

The Anterior Cingulate Cortex

The Evolution of an Interface between Emotion and Cognition

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ABSTRACT: We propose that the anterior cingulate cortex is a specialization of neocortex rather than a more primitive stage of cortical evolution. Functions central to intelligent behavior, that is, emotional self-control, focused problem solving, error recognition, and adaptive response to changing conditions, are juxtaposed with the emotions in this structure. Evidence of an important role for the anterior cingulate cortex in these functions has accumulated through single-neuron recording, electrical stimulation, EEG, PET, fMRI, and lesion studies. The anterior cingulate cortex contains a class of spindle-shaped neurons that are found only in humans and the great apes, and thus are a recent evolutionary specialization probably related to these functions. The spindle cells appear to be widely connected with diverse parts of the brain and may have a role in the coordination that would be essential in developing the capacity to focus on difficult problems. Furthermore, they emerge postnatally and their survival may be enhanced or reduced by environmental conditions of enrichment or stress, thus potentially influencing adult competence or dysfunction in emotional self-control and problem-solving capacity.

KEYWORDS: Anterior cingulate cortex; Cognition; Emotion; Problem solving; Self control; Spindle cells; Brain evolution

In 1878, Broca described *le grand lobe limbique* as a broad band of brain tissue wrapping around the corpus callosum and including parts of the ventral forebrain.¹ This is the source of the modern term *limbic*, which is used to describe this collection of brain structures; it is derived from the Latin word *limbus*, which means border, but which could also be taken to mean an interface. Broca believed that the great limbic lobe was

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primarily involved in olfaction, which led to the term *rhinencephalon*'s being attached to this assortment of structures; however, modern studies indicate that olfactory functions are restricted to only a small portion of the ventral part of the limbic lobe.

The dorsal part of Broca's great limbic lobe is the cingulate cortex, so named because it forms a *cingulum* or collar around the corpus callosum. In 1937, Papez wrote: "The cortex of the cingular gyrus may be looked on as the receptive organ for the experiencing of emotion as the result of impulses coming from the hypothalamic region, in the same way as the area striata is considered the receptive cortex for photic excitations from the retina."² Papez also noted that tumors pressing on the cingulate cortex produced "loss of spontaneity in emotion, thought and activity."² Thus, Papez made an analogy between the neural pathway proceeding from the retina to the thalamus to the area striata (V1), and the pathway from the neuroendocrine centers of the hypothalamus to the thalamus to cingulate cortex. He believed that both circuits were phylogenetically ancient and evolved in parallel during the course of vertebrate evolution.

In 1945, Smith studied the cingulate cortex of macaque monkeys and found that electrical stimulation of the anterior portion corresponding to Brodmann's area 24 elicited changes in heart rate, blood pressure, and respiration as well as vocalizations and facial expressions.³ He noted: "vocalization may occur alone, but in its fully developed form it is part of what appears to be a complex reaction characterized by opening of the eyes, dilatation of the pupils, and vocalization. Movements of the facial muscles, usually bilaterally, often accompany the vocalization, during which the lips may be protruded and rounded, or retracted, such as occurs in the ordinary life of the animal. The sounds emitted run nearly the whole gamut which the monkey is capable of producing. While the low-pitched guttural sound is the one most frequently obtained, it gives place at times to higher pitched cooing sounds, at other times to cries, soft and plaintive such as the animal makes at feeding time."³

In a long series of publications beginning in 1949, MacLean developed a concept of vertebrate brain evolution that he termed "the triune brain."⁴ Central to his concept is the idea that the mammalian brain evolved in a series of concentric shells around an ancient reptilian core. The innermost of these shells he termed "paleomammalian," and it included the cingulate cortex. He distinguished this from the outer shell, which he termed "neomammalian" and which comprised the neocortex. Sanides developed a related scheme for brain evolution in which he suggested that the cingulate cortex had a more primitive laminar structure than neocortex and preceded it in evolution.⁵

Comparative studies of the genetic regulation of the development of the forebrain in amphibians, reptiles, birds, and mammals have done much to elucidate the evolution of this part of the brain.⁶ These studies indicate that the mammalian cortex is homologous with the dorsal part of the forebrain in reptiles and amphibians and thus was a specialization derived from this area in the ancestors of mammals. This specialization involved the segregation of the cortex into layers with distinct inputs and outputs.⁷ Anterior cingulate cortex is distinct from much of neocortex in lacking layer 4, which is one of several layers receiving thalamic input. It also has a particularly well-developed layer 5, which contains outputs to subcortical structures. However anterior cingulate is similar in these laminar specializations to the motor areas of the neocortex, which lie adjacent to anterior cingulate cortex. Thus, rather than being ev-

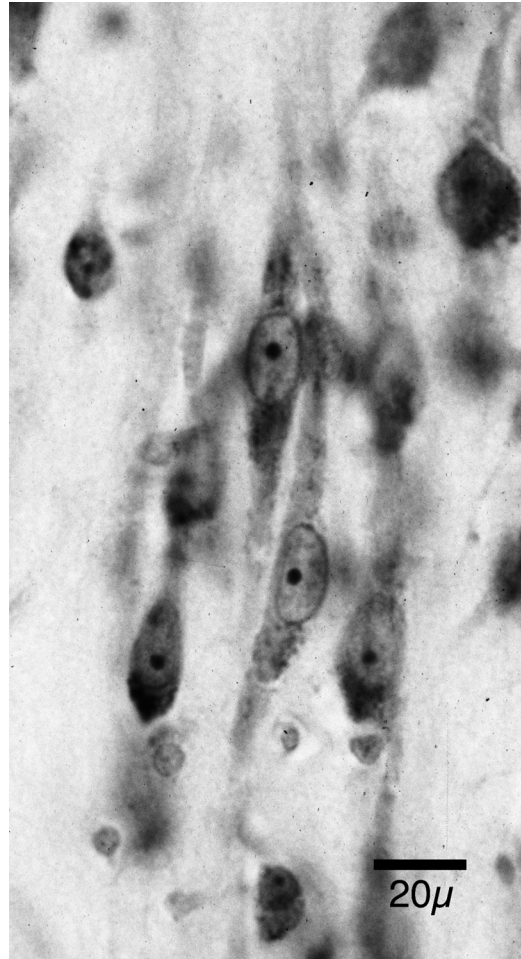


FIGURE 1. A pair of spindle cells in human anterior cingulate cortex.

idence that the cingulate cortex is more primitive than neocortex, these features indicate an affinity with the adjacent neocortical motor areas. These data, together with the comparative and functional findings to be reviewed subsequently, suggest that the anterior cingulate cortex is a specialized area of neocortex devoted to the regulation of emotional and cognitive behavior.

SPINDLE CELLS

In humans, layer 5b of Brodmann's area 24 of the anterior cingulate cortex contains a distinctive class of large spindle-shaped neurons.⁸ They differ from the ordinarily pyramidal neurons of layer 5 in lacking an array of basal dendrites radiating

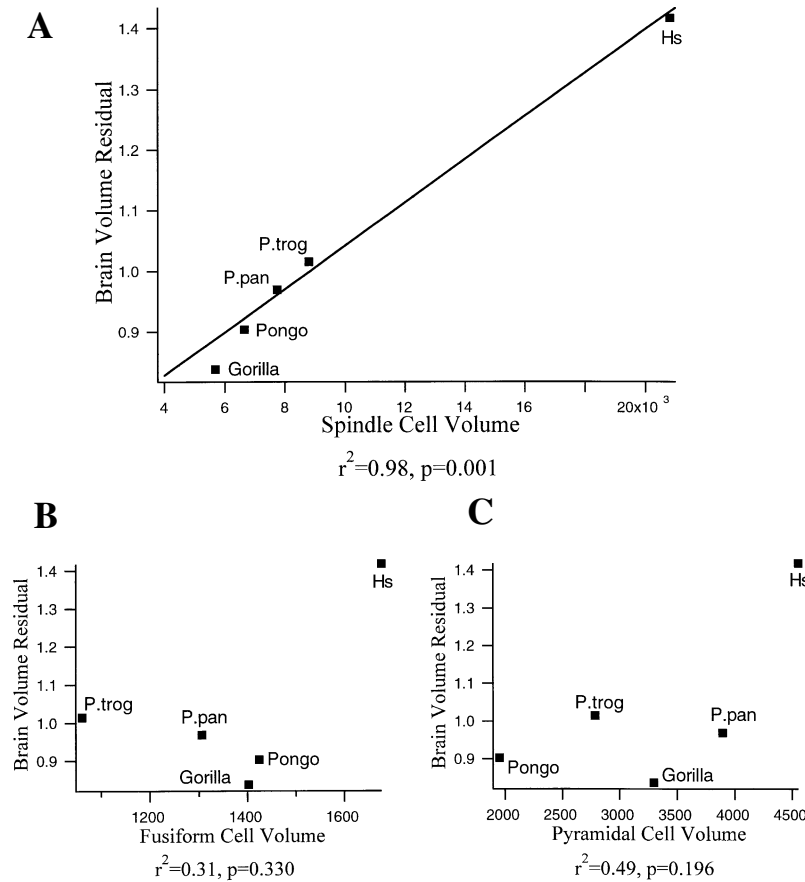


FIGURE 2. Whole brain volume residual versus cell volume from three different brain areas, for humans, bonobos, common chimpanzees, gorillas, and orangutans. Brain volume residuals were computed by subtracting the average brain volume for a given species from the expected brain volume for that species given its body weight, as determined by a linear regression. Residual values were added to one, to make all values positive. **(A)** Brain volume residual is well correlated with spindle cell volume. Brain volume residual is not significantly correlated with the volume of either **(B)** fusiform cells or **(C)** pyramidal cells. Hs = *Homo sapiens*; P. trog = *Pan troglodytes*, common chimpanzee; P. pan = *Pan paniscus*, bonobo; Gorilla = *Gorilla gorilla*; Pongo = *Pongo pygmaeus*, orangutan.

into layer 5 and instead have a single large basal dendrite (FIG. 1). The presence of a single apical dendrite extending upward and a single basal dendrite extending downward creates the characteristic spindle shape. The average volume of the cell body of a spindle cell is four times larger than that of the average pyramidal cell of layer 5.⁹ Injections of retrograde tracers into the cingulum fiber bundle indicate that the spindle neurons have long-distance projections, but their exact connections remain to be discovered. Recently, we have discovered that the spindle cells are

present only in humans and our closest relatives, the great apes.⁹ The concentration of spindle cells is greatest in humans and declines with increasing taxonomic distance from humans.^{9,10} Thus chimpanzees have more than gorillas, which have more than orangutans. We were unable to find any evidence of spindle cells after a careful search in 23 other species of primates and 30 nonprimate species.⁹ Spindle cells probably originated in the common ancestor of humans and great apes, which would have been a dyropithecine ape living about 15 million years ago.^{11,12} We have also found that the average volume of the cell bodies of the spindle cells varies as a function of relative brain size (encephalization) across humans and great apes (FIG. 2). This is not the case for the pyramidal neurons in layer 5 or the fusiform cells in layer 6 of anterior cingulate cortex. Because cell body size is probably related to the size of the axonal arborization, the axonal arborizations of the spindle cells may be extensive and on a scale with encephalization. This observation suggests that the spindle cells may have widespread connections with other parts of the brain. Recently, one of us (JMA) has studied the ontogenetic development of the spindle cells in humans by examining brains of different ages in the Yakovlev Brain Collection at the National Museum of Health and Medicine. The spindle cells cannot be discerned at birth and first appear at four months of age. It is conceivable that the spindle cells are present at birth but have not yet differentiated into their characteristic bipolar

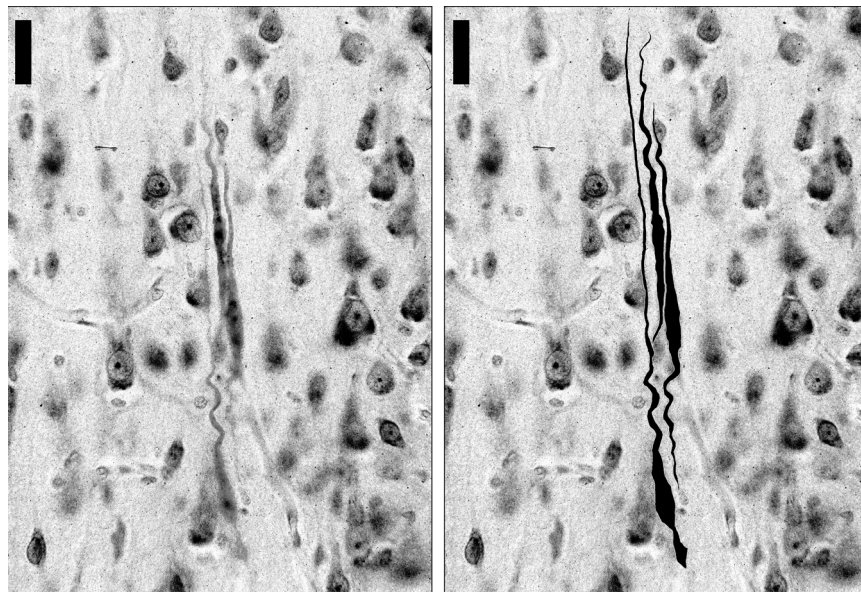


FIGURE 3. Three possible migratory spindle cells in the anterior cingulate cortex of a 7-month-old human infant. The photomicrograph on the left depicts these cells in a single optical plane. In the photomicrograph on the right, the three spindle cells have been encoded in black on the basis of their appearance in multiple optical planes. Note the undulations in the apical and basal dendrites. This morphology persists into adulthood in some spindle cells and led von Economo⁵⁵ to describe these neurons as the “corkscrew cells.” The *scale bars* in the upper left corners of each photomicrograph correspond to 15 μm .

shape. Some of the spindle cells in four- to eight-month-old infants bear the features of migratory neurons; they are elongated, densely staining, and have undulating leading and trailing processes (see FIG. 3).¹³⁻¹⁵ The emergence of the spindle cells in four-month-old human infants coincides with the infant's capacity to hold its head steady, smile spontaneously, track an object visually, and reach for that object.¹⁶ The spindle cells may participate in the neural circuitry responsible for these functions, which are related to focused attention and emotional expression.

EVIDENCE FROM FUNCTIONAL STUDIES

The spindle cells are a hominoid specialization of the neural circuitry of anterior cingulate cortex. How might the spindle cells contribute to the functioning of anterior cingulate cortex in hominoids? In humans the anterior cingulate receives one of the richest dopaminergic innervations of any cortical area.¹⁷ Although the spindle cells are not present in monkeys, data from monkeys are relevant to understanding the basic functions of anterior cingulate cortex in primates. These data show that the source of cortical dopaminergic input comes from cell bodies located in the ventral midbrain, which in behaving monkeys respond when the animal receives a reward or a reward-associated signal.¹⁸ These dopaminergic neurons pause in their firing when an expected reward is not received. There is also direct evidence from humans that the dopaminergic projection to anterior cingulate cortex is reward-related. This finding comes from an ingenious experiment in which blood flow in anterior cingulate cortex was monitored with positron emission tomography (PET) in normal subjects and in patients with Parkinson's disease. Parkinson's disease destroys the dopaminergic neurons in the ventral midbrain. The subjects and patients performed delayed-response tasks under baseline conditions with and without monetary rewards. When the normal subjects received monetary rewards, the anterior cingulate cortex was activated, but this activation was completely absent in the Parkinson's patients, implying that the lack of dopaminergic input resulted in the loss of reward-related activity.¹⁹ The anterior cingulate cortex also receives a strong projection from the amygdala, which probably relays negative, fear-related, information.^{20,21} Some neurons in anterior cingulate cortex respond when the monkey receives a reward after performing a serial motor task.²¹ About 8% respond when the monkey recognizes that it has made an error in the performance of the task.²² Shima and Tanji trained monkeys to perform two tasks: pushing or turning a handle.²³ They then differentially varied the reward given for performing each of these tasks. The monkeys responded to decreasing reward by switching their activity to the other motor task, that is, from pushing to turning or vice versa, thus optimizing their receipt of reward. In about a third of their sample of cells recorded from anterior cingulate cortex, Shima and Tanji found neurons that responded to decreasing reward but not to continuous levels of reward. They also found, on the occasions in which the monkeys failed to respond to the reduced reward by changing their behavior, that this type of neuron also failed to respond. They then injected in anterior cingulate cortex small amounts of the powerful GABA agonist, muscimol, which temporarily silences cortical activity. The muscimol injections caused the monkeys to fail to respond to changing reward. These elegant experiments indicate that anterior cingulate cortex monitors performance and reward and adjusts behavior so as to optimize payoff.

There is a remarkable counterpart to these monkey experiments in electroencephalographic (EEG) recordings made from scalp electrodes in humans. A large body of EEG data indicates that the anterior cingulate is the source of a 4- to 7-Hertz signal present when the subject is performing a task requiring focused concentration.²⁴ The amplitude of this signal increases with task difficulty.²⁵ When the subject is restless and anxious, the signal is reduced or eliminated; when the anxiety is relieved with drugs, the signal is restored.^{26,27} These findings suggest that one dimension in the functioning of anterior cingulate cortex varies between the poles of restless anxiety and focused problem solving. This is consistent with the common experience that focusing on a problem relieves anxiety. There is also evidence that, when the subject is aware of having made an error, there is a negative deflection in one cycle of this oscillation. This phenomenon has been referred to as “error-related negativity” and it arises from anterior cingulate cortex.^{28–30}

There is also a substantial body of data for anterior cingulate cortex from functional imaging studies in humans. In one of the earliest studies of cognitive function using positron emission tomography (PET), Petersen and his colleagues found that the anterior cingulate cortex was active when subjects generated word associations.³¹ This activation is linked to focused mental effort. When the subjects are highly practiced and the performance of these word-generation tasks become nearly automatic, the anterior cingulate activation is no longer present.³² A meta-analysis of over 100 PET investigations revealed that just as with the amplitude of the 4- to 7-Hertz signal, the activity of anterior cingulate cortex increased with task difficulty.³³

Strong evidence exists that the dorsal part of the anterior cingulate cortex is related to cognition, whereas the ventral part is more related to emotion.³⁴ This functional specialization is revealed by the sites activated during different Stroop tasks in functional magnetic resonance imaging (fMRI). Stroop tasks require the subject to respond in the presence of conflicting or confounding information. In the “counting Stroop” the subject is asked to report the number of words present on a screen. For example, in the cognitive version, the words are numbers such as “three” written four times; in the emotional version, the words are emotionally charged, such as “murder” written four times. The “counting Stroop” activates the dorsal part of the anterior cingulate cortex, whereas the “emotional Stroop” activates the ventral part. A large number of investigations are using different versions of the cognitive Stroop or other tasks involving conflicting information which activate the dorsal part of the anterior cingulate cortex. In PET studies, when normal subjects are asked to imagine angry or sad situations, the ventral part is activated.^{35,36} When phobic, obsessive-compulsive and posttraumatic stress syndrome patients are presented with stimuli that trigger their symptoms, the ventral part is also activated.^{37–40} In depressed patients with a parent or sibling who was also depressed, both the physical size and the metabolic activity of the ventral part of anterior cingulate cortex were reduced.⁴¹ Although the centers of activation or deactivation are largely separated in the dorsal and ventral anterior cingulate cortex, the total activity zones overlap, and the dorsal and ventral parts are probably anatomically interconnected. The functional distinction within anterior cingulate is also revealed by electrical stimulation in conscious patients. For example, stimulation of the ventral part produced intense fear or pleasure, whereas the more dorsal part produced a sense of anticipation of movement.^{42,43}

EVIDENCE FROM LESION STUDIES

Damasio and Van Hoesen have studied a series of stroke patients with large lesions of anterior cingulate cortex.⁴⁴ Immediately following the stroke, such patients lie in their hospital beds saying or doing little. Damasio and Van Hoesen described one left anterior cingulate stroke patient one month after her stroke: "The patient was remarkably recovered. She had considerable insight into the acute period of the illness and was able to give precious testimony as to her experiences then. Asked if she had ever experienced anguish for being apparently unable to communicate she answered negatively. She didn't talk because she had nothing to say. Her mind was empty. She apparently was able to follow our conversations even during the early period of the illness, but felt no will to reply to our questions."⁴⁴ Recently Cohen and his colleagues have studied a series of 18 patients who suffered from intractable pain and were treated with small bilateral lesions, 5 mm in diameter, in the anterior cingulate cortex.⁴⁵ More than a year after the surgery they studied the behavior of these patients in comparison with a control group of chronic pain patients who had not received the cingulate lesions. They found that the cingulate-lesioned patients did gain relief from pain. They reported that the pain was still present but that it no longer bothered them as much. The lesioned patients showed reduced levels of spontaneous behavior. They produced fewer verbal utterances during interviews than controls. In a written task, they also produced shorter statements. When asked to make objects from Tinker Toys, they produced fewer and simpler objects. Thus, the spontaneity of their behavior was reduced over the long term by these small lesions of the anterior cingulate.

ANTERIOR CINGULATE CORTEX AND SELF-CONTROL

Posner and Rothbart have proposed that the anterior cingulate cortex is involved in the maturation of self-control as the individual progresses from infancy to childhood to adulthood.⁴⁶ In the classic condition of lack of self-control, attention deficit hyperactivity disorder (ADHD), the normal response to the "counting Stroop" task is absent from anterior cingulate cortex.⁴⁷ There is also evidence of increased functioning in anterior cingulate cortex in individuals with greater social insight and maturity. Lane and colleagues found that the activity of the anterior cingulate cortex was greater in subjects who had higher levels of social awareness based on objectively scored tests.⁴⁸ In these tests the subjects wrote about how they would perceive a particular social situation and how they would imagine one of the participants to perceive that same situation. The discrimination of affect in faces, which contributes to social awareness, also selectively activated anterior cingulate cortex.⁴⁹

SUMMARY AND SPECULATIONS

In conclusion, we propose that the anterior cingulate cortex is a specialization of neocortex rather than a more primitive stage of cortical evolution. The evidence from single-neuron recording, electrical stimulation, EEG, PET, fMRI, and lesion studies

indicates that the anterior cingulate cortex has an important role in emotional self-control as well as focused problem-solving, error recognition, and adaptive response to changing conditions. These functions are central to intelligent behavior. They are juxtaposed in this structure and probably are intimately interconnected. The spindle cells are a novel specialization of the neural circuitry of anterior cingulate cortex that arose about 15 million years ago in an ancestor of great apes and humans.⁹ This new circuitry probably augmented emotional self-control and focused problem-solving behavior in these animals and their descendants. Specifically, the spindle cells may possess widespread connections with other parts of the brain and may serve to coordinate the activity of these diverse parts to achieve self-control and the capacity to focus on difficult problems. The spindle cells appear to emerge postnatally and their development may be particularly influenced by environmental factors. This possibility is suggested by findings for the two populations of neurons in the hippocampus and the olfactory bulb that are well established as originating after birth.^{50–53} The survival of postnatally originating neurons in the dentate gyrus of the hippocampus is enhanced by environmental enrichment; by contrast, stress diminishes the production of these neurons.^{50,51} The survival of postnatally originating neurons in the olfactory bulb is dependent on olfactory stimulation and the presence of brain-derived neurotrophic factor (BDNF), which is enhanced by maternal care in the hippocampus of rat pups.^{52–54} Thus it is conceivable that environmental stimulation, stress, and the quality of parental care might also affect the survival and development of the spindle cells during infancy, thus influencing adult competence or dysfunction in emotional self-control and problem-solving capacity.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health Grants AG14308 and EY11759 and the Hixon Fund. We thank Karli Watson, Eliot Bush, Stephen Shepherd, and Kathy Vlahos for their helpful comments on the manuscript and Archie Fobbs for his valuable assistance in using the Yakovlev Brain Collection at the National Museum of Health and Medicine.

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