtle deficits. Second, contrary to what has been reported in virtually all previous studies of familial abnormalities in schizophrenia, the relatives in this study did not show an intermediate deficit (i.e. a deficit whose magnitude was between that of patients and controls). Rather, the relatives' deficit was equal to that of patients (Figure 16.8). This implies a much greater genetic contribution to, and less environmental modification of, this neural response – i.e. greater heritability – indicating that it could be a more useful endophenotypic vulnerability marker.

Summary

These studies have broken new ground in demonstrating the existence of physiological and anatomical abnormalities in the olfactory system in schizophrenia. The similar findings in unaffected family members support a genetic contribution to these deficits and, in conjunction with nasal cavity abnormalities, suggest early neurodevelopmental aetiology. Initial hypotheses,

which were based on the evidence for limbic and frontal lobe pathology in schizophrenia, focused on abnormalities in 'olfactory eloquent' cortical regions of the CNS. However, studies from our lab indicate that there are also structural and developmental physiological abnormalities in the most peripheral elements of the olfactory system.

One concern may be the relevance of findings in peripheral olfactory components to processes occurring in the cerebrum. Embryologically, the olfactory epithelium and bulbs are closely related to important limbic and neuroendocrine parts of the brain (Dryer & Graziadei, 1994; Farbman, 1994; Wray *et al.*, 1989). Many of the same molecular pathways that guide development in the cerebrum do so in the olfactory structures. While much attention has focused on limbic and frontal regions in schizophrenia (Harrison & Roberts, 2000), there are also numerous studies indicating neurobiological abnormalities throughout the CNS (Puri *et al.*, 1996; Tran *et al.*, 1998). The reason the predominant symptoms of schizophrenia may preferentially involve higher cognitive, emotional and social domains may be that the neurobiological abnormalities of the illness have their greatest impact in brain regions that exhibit the necessary plasticity for higher cognitive processes. If this is true, then the peripheral olfactory system, with its ongoing dynamic developmental and regenerative capacity, may represent an accessible model in which the neurodevelopmental abnormalities underlying schizophrenia are constantly recapitulated.

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17

Olfactory hallucinations

Dennis Velakoulis

Introduction

Traditional teaching in psychiatry has been that until proven otherwise the presence of olfactory, gustatory and visual hallucinations is a marker of underlying organic pathology. Visual hallucinations are seen in delirium or Lewy body disease, while olfactory and gustatory hallucinations raise the possibility of medial temporal pathology, especially epilepsy. The aims of this chapter are first to review the literature on olfactory hallucinations and second to discern any characteristics of olfactory hallucinations which allow those of organic aetiology to be distinguished from those of functional origin, such as those related to schizophrenia.

The subjective experience of olfactory phenomena in the absence of a stimulus has been generally referred to as an olfactory hallucination, though when experienced in the context of epilepsy the term olfactory aura has been preferred. In addition, other terms used to describe the same phenomenon have included olfactory reference syndrome, experiential hallucinations, and experiential responses. Each of these terms will be used in the course of this review and their origins explained. The available literature is replete with case series, case reports, highly selected populations and widely differing methods of assessment. While this limits the comparisons between studies, it is still possible to estimate the prevalence and nature of the olfactory hallucinations in many of the studies.

Epilepsy and olfactory auras

Numerous studies have examined groups of patients with regard to the presence and characteristics of olfactory hallucinations but there has been no attempt to

standardise the descriptions across different studies, an understandably difficult task. The literature is dominated by several series of patients with epilepsy, case reports and individual patient descriptions of their experiences, reflecting the nature of scientific publications in the first half of the twentieth century. Similarly it is difficult to elicit from the available studies how often olfactory hallucinations are associated with other phenomena or make up the sole symptom of an aura. A further obstacle in the interpretation of the literature relates to the varying classifications and diagnoses of epilepsy over the last 100 years.

An epileptic aura is defined as 'that portion of the seizure which occurs before consciousness is lost and for which memory is retained afterwards.' (Commission on classification and terminology of the International League against Epilepsy, 1981) The term was first used by Pelops, the master of Galen, who noted the 'breath of air' which patients described before a seizure and which he attributed to wind passing up the veins. (Lennox and Cobb, 1933; Taylor and Lochery, 1987). An early study of the prevalence of auras by Lennox and Cobb found that 56.2% of the 1359 epilepsy patients described an aura, a figure almost identical to the 57% cited for an earlier study by Gowers (Lennox and Cobb, 1933). Lennox and Cobb described 226 different types of aura amongst the 1059 auras described by the 750 patients. A more recent study of patients with temporal lobe epilepsy identified an aura in 64% of 290 patients (Gupta *et al.*, 1983). The commonest auras described by patients across these studies were of epigastric sensations, motor phenomena, affective states, déjà vu and vertiginous sensations. Though olfactory hallucinations are often quoted as characteristic of an epileptic aura, the available evidence would suggest that they are indeed uncommon. In patients unselected for the type of epilepsy, about 1% describe olfactory hallucinations (Jackson and Stewart, 1899; Lennox and Cobb, 1933), while in studies of patients with temporal lobe epilepsy the figures range from 0.03 to 13% (Acharya *et al.*, 1998; Chen *et al.*, 2003; Feindel and Penfield, 1954; Fried *et al.*, 1995; Gupta *et al.*, 1983; Penfield and Perot, 1963; Taylor and Lochery, 1987).

One of the first published descriptions of olfactory hallucinations during an epileptic aura was by Hughling Jackson (Jackson, 1899) in a man with presumed but not pathologically confirmed right temporal lobe pathology who described a strong smell like camphor or ether. Jackson subsequently proposed the term 'uncinate fits' for fits preceded by sensations of smell or taste, together with orobuccal chewing, lip smacking and masticatory movements (Jackson, 1899). Sixty years later, Daly (1958) revived the term 'uncinate fits' in a description of 55 patients of whom 20 (36%) had olfactory and gustatory phenomena associated with seizures of various aetiology. Daly postulated that common to all

these seizures was involvement of the uncus, which he considered to be the cortical centre for smell. Daly divided olfactory experiences into hallucinations and illusions, the latter referring to alterations in the nature of olfactory sensation during the seizure; e.g. odours become more intense. Patients with olfactory hallucinations described unrecognisable odours which were usually neutral in nature, though both pleasant and unpleasant odours were experienced. In the patients with olfactory auras, associated auras and sensations were common but not quantified by the authors.

In a study published in 1933, Lennox and Cobb conducted a survey of U.S. neurologists and physicians who worked with epilepsy patients (Lennox and Cobb, 1933). 56.2% of the 1527 cases described 327 different sensations which met the author's criteria for an aura. There were no differences in the experience of an aura identified by gender or epilepsy aetiology. Auras were found to be more frequently associated with intellectual disability ('mental deterioration') and duration of epilepsy. Fifteen patients (1.0%) had olfactory hallucinations which were described as disagreeable (9), peculiar (2), like bananas, camphor or the smell of ironing (1 each). It is not possible from the data available nor the text of the article to ascertain the relationship of the olfactory auras to any clinical variables.

Temporal lobe epilepsy (TLE)

A 1983 study of the relationship between EEG abnormalities and aura investigated 209 patients with TLE patients (Gupta *et al.*, 1983). The majority of patients described an aura (89%) but only 5 (2.4%) reported olfactory auras. Taylor and Lochery (1987) identified an olfactory aura in 10/88 (11.4%) TLE patients but they do not provide any further discussion of the nature of the smells. Neither study provides information specific to the patients with olfactory auras.

The relationship between auras and focal epilepsy pathology before and after epilepsy surgery has been examined more recently (Fried *et al.*, 1995) (see also Chapter 2). Ninety patients with a known history of auras and intractable epilepsy included 43 patients with hippocampal sclerosis, 30 patients with other temporal lobe lesions and 17 patients with extratemporal lesions. The 90 patients in the study described 125 auras (mean 1.4 auras per patient). Despite a detailed assessment of aura in the patient group, it is not possible to discern the relationship between different types of auras, i.e. how many patients had isolated auras multiple auras or the types of auras associated together. Of the 11 patients (12.2%) who experienced olfactory/gustatory auras (the study grouped these two together), nine had hippocampal sclerosis. The only other aura type to differ significantly between the pathology groups were epigastric

auras, which were also significantly more common in patients with hippocampal sclerosis. The quality of the auras was not described in the study. Following surgical resection, only one of these 11 patients experienced ongoing olfactory/gustatory auras. This patient had a pathological diagnosis of hippocampal sclerosis.

One recent study assessed olfactory hallucinations before and after surgery in 217 patients who had undergone temporal lobectomy for intractable TLE (Chen *et al.*, 2003). Twelve (5.5%) of the patients described olfactory auras but only one patient had a gustatory aura. Hippocampal sclerosis was present in seven patients, four patients had a tumour and one patient had an arterio-venous malformation. At post surgical follow-up no patients had ongoing auras though the length of the follow-up is not stated. All patients described the experience as unpleasant, with descriptions of the smell as 'fetid, rotten or stink' food, burning, charred things, alcohol, or medicine. Only one patient (8.3%) had isolated olfactory hallucinations, while the more commonly associated feelings in the other 11 patients were of abdominal sensations, fear, autonomic or visual symptoms. Most patients could not identify any temporal sequence of aural phenomena, though two patients described that the olfactory hallucinations were preceded by abdominal sensations. Laterality of the pathology was not a factor in the olfactory hallucinations. Based on their observations and their review of the literature, the authors speculate that amygdala pathology is critical in the generation of olfactory auras.

In 1998, Acharya and colleagues identified 14 patients with olfactory hallucination in a group of 1423 patients (0.9%). Nine patients described the smell as familiar (burning, sulphur, peanut butter, toothpaste, flowers) while five could not identify the smell. Seven patients described the smell as unpleasant, five were neutral, and two said the smell was pleasant, like that of flowers. Five of the patients had associated gustatory auras, one had abdominal aura, one visual, four had psychic auras and one heard the sound of the ocean. Thus in this group only 2/14 (14%) patients had isolated olfactory hallucinations and 12/14 patients described associated auras. Nine patients were diagnosed with a temporal lobe tumor, seven involved the amygdala and hippocampus, while two were restricted to the amygdala. One patient had hippocampal sclerosis and was the only patient to describe abdominal auras. One patient had a left temporal/frontal lobe tumour. MRI findings in the remaining patients were normal. Eight of the nine patients who went on to surgery were free of seizures and aura following surgery. Like Chen and colleagues (2003), the authors propose that the amygdala are the site of the olfactory auras and that the presence of an olfactory aura provides potential anatomical localisation to the amygdala. In contrast to the Chen *et al.* (2003) and Fried *et al.* (1995) studies,

these authors identified tumours as the more common underlying pathology in patients with olfactory auras.

Experiential responses evoked by brain stimulation

Penfield and Perot (1963) described patient responses to electrical stimulation of the cortex during neurosurgery as 'experiential responses' and used the term 'experiential hallucinations' for the same phenomena occurring during a spontaneous seizure. Their review of 1132 consecutive operations revealed that only stimulation of the temporal cortex produced experiential responses. No patient described olfactory experiences during these procedures though only a small proportion of patients were stimulated within the medial temporal region. Nearly 30 years later, Gloor and colleagues (Fish *et al.*, 1993; Gloor, 1990) reported a study in which limbic structures were stimulated in 29 patients using sterotaxically implanted electrodes in the amygdala and anterior hippocampus. Of the 18 patients who reported experiential responses, only one reported an olfactory experience during stimulation of the left amygdala.

Summary

Olfactory hallucinations/auras are rare in patients with epilepsy (about 1%) but may be more common when the epilepsy type is restricted to TLE (up to 10%). Olfactory auras are generally unpleasant and rarely occur in isolation either from other auras or associated seizure phenomena. Olfactory auras do not seem to be associated with any one specific pathology but may be of localising value, given the observed relationship between olfactory hallucinations and pathology of the amygdala.

Olfactory hallucinations in other neurological disorders

Olfactory hallucinations have been rarely reported as the presenting symptom for other cerebral pathology. Silberstein and colleagues (2000) describe olfactory aura in a man with cluster headaches 'a bad citrus fruit smell', which preceded the headache by 3 to 4 minutes. Olfactory hallucinations as an aura for migraines have also been reported and reviewed by Fuller and Guiloff (1987). The smells reported by migraine sufferers tended to be unpleasant, with descriptions such as decaying animals, burning cookies, cigars, peanut butter and cigarette smoke.

Nye and Arendts (2002) report the sudden onset of a smell 'like burning paint mixed with rotting flesh' in a 58-year-old woman. The patient described episodes of the smell lasting 2 to 3 minutes and gradually increasing in frequency over

four days. Investigation revealed a left-sided uncinate intracerebral haemorrhage. The symptoms resolved gradually with anticonvulsant treatment.

Olfactory hallucinations have been reported to precede the motor manifestations of Parkinson's Disease (Sandyk, 1981) and to have benefited from *l*-dopa treatment. A longitudinal study of Parkinsonian patients treated with *l*-dopa found that the early development of hallucinations (predominantly visual but also tactile, auditory and olfactory) signalled either a co-morbid psychotic illness or an evolving Parkinsonism-plus syndrome (Goetz *et al.*, 1998).

Olfactory hallucinations of gasoline, faeces, urine and garbage have been described in patients with chronic cocaine use (Siegel, 1978) and tend to be associated with hallucinations in other modalities.

Olfactory hallucinations have been reported as an unexpected complication of the administration of intravenous (Nickell and Uhde, 1994) and oral (Koenigsberg *et al.*, 1993) caffeine boluses in normal and panic disorder subjects during research studies of panic and anxiety disorders.

Two cases of idiopathic olfactory hallucinations were reported to have responded to anticonvulsant treatment (Majumdar *et al.*, 2003), while a case of unilateral paroxysmal olfactory hallucinations resection of the ipsilateral olfactory bulb led to cure.

Summary

While the literature related to organic states and olfactory hallucinations is limited by the predominance of case reports, the olfactory experiences of patients with a range of 'organic' pathologies are remarkably uniform in their quality. As described by patients with epilepsy, the perceived smells are unpleasant and usually of burning, rotting, fecal, or other organic material.

Psychiatric disorders

The very early literature regarding the identification of olfactory hallucinations in psychiatric patients is summarised by Rubert and colleagues (Rubert *et al.*, 1961). Alliez and Nosida examined 8800 patients in a French asylum and identified olfactory hallucinations in 1% of the patients. Davidson identified a 4% prevalence of olfactory hallucinations in 500 patients, while Bellak was quoted to have identified olfactory hallucinations in 1.6% of cases. The diagnostic breakdown of these patient groups is not provided by the Rubert review. Subsequently, a number of studies have examined psychiatric populations for the prevalence of olfactory hallucinations.

Goodwin and colleagues (1971) interviewed consecutively admitted patients who described hallucinations across a number of diagnostic categories including schizophrenia, manic depression, alcoholism, hysteria and organic brain states. Olfactory hallucinations were found in 20% of patients with schizophrenia, 18% of patients with an affective disorder, 11% of patients with an organic brain syndrome and 62% of patients with hysteria. No patient with alcoholism described olfactory hallucinations. Olfactory hallucinations were usually unpleasant (perfume, smoke, body odours, animal smells) though their quality did not differ between diagnostic groups and 'almost always' occurred as part of a delusional system.

Olfactory hallucinations have been consistently reported in patients suffering from schizophrenia. Stedman and colleagues (1998) found that 26% of their patient group reported olfactory hallucinations but the authors do not detail the nature of the hallucinations. They did not identify any relationship between olfactory hallucinations and olfactory impairment. Pearlson and colleagues (1989) also identified olfactory hallucinations in 17% of 130 patients with schizophrenia. Olfactory hallucinations were identified in 28% of patients with late onset schizophrenia and 13% of younger patients with early onset schizophrenia. No patient in their third group of elderly patients with early onset schizophrenia described olfactory hallucinations. There is no further comment made about the nature of the olfactory hallucinations or their relationship to the symptoms.

Mueser and colleagues (1990) interviewed 117 consecutively admitted patients with schizophrenia for their lifetime history of hallucinations. The respective rates for auditory, visual, tactile and olfactory/gustatory hallucinations were 72, 16, 17 and 11%. The authors observed that the majority of patients with non-auditory hallucinations (92% of patients with olfactory/gustatory hallucinations, 84% of patients with tactile and 84% of patients with visual hallucinations) described auditory hallucinations. The presence of tactile and olfactory/gustatory hallucinations were highly correlated to each other, i.e. patients with a hallucination in either modality were also likely to have the other. Both tactile and olfactory/gustatory hallucinations (but not auditory or visual hallucinations) were correlated with the severity of delusions.

The questions of diagnostic specificity and the relationship of the olfactory hallucinations to gender and olfactory identification was addressed in a study of 131 patients with schizophrenia, 21 patients with depression, 31 patients with eating disorders and 77 normal control subject (Kopala *et al.*, 1994). Olfactory hallucinations were described by patients from all three patient groups but not in the control group (schizophrenia 35%, depression 19%, eating disorders 29%) and the prevalence was not significantly different by group. Women with

schizophrenia were more likely to describe olfactory hallucinations than males. Patients with schizophrenia and depression generally described unpleasant smells, while the eating disorder patients described hallucinations that were food related and generally pleasant. Patients with depression and eating disorders, but not those with schizophrenia, were aware that their perceptions were abnormal and illness related. No relationship was identified between olfactory hallucinations and olfactory identification.

Olfactory hallucinations have also been noted in non-Western cultures. Teggin and colleagues (1985) reported that 59% of black African patients described olfactory hallucinations compared to 20% of white and 27% of coloured patients. The black African patients' description of the hallucinations was often related to death or decay. There was no consistent description in the other groups, leading the authors to speculate that this may have been a culture-bound syndrome. Ndetei and Singh (1983) identified olfactory hallucinations in 25% (13/51) of a group of patients with schizophrenia identified in a Kenyan hospital. None of the 29 patients with other psychiatric diagnoses described olfactory hallucinations. In a second Kenyan study, only 3% of 141 patients with schizophrenia were found to have olfactory hallucinations (Ndetei & Vadher, 1984). No details were given regarding the nature of the olfactory hallucinations in either of these two latter studies. The World Health Organization 10-country study of 1288 patients with first-episode schizophrenia published in 1992 identified olfactory hallucinations in 13% of patients in developed countries and 9% of those patients from developing countries (Jablensky *et al.*, 1992).

In summary, the prevalence of olfactory hallucinations in psychiatric populations has varied widely. Olfactory hallucinations have been described in patients with differing diagnoses including schizophrenia, affective disorders, eating disorders and hysteria. More recent studies which have investigated populations of patients with schizophrenia have also varied widely in their estimates, with the prevalence of olfactory hallucinations ranging from 3 to 59%. It is difficult to compare these studies, given the differing nature of their recruitment, their rating tools and the study designs.

The qualitative nature of olfactory hallucinations

In addition to the qualities of olfactory hallucinations explained in the studies described above, several studies have investigated patients known to have hallucinations, either olfactory or other, in order to elucidate the qualitative features of the hallucinations.

Bromberg and Schilder (1934) provide one of the earliest specific descriptions of olfactory phenomena in psychiatric patients. They identified 40 patients with olfactory hallucinations, 22 of whom had a diagnosis of schizophrenia, 10 with alcoholism, 2 with epilepsy and one each with syphilis, cancer, dementia, depression and neurosis. Regardless of the diagnosis, the perceived smells were unpleasant and were usually related to the body or bodily excrement.

Rubert and colleagues (1961) interviewed 24 patients with schizophrenia and hallucinations. Eighty-three percent reported olfactory hallucinations that were predominantly unpleasant, including smells of gas, gunpowder, bug bombs, ammonia, dogs, incense and perfume. No patient had olfactory hallucinations without having hallucinations in another modality. The authors disputed the 'widely held' belief of the time that olfactory hallucinations in schizophrenia were predictive of poor prognosis. The authors suggest that olfactory hallucinations were nearly as common as auditory hallucinations but that psychiatrists did not routinely ask specifically about olfactory hallucinations. They speculate that perhaps only those patients with chronic illness and disturbed ego boundaries volunteered olfactory symptoms spontaneously.

In one of the largest single series of patients with olfactory hallucinations, Pryse-Phillips identified 137 patients, 99 of whom he interviewed, with olfactory hallucinations by surveying local neurologists, psychiatrists and psychiatric institutions (Pryse-Phillips, 1970; 1975). He classified the majority of patients into one of the four groups: schizophrenia, depression, TLE and a fourth diagnostic group which he termed 'olfactory reference syndrome' (see also Chapter 18). In DSM-IV, this latter diagnosis would now be considered as a delusional disorder — somatoform type. A similar syndrome was termed 'chronic olfactory paranoid syndrome' by Videbech (1967), though this article was based on a case series of five patients.

Pryse-Phillips identified intrinsic and extrinsic olfactory hallucinations. Intrinsic hallucinations were those in which the patient believed that the smell was of himself and that it emanated from his body. Such patients were usually pre-occupied by the smell and its effects and were more commonly diagnosed with olfactory reference syndrome. Extrinsic hallucinations were those in which the patient believed that the smell was put upon them by an outside agency or person and were observed in patients with schizophrenia, depression and organic illness.

Pryse-Phillips made several other observations on the basis of his research in patients with olfactory hallucinations. In particular he noted that olfactory hallucinations of organic cause are usually episodic and that continuous perception of smell was more indicative of a functional psychiatric disturbance. Further, patients with schizophrenia usually display extrinsic hallucinations

which were usually associated with first-rank symptoms and other signs of schizophrenia. Similarly he noted that olfactory hallucinations in patients with epilepsy usually co-exist with other epileptiform symptoms. Patients with olfactory reference syndrome could be distinguished from the other groups by the intrinsic nature of their hallucinations and their 'contrite' response (embarrassed, shamed and believing that they offend others).

Summary

Olfactory hallucinations are observed in patients with schizophrenia but usually in combination with the other symptoms of schizophrenia and with hallucinations in other modalities. There are no clear-cut qualitative differences between the olfactory hallucinations described by patients with schizophrenia compared to patients with 'organic states', though the presence of continuous olfactory hallucinations is more suggestive of a psychiatric diagnosis. As a rule, olfactory hallucinations regardless of aetiology tend to be unpleasant smells of burning, rotting or excremental features.

Conclusions

Patients who describe olfactory hallucinations are likely to describe or exhibit other symptoms depending on the underlying condition. Isolated olfactory hallucinations are rare and not a feature of either schizophrenia or epilepsy with a focus in the temporal lobe. The presence of episodic olfactory hallucinations may suggest organic pathology, but a careful history for other features of schizophrenia (auditory hallucinations, delusions, thought disorder) or epilepsy (aura followed by seizure activity in the form of motor movements) is essential in formulating a diagnosis. The quality of the olfactory hallucinations will not usually provide diagnostic information but may be of significance in the psychotic patient who seeks to identify the source of the smell or the patient with a delusional disorder who becomes socially isolated and depressed as a result of their belief that others are offended by them.

The amygdala is considered to be an important anatomical substrate for both epilepsy associated with olfactory hallucinations and schizophrenia. The successful treatment of olfactory hallucinations in three patients with epilepsy and three patients with schizophrenia who underwent amygdalotomy is therapeutically now of historical interest but provides further support for the role of the amygdala in the genesis of olfactory hallucinations (Chitanondh, 1966).

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18

Delusions of body malodour: the olfactory reference syndrome

Katharine Phillips, Craig Gunderson, Uschi Gruber, and David Castle

He said: 'For the past three months I've been giving off a body odor. It smells like a swamp, dug up mud, a rotten smell; it comes from my guts. I can't go anywhere. I don't want to go with my friends, and I think I've lost them on account of that .... I smell it through my nose. I smell it all over the body. I think it stays 6 feet around me. It smells more in front of me. Sometimes it smells like a swamp. I never experienced something similar....'

Gabriel Garcia Marquez

Introduction

The olfactory reference syndrome (ORS) is an under-recognised type of delusional disorder that has been described for more than a century. It consists of a false belief that one emits an offensive body odour and is often accompanied by prominent delusions of reference and repetitive behaviours aimed at checking or reducing the perceived odour. ORS is associated with significant distress and impaired functioning, especially in the social realm. Many patients seek nonpsychiatric treatment from gastroenterologists, dermatologists, proctologists, dentists and other specialists; however, such treatments appear to be generally ineffective. In contrast, although data are limited, certain psychotropic medications and behavioural interventions are promising.

This chapter discusses ORS's history, clinical features, prevalence, treatment response, possible pathogenesis, nosological status and relationship to other psychiatric disorders, including mood disorders, schizophrenia, social phobia, and obsessive compulsive disorder (OCD). It is based on a review of several

hundred cases reported in the literature over the past century, including what are to our knowledge the largest reported series of ORS; these series include 15 to 38 patients each and are from Canada, Japan, Nigeria and Saudi Arabia (Iwu & Akpata, 1990; Osman, 1991; Pryse-Phillips, 1971; Yamada *et al.*, 1977).

History

ORS has a long and rich history, having been described for more than a century (Potts, 1891; Tilley, 1895). Two cases of 'hallucination of smell,' for example, were reported in the United States in 1891 (Potts, 1891). One patient, a 50-year-old man described as delusional, stated that 'he had been troubled for the past three months with smelling a very bad odour, which he likened to that of a ''back-house,'' and which came from his own person. [He believed] this smell was so very strong that other men objected to working with him . . . .' The other patient, a 47-year-old man, believed that he 'smelt like ''a heavy sweat,'' and wherever he goes he hears people talking about it. He smells it himself, but admits that his wife does not. It is so offensive that men will not work near him.'

During the past century, cases of ORS have been reported around the world, including France, Italy, Germany, Scandinavia, England, Nigeria, Saudi Arabia, Japan, Canada and the United States. Terms for ORS have varied and include hallucinations of smell, parosmia, autodysosmophobia, bromidrosiphobia, delusions of bromosis (bromhidrosis referring to actual malodorous perspiration), olfactory hallucinatory state, olfactory hallucination, chronic olfactory paranoid syndrome, delusional halitosis, hallucinatory halitosis, olfactory delusional syndrome and imaginary halitosis. In the German literature, this condition has been referred to as 'Eigengeruchspsychose,' in France as 'délire olfactif' (olfactory delusional state), and in Japan as 'offensive corporal smell' and 'fear of emitting bad odours.'

Individuals with ORS have been noted (Bishop, 1980) to meet Kraepelin's criteria for 'paranoia' in that they manifest a 'permanent and unshakeable delusional system resulting from internal causes, which is accompanied by perfect preservation of clear and orderly thinking, willing and acting' (Kraepelin, 1976). ORS has also been considered a type of monosymptomatic hypochondriacal psychosis – a single, isolated delusional or 'delusion-like' belief of having a disease (Bishop, 1980). Delusions of parasitosis and delusional body dysmorphic disorder (the belief that an aspect of one's appearance is ugly or deformed) are also commonly included under this rubric (Bishop, 1983). ORS has never been categorised as a separate disorder in Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association, nor in the

World Health Organisation's International Classification of Diseases (ICD). Indeed, it was not specifically mentioned until DSM-III-R (APA, 1987). It is included in DSM-IV (APA, 1994) and ICD-10 (WHO, 1992) as an example of delusional disorder, somatic type (the modern equivalent of monosymptomatic hypochondriacal psychosis), although its non-delusional variant is not specifically mentioned. Neither DSM-IV nor ICD-10 allows the diagnosis if criterion A (G1 for ICD-10) for schizophrenia has ever been met or if the symptoms are due to the direct physiologic effects of a substance or a general medical condition.

Clinical features

Symptoms

Individuals with ORS are preoccupied with the belief that they emit an unpleasant or offensive body odour, which they falsely believe can be perceived by others. The perceived odour is often noted to be constantly present. The most commonly reported odours are flatulence/fecal/anal odour, general body odour, halitosis (also referred to as 'flatophobia') and genital odour (Iwu & Akpata, 1990; Osman, 1991; Pryse-Phillips, 1971). Other reported odours are of sweat, armpit odour, sperm, urine and supposedly malodorous and clammy hands and feet (e.g. Iwu & Akpata, 1990; Osman, 1991; Pryse-Phillips, 1971). Occasionally, the odour is said to resemble such nonbodily smells as ammonia (Tilley, 1895), detergent (Ross, 1987), 'burnt rags' (Harriman, 1934), candles (Tilley, 1895) or rotten onions (Sutton, 1919). Some patients, however, describe the smell and its source in vague terms, without specific identification with a 'known' smell.

In DSM-IV (APA, 1994), the skin, mouth, rectum and vagina are noted to be sources of the perceived odour. Sources noted in the literature are the anus, mouth (in cases of halitosis or fecal odour), feet, nose, axilla and genitalia. In several cases, the odour was attributed to a supposed underlying illness, such as a 'diseased womb' (Nelki, 1988), a skin disease (Harriman, 1934), an incompetent anal sphincter or stomach problems or an unknown organic disorder (Videbech, 1966). Some patients can identify a source of the odour at some times but not others. Of interest, in some cases the odour's characteristics do not correspond to its supposed source. While most reports suggest that only one odour is the focus of concern, some describe a concern with several odours simultaneously (e.g. flatus and bad breath (Beary & Cobb, 1981) or with different odours over time (Johanson, 1964; Sutton, 1919). In one case, for example, the odour initially was believed to originate in the trunk and axillae but then gradually moved downward and became confined to the patient's ankles and feet (Sutton, 1919).

Although persons with ORS universally believe that they emit an odour, they do not always actually perceive the odour. In many cases, however, an olfactory hallucination is present (Bishop, 1980; Harriman, 1934; Munro, 1988; Pryse-Phillips, 1971). In such cases the delusional belief can be considered to either result from, or lead to, the hallucination (Malasi *et al.*, 1990). Pryse-Phillips (1971), who selected her 36 cases on the basis of the presence of olfactory hallucinations, described the hallucinations as 'a real and immediate perception ... often perceived in the absence of other odours.' Patients who do not actually perceive their odour usually infer its presence from the behaviour of other people (Marks & Mishan, 1988). Iwu & Akpata (1990), for example, noted that most of their patients with delusional halitosis did not claim to smell their breath; rather, they assumed that they had halitosis 'by misinterpreting the attitudes of people around them,' and Alvarez (1958) described several cases in which patients knew they emitted a bad odour 'because (other people) sniff, or rub their nose, or clear their throat.' Some patients who do not perceive an odour attribute this to a malfunctioning of their olfaction (Videbech, 1966). Munro (1982) notes that it is unclear whether ORS is a hallucinatory disorder, since the patient often describes the odour graphically, but traditionally the core of the illness is regarded as delusional, with possible secondary illusional misinterpretations and ideas of reference.

The ORS belief involves significant preoccupation and is sometimes described as an obsession (Alvarez, 1958; Hawkins, 1987; Osman, 1991). Individuals with this syndrome may spend many hours a day thinking about the perceived odour, to the point where the concern 'can become an obsession that dominates the victim's life' (Hawkins, 1987). In a series of cases with delusional halitosis, 'the patients' lives were entirely dominated by their imagined bad breath' (Iwu & Akpata, 1990). These observations raise the question of whether ORS may be related to, or even a variant of, OCD.

Most descriptions emphasise the syndrome's interpersonal aspects. Patients are often noted to be ashamed, embarrassed and concerned about offending others with their odour (Alvarez, 1958). They have been described as having a 'contrite reaction' — that is, a 'deeply ashamed, embarrassed, self-abasing, (and) sensitive reaction' to the supposed odour, because they 'believed that their bodies stank and were a perpetual source of displeasure or disgust to people near them' (Pryse-Phillips, 1971). Indeed, the syndrome is sometimes defined in terms that emphasize the fear of offending others — for example, 'an anxious fear or conviction that one emits bad odours that offend other persons' (Bourgeois & Paty, 1972).

ORS beliefs are generally considered delusional, although nondelusional forms have occasionally been described. Osman (1991), for example, noted that some

patients appeared to have overvalued ideas rather than delusional thinking, and Bishop (1980) reported that 'delusions of bromosis occur in both neurotic and psychotic patients.' Several authors have commented on the difficulty in some cases of evaluating the nature of the belief and differentiating delusions from overvalued ideas (Malasi *et al.*, 1990; Osman, 1991).

As implied by the syndrome's name, delusions of reference related to the odour are frequently mentioned in the literature. Nearly all (97%) of Pryse-Phillips's 36 cases experienced referential thinking (1971). Indeed, as previously noted, some individuals cannot actually smell the odour but rather infer its presence from the behaviour of others (Alvarez, 1958; Iwu & Akpata, 1990). Referential thinking includes hearing others comment on the odour (e.g. Bishop, 1980; Malasi *et al.*, 1990; Marks & Mishan, 1988; Potts, 1891) (such as 'old smelly' or 'stinker'; Pryse-Phillips, 1971) or refer to such things as perfumes or baths (Bishop, 1980). While such experiences sometimes appear to constitute an auditory hallucination, this is not always the case, with the individual noting that he or she 'knows' that comments are being made (Potts, 1891; Videbech, 1966). Referential thinking may also result from events such as receiving bath oil as a gift, or observing others opening windows to get fresh air, touching or holding their nose, clearing their throat, looking or moving away from or toward the individual, putting newspapers in front of their face, or making other movements or 'gestures of disdain' (e.g. Alvarez, 1958; Beary & Cobb, 1981; Bishop, 1980; Davidson & Mukherjee, 1982; Iwu & Akpata, 1990; Pryse-Phillips, 1971). If other people do not behave in these kinds of ways, the patient may attribute this to politeness (Davidson & Mukherjee, 1982). Iwu & Akpata (1990) stated that 'these attitudes were usually brought about by the patients themselves,' noting, for example, that a student might sit at the periphery of the class and then complain that other students avoid sitting near him.

The literature also describes characteristic behaviours, many of which could be conceptualised as repetitive ritualistic behaviours or as 'safety' behaviours that are intended to eliminate, camouflage or mask the supposed odour. Such behaviours have been referred to as 'counterphobic rituals' (Bishop, 1980) and 'contrite reactions' (Pryse-Phillips, 1971) that are performed to avoid offending others. The most frequently mentioned behaviour is excessive showering or washing (e.g. Bishop, 1980; Brotman & Jenike, 1984; Marks & Mishan, 1988; Ross *et al.*, 1987). Frequent clothes changing or laundering are also common (Bishop, 1980; Ross, 1987). Individuals with ORS may also use excessive amounts of deodourant, soap, cologne or powder, with Pryse-Phillips (1971) reporting that 82% of her cases used deodourants or washed 'to excess'. Individuals with halitosis concerns may eat excessive mints or use large amounts

of mouthwash or toothpaste, avert their head or cover their mouth with their hand, smoke incessantly or eat special diets (Iwu & Akpata, 1990; Malasi *et al.*, 1990). Other behaviours include wearing several layers of clothes (e.g. underwear) (Brotman & Jenicke, 1984), using the toilet excessively (Marks & Mishan, 1988) or wrapping one's feet in plastic and wearing special shoes to combat 'smelly, sweaty' feet (Johanson, 1964). Such behaviours usually appear to result in little or no symptomatic relief. In one report, excessive washing resulted in eczema (Videbech, 1966).

Checking behaviours—usually consisting of attempts to detect the presence of the odour—are also characteristic of ORS. One individual, for example, 'would sit at home and sniff at herself,' and another checked his anal area for seepage several times a day (Brotman & Jenicke, 1984). Persistent reassurance seeking has also been described (Marks & Mishan, 1988). Reassurance from others that no odour is detectable does little to diminish the concern and is usually considered an attempt to be kind (Bishop, 1980; Davidson & Mukherjee, 1982). Avoidance behaviours include sitting far from others or moving as little as possible to avoid spreading the supposed odour (Beary & Cobb, 1981; Bishop, 1980; Marks & Mishan, 1988).

Demographic characteristics and course of illness

In clinical series, the ratio of men to women in reported cases is approximately 2:1, and the majority of sufferers are unmarried. The average age at onset of ORS reported in the literature is the mid 20s, although Yamada *et al.* (1977), who evaluated a Japanese student population, found an age of onset of 17.1 years and noted that the syndrome's onset is most often at the time of puberty or adolescence. Onset has been noted to be either gradual or acute and sometimes preceded by an apparent precipitant (Johanson, 1964; Malasi *et al.*, 1990; Ross *et al.*, 1987).

Because of a lack of follow-up studies, little is known about the longitudinal course of ORS. However, most authors suggest that the course is usually chronic. In Pryse-Phillips's two-year follow-up study (1971), 10 of 11 patients' ORS symptoms persisted relatively unchanged, indicating that the disorder tends to be chronic and also has diagnostic stability. Most other published reports are consonant with this conclusion, suggesting that, when untreated, ORS usually persists for years, if not decades, without spontaneous remission or transformation to another psychiatric disorder. Videbach (1966), who followed five cases for an average of 15 years after onset, concluded that 'the course is chronic and gradually induces a marked tendency to isolation.' A number of

authors reported that without treatment, the symptoms worsen over time (Davidson & Mukherjee, 1982; Sutton, 1919; Tilley, 1985).

Some authors have raised the issue of ORS's possible transformation into schizophrenia (Munro & Pollock, 1981). However, other authors have concluded that there is little evidence that ORS may evolve into schizophrenia, and it is likely that schizophrenia was defined too broadly in some cases (e.g. Davidson & Mukherjee, 1982; Forte, 1952). In Pryse-Phillips's series (1971), for example, in which patients with ORS were carefully distinguished from those with schizophrenia, only one of 11 patients followed over two years developed possible schizophrenia.

Complications

ORS can be associated with significant academic, occupational and—most frequently—social impairment. As Osman (1991) noted, monosymptomatic hypochondriacal psychosis, including ORS, 'has devastating effects on the social and occupational functioning of the patient'. Indeed, Pryse-Phillips (1971) found that only 3% of her ORS series was 'socially active'. The social isolation usually results from embarrassment or a concern that others will be offended by the smell (e.g. Davidson & Mukherjee, 1982; Ross *et al.*, 1987). Individuals with ORS avoid other people — including strangers, friends and even family members — or believe that others avoid them (e.g. Malasi *et al.*, 1990; Tilley, 1895). Because of their symptoms, they may restrict activities outside the home, avoid dating, break off engagements, refuse to travel or move to another town (Bishop, 1980; Marks & Mishan, 1988; Malasi *et al.*, 1990; Pryse-Phillips, 1971). One patient, for example, avoided leaving her house because of her supposedly smelly feet, and on warm days she 'crept along the back streets' (Johanson, 1964).

ORS patients often have impaired academic and occupational functioning. Although most of Pryse-Phillips's patients were able to work, the literature often notes that sufferers may avoid school or work, change jobs repeatedly (Pryse-Phillips, 1971) or stop school or work altogether (Bishop, 1980; Davidson & Mukherjee, 1982; Iwu & Akpata, 1990; Malasi *et al.*, 1990; Marks & Mishan, 1988). This complication is generally attributed to shame and embarrassment associated with the symptoms or to ideas or delusions of reference consisting of the belief that co-workers are talking about or making veiled references to the supposed odour (Alvarez, 1958; Brotman & Jenike, 1984; Potts, 1891). Impairment has also been noted to result from the large amount of time spent thinking about the odour and engaging in behaviours aimed at diminishing the smell.

The distress caused by ORS has been reported to lead to psychiatric hospitalisation (Davidson & Mukherjee, 1982; Johanson, 1964; Malasi *et al.*, 1990; Marks & Mishan, 1988), depression (Davidson & Mukherjee, 1982), suicidal ideation (Bishop, 1980, Malasi *et al.*, 1990), suicide attempts (Beary & Cobb, 1981; Davidson & Mukherjee, 1982; Johanson, 1964; Ross *et al.*, 1987) and completed suicide (Videbech, 1966). Of Pryse-Phillips's (1971) 36 patients, 15 (43%) experienced 'suicidal ideas or action', and two (5.6%) committed suicide.

Associated psychopathology

Depression, which may be severe, is the comorbid disorder most commonly noted in the literature (e.g. Alvarez, 1958; Malasi *et al.*, 1990). Depression is often considered to be secondary to ORS (Davidson & Mukherjee, 1982; Ross *et al.*, 1987), although Pryse-Phillips (1971) evaluated 50 additional patients with ORS symptoms who had a 'primary' depressive disorder. In her 36 ORS cases (who did not have a primary depressive disorder), the mean score on the Hamilton Depression Scale was 38, reflecting marked depressive symptoms. Other reported comorbid disorders include body dysmorphic disorder, bipolar disorder, personality disorder, schizophrenia, hypochondriasis, alcohol and/or drug abuse and OCD (e.g. Harriman, 1934; Marks & Mishan, 1988; Pryse-Phillips, 1971; Yamada *et al.*, 1978). In the detailed case descriptions of Videbech (1966), it appears that four of five patients with ORS may have had comorbid OCD, although two of these cases were recruited because they had an 'anancastal syndrome'.

Family history

We are aware of no published reports on ORS that have systematically assessed family history of mental illness. Yamada and colleagues (1977) examined the family histories of 38 patients with ORS, using unspecified methodology, and found 'schizophrenia' in the first-degree relatives of two patients and 'heavy' drinking and suicide in first-degree relatives of two further patients. Presumably, these findings underestimate the actual rate of familial psychiatric illness in this cohort. Other authors have reported unspecified psychotic illness, affective disorders, OCD, alcoholism and epilepsy in first-degree relatives of patients with ORS (e.g. Bishop, 1980; Malasi *et al.*, 1990; Pryse-Phillips, 1971). Alvarez (1958) reported a family history of 'insanity', 'paranoia', suicide and alcoholism.

Prevalence

Information on the prevalence of ORS in community and clinical samples is limited. DSM-IV states that the lifetime prevalence of all types of delusional disorder combined is 0.05%–0.1%, although this is certainly an underestimate. Several Western authors have noted that ORS is probably rare among hospitalised psychiatric patients (e.g. Bishop, 1980). However, in a tertiary referral unit for the behavioural treatment of psychiatric disorders (the Psychological Treatment Unit at the Maudsley Hospital in London), 9 of 2000 patients (0.5%) spontaneously reported ORS symptoms (Marks & Mishan, 1988). This figure may well be an underestimate, given the secrecy that often characterises ORS and the frequency with which non-psychiatric treatment is sought (see below). A self-report survey of 2,481 university students in Japan found that 2.1% had been concerned with emitting a strange bodily odour during the previous year (Kasahara & Kenji, 1971). While these authors acknowledge that this symptom is not necessarily equivalent to a clinical diagnosis of ORS, they nonetheless imply that ORS is relatively common in Japan and conclude that in Japan 'fears of. . .bodily odour are. . .encountered almost every day'.

Indeed, several authors have suggested that ORS is more common than is usually recognised (Forte, 1952). Iwu and Akpata (1990), for example, noted that delusional halitosis 'may be frequently encountered by the dental surgeon', and Osman (1991) concluded that the monosymptomatic hypochondriacal psychoses as a group are likely to be underreported and 'form an important and not uncommon cause of psychiatric morbidity in (developing countries).'

Treatment

Non-psychiatric medical interventions

Because individuals with ORS believe they have a physical problem, they often seek evaluation and treatment from nonpsychiatric physicians (Bishop, 1980; Davidson & Mukherjee, 1982; Iwu & Akpata, 1990; Malasi *et al.*, 1990; Osman, 1991). They may consult a variety of health professionals, including dentists, general surgeons and ear, nose and throat specialists for supposed halitosis. Iwakura and colleagues reported that the majority of patients with a primary complaint of halitosis at a dental clinic in Japan actually had an 'imaginary halitosis', similar to ORS (1994). For supposed anal odours, patients may consult proctologists, surgeons and gastroenterologists. Requested procedures include removal of supposedly odiferous tonsils and sweat glands. Iwu and Akpata (1990) noted that these individuals may 'speak very convincingly' about the supposed odour and go to 'extraordinary lengths' to seek a nonpsychiatric cure.

Despite negative medical workups, which may be performed repeatedly, some individuals eventually succeed in receiving procedures such as the removal of 'smelly' axillary glands (Marks & Mishan, 1988) or tonsils (Davidson & Mukherjee, 1982; Malasi *et al.*, 1990; Pryse-Phillips, 1971). Such treatment generally appears to be ineffective (Forte, 1952; Iwu & Akpata, 1990; Pryse-Phillips, 1971) and associated with patient dissatisfaction (Iwakura *et al.*, 1994). However, controlled prospective studies have not, to our knowledge, been conducted. Forte (1952) warned that surgery 'should not be undertaken lightly because of the danger of precipitating an acute psychosis'. Reassurance and attempts to convince patients of the falsity of their belief are noted to be ineffective (Bishop, 1980; Davidson & Mukherjee, 1982; Iwu & Akpata, 1990).

Psychiatric interventions

Although non-psychiatric physicians might recommend psychiatric consultation, patients may resist referral and fail to comply with psychiatric treatment (Bishop, 1980; Forte, 1952; Osman, 1991). As noted by Iwu and Akpata (1990), patients with delusional halitosis 'would rather go in search of a ''better dentist'' than go to a psychiatrist'.

Nonetheless, these patients may be seen and treated by mental health professionals. Psychiatric treatments include a variety of psychotropic agents and psychotherapies. The literature consists largely of case reports and small case series and is limited by an absence of controlled treatment trials. Few studies employed standardised measures of psychopathology.

Medications

Antipsychotics: Most reports on medications for ORS focus on antipsychotics or antidepressants. Pimozide has been the most studied agent, with 15 of 31 (48%) cases responding (e.g. Munro, 1988; Osman, 1991; Ross *et al.*, 1987; Suzuki *et al.*, 2004; Stein *et al.*, 1998; Ulzen, 1993). In a series of 12 of these patients, pimozide responders received 2 to 4 mg/day, except for one patient who required 6 mg/day (Munro, 1982; Riding & Munro, 1975). Response usually occurred within one to four weeks (an average time to response was not reported). In two cases in which pimozide was discontinued during a follow-up period of 1 to 12 months, ORS symptoms recurred but then remitted with reinitiation of pimozide (Riding & Munro, 1975). Osman (1991) subsequently reported that half of his 14 cases responded to pimozide. He did not provide further information except to note that only patients with delusions involving genital odours responded. Other investigators have found that, despite improvement with pimozide, some patients maintain their delusional conviction that the odour is present (Ross *et al.*, 1987).

A number of other antipsychotics (including trifluoperazine, thioridazine and chlorpromazine) have also been tried. The results are largely negative, with a positive response reported in only 2 of 19 (11%) cases (e.g. Kong & Tan, 1984; Malasi *et al.*, 1990; Suzuki *et al.*, 2004). Furthermore, a number of patients who did not respond to other antipsychotics did respond to pimozide (Munro, 1982). This raises the question of whether ORS may respond specifically to pimozide as opposed to other antipsychotics; this warrants systematic investigation.

Antidepressants: Reported responses to antidepressants when used as single agents are mixed. However, some trials used relatively low doses and arguably too brief a duration of treatment, although what constitutes an adequate therapeutic trial for ORS is not known. Furthermore, many trials did not explicitly state the symptom domains that were assessed. Published cases raise the question of whether SRIs are more effective than other antidepressants, as a beneficial effect was reported in 10 of 15 (67%) cases, most of which used clomipramine (e.g. Dominguez & Puig, 1997; Kizu & Miyoshi, 1994; Lochner & Stein, 2003; Ross *et al.*, 1987; Stein *et al.*, 1998; Suzuki *et al.*, 2004). The response rate to non-SRI antidepressants is somewhat lower (6 of 15 cases, or 43%) (e.g. Brotman & Jenike, 1984; Davidson & Mukherjee, 1982; Stein *et al.*, 1998). However, the small number of cases and lack of head-to-head comparisons precludes any definitive conclusions. In some reports, patients responded to an antidepressant after failing an antipsychotic. One patient, for example, who experienced remission of her olfactory hallucinations but not her delusional belief on pimozide subsequently experienced remission of all ORS symptoms and depression with clomipramine 200 mg/day (Ross *et al.*, 1987). Although data are limited, the combination of an antidepressant and an antipsychotic agent appears promising (e.g. Malasi *et al.*, 1990), with response in 10 of 17 (59%) cases (e.g. Davidson & Mukherjee, 1982; Malasi *et al.*, 1990; Osman, 1991). This, too, needs further study.

Other Somatic Treatments: Several benzodiazepines have been reported to be ineffective, as has ECT alone (Bishop, 1980; Videbech, 1966) and ECT plus trifluoperazine 15 mg/day (Malasi *et al.*, 1990). The literature contains one report of an unsuccessful outcome with leucotomy and a report of partial response with bilateral partial division of the thalamo-frontal tract (Videbech, 1966). Clearly no definitive conclusions can be drawn regarding such treatments.

Psychological treatments

A range of psychological approaches have been adopted in treating ORS, including individual psychotherapy, analytic psychotherapy, relaxation, paradoxical intention and behavioural therapy, such as exposure (e.g. Beary & Cobb, 1981; Brotman & Jenike, 1984; Osman, 1991; Marks & Mishan, 1988).

All are either single case reports or small series, and none have used a control intervention. The details of the interventions are often not specified, and the number and duration of sessions are often not clear. Thus, any conclusions about the efficacy of these treatments must be considered preliminary.

Various individual psychodynamic interventions, including a case in which analytical psychotherapy was conducted for a year (Beary & Cobb, 1981), generally showed no benefit for ORS symptoms. There is a single report of a patient with concerns about flatulence who responded to paradoxical intention consisting of instructions to emit gas as soon as it was experienced; at one-year follow-up her symptoms had not recurred (Milan & Kolko, 1982). There are several reports of behavioural treatment for ORS in a total of 14 patients involving exposure and response prevention conducted over weeks to months (Beary & Cobb, 1981; Gomez-Perez *et al.*, 1994; Marks & Mishan, 1988). These treatments involved exposure to avoided social situations and response prevention, which consisted of refraining from excessive showering, use of deodourants, or visits to the toilet. Behavioural treatment was generally efficacious for ORS, although habituation was noted to require a long time, and Gomez-Perez and colleagues (1994) noted that gains were less than after exposure therapy for disorders such as social phobia and OCD.

Thus, there is some preliminary evidence of benefit from behavioural interventions, but these treatments have not been well studied. The precise treatment components that may be responsible for improvement are not established, and it is not clear whether adding a cognitive component to the behavioural therapy enhances efficacy. Furthermore, it can be difficult to engage patients in behavioural treatment, and adherence to behavioural homework requires motivation. The combination of psychotherapy and medication has not been systematically explored.

Treatment summary

In summary, although treatment data are very limited, they most strongly support use of an SRI. Available data also offer some support for an antipsychotic plus an antidepressant. Support for the use of pimozide alone or in combination with an antidepressant is somewhat weaker, although the data suggest that pimozide may be more efficacious than other antipsychotics, with efficacy reported for 15 of 31 cases with pimozide versus only 2 of 19 cases with other typical antipsychotics reported to be effective when used as single agents. However, studies of atypical antipsychotics are needed. Although the literature contains relatively few reports on SRIs, in our view it would seem

reasonable to use an SRI, either alone or in combination with pimozide or perhaps another antipsychotic. It should be kept in mind that the combination of pimozide with clomipramine is contraindicated.

Although data on nonpharmacologic treatments are also limited, behavioural approaches have promise in the treatment of ORS. Beary and Cobb (1981) speculate that medication and behavioural treatment might have a 'complementary effect', but this has not been empirically investigated.

Pathogenesis

A variety of theories about the pathogenesis of ORS have been proposed. Although most individuals with ORS have a negative medical workup, the syndrome is sometimes associated with a bona fide medical condition. In such cases it has been proposed that the medical condition is aetiologically related to the development of ORS, if only as a triggering factor. Onset of ORS has been reported, for example, following a colostomy (Pryse-Phillips, 1971). It is difficult to determine, however, whether a coexisting medical condition is causally related to the onset of ORS, most likely as a precipitating factor, or is only a coincidental event.

Of particular interest is the association, in a number of cases, of ORS symptoms with intracerebral abnormalities, most notably temporal lobe epilepsy (TLE). Toone (1978), for example, described a patient with TLE and a right frontal lobe arterio-venous malformation who believed that he emitted a foul odour similar to burning leaves. This delusion was accompanied by ideas of reference, social avoidance and excessive deodorant use and washing. The patient also smelled odours from other sources, such as meals that did not exist. Toone (1978) believed that both the TLE and ORS were related to the arterio-venous malformation, which he hypothesised served as a 'biological substrate favourable to the development of olfactory reference syndrome'. In several other cases, ORS symptoms have occurred in association with EEG abnormalities (although negative EEGs have also been reported); the relationship between these abnormalities and ORS symptoms is unclear (e.g. Johanson, 1964; Pryse-Phillips, 1971; Ross *et al.*, 1987). It should be emphasized, however, that true olfactory hallucinations occurring as a symptom of a medical condition, such as TLE or a brain tumour, are not considered to constitute ORS.

From a psychodynamic perspective, it has been suggested that ORS symptoms reflect displacement and express 'a wide and deep split in the self' (Bishop, 1980). The symptoms are conceptualised as a 'wishful escape from harsh reality' (Harriman, 1934) or 'a strategy to encapsulate areas of difficulty', such as

unacceptable feelings of anger and jealousy, inferiority, hostility or poor social adjustment (Bishop, 1980). ORS symptoms have also been noted to reflect repressed conflict about sexuality, homosexuality, aggression and femininity (Bishop, 1980; Malasi *et al.*, 1990).

Environmental factors, including stressful events, have also been postulated to contribute to the initiation, type and severity of ORS symptoms (Malasi *et al.*, 1990; Osman, 1991). In 6 of Osman's 15 cases, ORS symptoms 'emerged after a severe psychological trauma with a strong affective component', such as 'psychosexual' stress, being in jail or arguing with a spouse (Osman, 1991). Chronic teasing, in some cases about body odour, has also been noted to precede onset of ORS symptoms (Pryse-Phillips, 1971). In addition, cases have been reported in which a comment about body odour (for example, that someone smelled bad) appeared to trigger the onset of symptoms (Malasi *et al.*, 1990; Marks & Mishan, 1988).

Several authors have postulated that a certain personality type may predispose to or characterise patients with ORS (see Bishop, 1980). Descriptions include Kretschmer's 'sensitive type' (Pryse-Phillips, 1971) and 'sensitive, insecure personalities. . . . [with] a tendency to feelings of inferiority' (Videbech, 1966). On the 16 Personality Factor test, ORS patients were found to have features of 'inferiority, shyness, and difficulty in expressing emotion. . . and many obsessional features' (Pryse-Phillips, 1971).

Possible social and cultural contributions to ORS are also described. Osman (1991), for example, emphasised that body odour is indicative of poverty and lack of personal hygiene, both of which carry great social stigma in developing countries and may have a role in the development of ORS.

It is difficult to evaluate the validity of the above theories, as they are generally based on clinical observation rather than systematic, methodologically rigorous investigation. Nonetheless, it seems likely that the pathogenesis of ORS is multifactorial, deriving from biological, psychological, psychosocial and cultural factors. It appears to in some cases be triggered by more proximal factors, such as a negative comment or a traumatic experience, in individuals who are presumably predisposed to developing the syndrome. To the extent that ORS may be related to other psychiatric disorders, it would be expected to share aetiologic factors with them.

Discussion

Despite the many terms used over the years to describe patients with features of ORS, and the lack of diagnostic criteria specific to this syndrome, there is a striking consistency in the literature regarding the clinical presentation.

The main feature — a belief that one emits a malodorous smell — is usually accompanied by referential thinking and repetitive behaviours aimed at checking or eliminating the perceived odour. The belief typically leads to avoidance of social situations and may impair other areas of functioning, sometimes to a debilitating degree. There are no adequate epidemiological studies of ORS, and it is probable that it is often missed in clinical settings, given patients' shame and embarrassment about their symptoms. Further contributing to its underdiagnosis, patients appear to often seek help from nonpsychiatric physicians and often avoid mental health professionals. Despite the lack of controlled treatment trials, it appears that certain medications and behavioural treatments may be effective.

The published literature on ORS has significant methodological limitations, including small sample sizes and ascertainment of cases primarily through treatment settings. Psychiatric comorbidity has not been assessed with standardised diagnostic instruments, degree of delusionality (insight) and the presence of referential thinking have not been consistently evaluated and aetiological factors have not been investigated systematically. Treatment trials are limited by small sample size, a lack of control groups or use of standardised scales to assess outcome and inconsistent reporting of symptom domains.

An immediate problem for the field is the lack of specific diagnostic criteria for ORS. Consequently, authors have tended to use their own clinical judgment to identify cases. In DSM-IV (APA, 1994) and ICD-10 (WHO, 1992), diagnostic criteria for ORS are limited to those for delusional disorder. These criteria are not specific to ORS, and they require that the belief be held with delusional conviction. It is not clear how ORS symptoms characterised by a nondelusional belief would be classified according to these classification systems. Although this review identified only one case in which the belief was not considered delusional, in our clinical experience the belief is not always delusional and may span a spectrum of insight. An additional problem with the DSM-IV criteria for delusional disorder is their specification that any co-occurring mood symptoms must be brief relative to the duration of the delusional periods. This requirement may not be valid; in our clinical experience some patients with ORS experience protracted depressive symptoms that appear secondary to the ORS symptoms and do not appear better accounted for by another diagnosis such as psychotic depression.

Given the lack of diagnostic criteria for ORS, we propose the following working definition for this syndrome. This proposed definition is similar to definitions for OCD and body dysmorphic disorder, which have many similarities to ORS:

- A persistent false belief that one emits a malodorous smell; this belief may encompass a range of insight (i.e. it does not have to be delusional);

- The belief causes clinically significant distress, is time-consuming (i.e. preoccupies the individual for at least an hour a day) or results in significant impairment in social, occupational or other important areas of functioning;
- The belief is not better accounted for by another mental disorder or a general medical condition.

There is enormous scope for further research on ORS. The syndrome's clinical characteristics require further description and clarification, using operationalised and adequately specific diagnostic criteria, such as those proposed above. Such studies can in turn help refine the proposed criteria and address such issues as whether referential thinking or repetitive behaviours aimed at checking or eliminating the odour should be required symptoms.

Once the clinical presentation is better clarified, specific diagnostic measures need to be developed. Severity rating scales are also necessary — for example, an adaptation of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman *et al.*, 1989), as has been done for body dysmorphic disorder (Phillips *et al.*, 1997). In our clinical experience, this scale can be easily adapted to assess ORS severity, although it does not include assessment of such features as referential thinking, which is an important component of the syndrome.

Methodologically sound epidemiologic studies should be conducted in a variety of clinical and non-clinical settings so that prevalence rates, demographic characteristics (e.g. gender differences, age at onset) and comorbidity can be established. Factors contributing to the development and maintenance of the disorder also require further investigation. Rigorous treatment trials, using a controlled experimental design, are greatly needed. Such studies should use standardised outcome measures and should encompass an array of ORS symptoms and other domains (e.g. mood, disability and quality of life).

Another important issue requiring investigation is the nature of the relationship of ORS to other psychiatric disorders. Whether ORS is related to, and should be classified with, other types of delusional disorder is unclear—a problem confounded by the paucity of research on most other types of delusional disorder. As previously noted, the classification of ORS as a type of delusional disorder presumes the presence of delusional thinking, leaving it unclear how non-delusional ORS (e.g. with poor or fair insight) should be classified. This problem is similar to that faced by body dysmorphic disorder and hypochondriasis—disorders whose non-delusional form is subsumed under the somatoform disorders and whose delusional form is subsumed under delusional disorder. It seems unlikely that these disorders' delusional and non-delusional variants actually constitute separate disorders; a more parsimonious model

is that these variants constitute a single disorder characterised by a spectrum of insight (Phillips *et al.*, 2003).

With respect to the relationship of ORS to other psychotic illnesses, it should be recognised that the belief of emitting a bad smell can be a symptom of schizophrenia. According to DSM-IV and ICD-10, the schizophrenia label should trump the diagnosis of ORS if other symptoms of schizophrenia are present. Similarly, patients with severe depression may believe that they smell bad as part of a nihilistic delusional belief system (for example, in Cotard's syndrome). It may be unclear in a given case, however, whether to conceptualise a false belief about body odour as constituting a symptom of depression or as ORS with comorbid or secondary depression.

Marks (1987) includes ORS under the dysmorphophobia (body dysmorphic disorder) rubric. He notes that ORS patients would not universally be called dysmorphophobic but that the clinical features of ORS have many similarities to those of body dysmorphic disorder, the primary symptom of both disorders being a fixed conviction of a bodily defect, leading to anxious avoidance of relevant (often social) situations. While in our clinical experience body dysmorphic disorder and ORS share many features, there are some apparent differences. For example, although treatment data are limited for both disorders (Phillips, 2002), in a placebo-controlled study body dysmorphic disorder did not respond to pimozide (Phillips, 2005). Systematic investigation of these disorders' similarities and differences is needed to clarify their relationship to each other. In the meantime, in the absence of evidence it would seem best not to assume that these syndromes constitute the same disorder.

Some authors consider ORS a severe form of social phobia, or taijinkyofusho (or, more specifically, jiko-shu-kyofu) (Chang, 1997; Kasahara & Kenji, 1971; Suzuki *et al.*, 2004). Taijinkyofusho, which is often linked to social phobia, consists of an obsession that a person will displease or embarrass others by his/her somatic symptoms, such as blushing, a defect in appearance, or a foul body odour (Susuki *et al.*, 2004). ORS and severe social phobia do have some common features; however, the mere fact that the symptoms may cause social anxiety or avoidance of social situations is not sufficient evidence to consider ORS a form of social phobia. Indeed, many disorders, such as OCD, body dysmorphic disorder, schizophrenia, and panic disorder may lead to social avoidance but are not considered forms of social phobia. Furthermore, the specific type of cognitive distortion that characterises ORS differentiates it from the broader 'fear of negative evaluation' which underpins social phobia.

The relationship of ORS to OCD is also of interest, as many of ORS's features, notably the intrusive ruminations and repetitive behaviours—mimic OCD

symptoms (Stein *et al.*, 1998). Of interest is that body dysmorphic disorder, too, has been considered by some authors to be part of an OCD spectrum of disorders (Castle & Phillips, 2006), but the literature is less compelling with respect to ORS, largely because of the paucity of studies of this syndrome. Should future studies find that ORS has similarities to OCD in multiple domains, such as treatment response, familial aggregation with OCD and neurobiological characteristics, a more convincing case could be articulated for including ORS in the putative OCD spectrum.

In summary, ORS is a fascinating psychiatric syndrome that, despite more than a century of description, remains understudied and likely under-diagnosed in clinical settings. Further investigation of this condition is clearly warranted to further characterise its clinical features, elucidate its relationship to other psychiatric disorders, identify effective treatment and enhance its recognition by clinicians.

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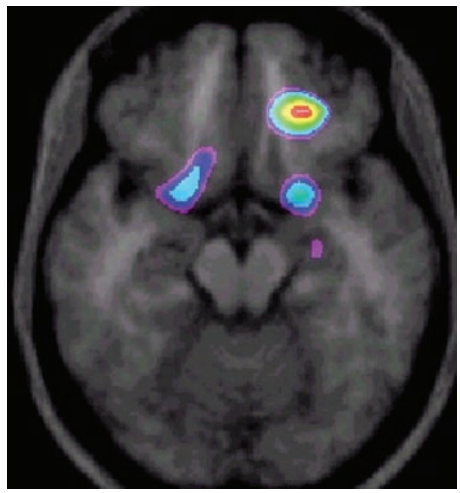

Plate 1 Cortical regions activated by olfactory stimulation: the piriform cortex bilaterally, and the right orbitofrontal cortex. Data reported in Zatorre et al. (1992).

Plate 2 A sea squirt Cnemidocarpa verrucosa (Photograph by Martin Riddle).

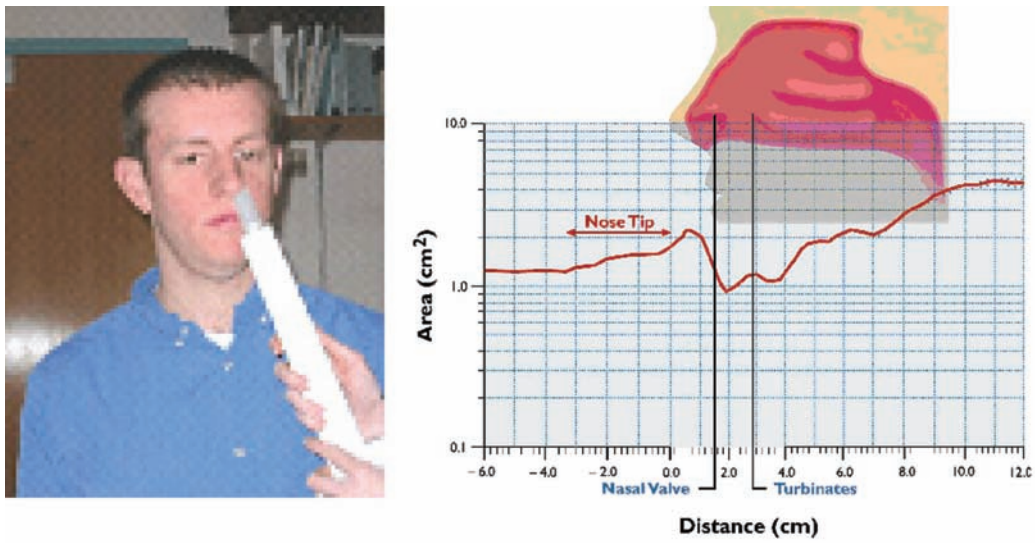

Plate 3 Acoustic rhinometry instrumentation and data readout.

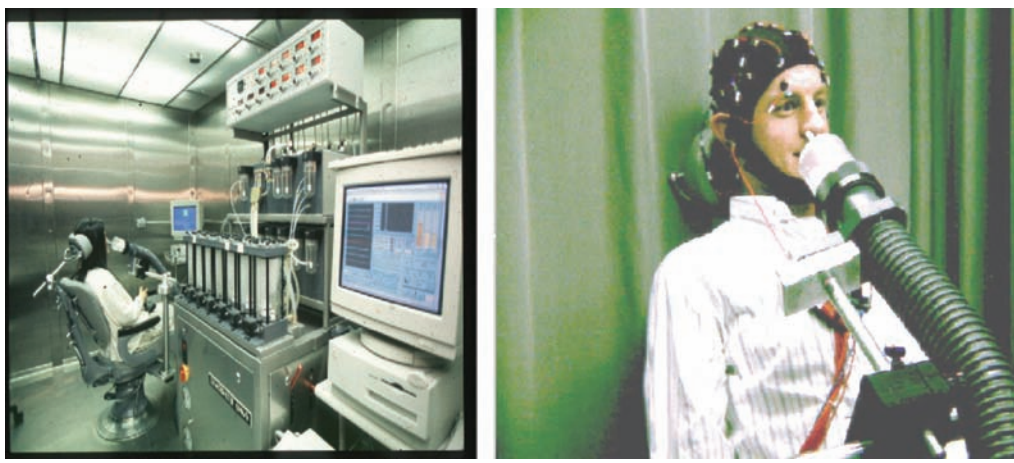

Plate 4 Olfactometer for odour delivery during ERP studies.