The von Restorff Effect in Visual Object Recognition Memory in Humans and Monkeys: The Role of Frontal/Perirhinal Interaction

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Abstract

■ This study reports the development of a new, modified delayed matching to sample (DMS) visual recognition memory task that controls the relative novelty of test stimuli and can be used in human and nonhuman primates. We report findings from normal humans and unoperated monkeys, as well as three groups of operated monkeys. In the study phase of this modified paradigm, subjects studied lists of two-dimensional visual object stimuli. In the test phase each studied object was presented again, now paired with a new stimulus (a foil), and the subject had to choose the studied item. In some lists one study item (the novel or *isolate* item) and its associated foil differed from the others (the *homogenous* items) along one stimulus dimension (color). The critical experimental measure was the comparison of the visual object recognition error rates for isolate and homogenous test items.

This task was initially administered to human subjects and unoperated monkeys. Error rates for both groups were reliably lower for isolate than for homogenous stimuli in the same list position (the von Restorff effect). The task was then administered to three groups of monkeys who had selective brain lesions. Monkeys with bilateral lesions of the amygdala and fornix, two structures that have been proposed to play a role in novelty and memory encoding, were similar to normal monkeys in their performance on this task. Two further groups—with disconnection lesions of the perirhinal cortex and either the prefrontal cortex or the magnocellular mediodorsal thalamus—showed no evidence of a von Restorff effect. These findings are not consistent with previous proposals that the hippocampus and amygdala constitute a general novelty processing network. Instead, the results support an interaction between the perirhinal and frontal cortices in the processing of certain kinds of novel information that support visual object recognition memory. ■

INTRODUCTION

There are good grounds for arguing that the detection of novelty is important for encoding information into memory. This argument can been couched in evolutionary terms, whereby novelty detection affords an advantage in that it may reduce the demands placed upon long-term memory, presumably by influencing what or how information is encoded (Brown, 1996; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994). Further evidence for the importance of stimulus novelty in memory encoding comes from demonstrations that, at least in some large-scale mathematical models of memory storage and retrieval (e.g., the CHARM model), encoding depends upon an assessment of the similarity of new material to the contents of the existing memory store (Metcalfe, 1993).

Recent studies using brain-imaging or event-related potential (ERP) measures have identified a number of brain regions that may be implicated in the detection of novelty. Knight (1996) recorded event-related potentials to trains of individually presented stimuli, a minority of which deviated along one stimulus dimension (for example, tone pitch). ERPs were recorded and compared for the regular and deviant stimuli in normal controls and in patients with damage to the posterior portion of the hippocampus. A characteristic ERP signal to novel stimuli was evident only in the controls, suggesting a role for this region of the hippocampus in novelty detection. Complementary evidence for the role of the hippocampus in novelty detection comes from a number of positron emission tomography (PET) studies that have contrasted the brain regions activated when items are presented to subjects for the first or second time (novel versus familiar items). The brain regions that were selectively more active during the processing of novel stimuli include the hippocampal formation, medial dorsal thalamus, anterior cingulate, and medial and ventral regions of the prefrontal cortex (Dolan & Fletcher, 1997; Tulving & Markowitsch, 1997; Tulving, Markowitsch, Craik, Habib, & Houle, 1996; Tulving et al., 1994).

The brain regions identified in these imaging studies

are, for the most part, consistent with the data from single-unit recording studies of novelty responsive cells in awake behaving monkeys. Neurons have been identified that are more responsive to the initial presentation of an item than they are to subsequent presentations of the same item—the so-called decremental response. Cells showing this response characteristic have been located in the amygdala (Wilson & Rolls 1993), hippocampus (Rolls, Cahusac, Feigenbaum, & Miyashita, 1993), perirhinal cortex (Brown, Wilson, & Riches, 1987; Fahy, Riches, & Brown, 1993; Riches, Wilson, & Brown, 1991), and ventral striatum (Williams, Rolls, Leonard, & Stern, 1993). Although the results from these electrophysiological and regional cerebral blood flow studies have begun to identify the neural substrates involved in processing novel stimuli, they do not differentiate structures critical for the detection of novelty in memory encoding per se from structures that may reflect additional processes (such as increased levels of arousal).

The central aim of the study reported here was to identify structures critical for the memory-related processing afforded novel stimuli. This was achieved by comparing memory performance for two classes of test items that differed in their degree of novelty. We developed a variant of the von Restorff paradigm (Hunt, 1995; von Restorff, 1933) to use as a behavioral task for human and nonhuman primates. In many experiments using the original version of this paradigm, human subjects were presented with a list of items, one of which (the isolate) differed from the others along some dimension, such as a random letter amongst a list of numbers (for a review, see Hunt, 1995). The von Restorff effect is the finding that, on tests of recall, memory for isolates is better than memory for nonisolates (homogeneous items) presented in the same serial list position (Hunt 1995; Saltz & Newman 1959; Wallace 1965).

Understandably, this effect has not been seen in nonhuman primates because there is no established monkey analogue of a recall task. Accordingly, the experiment reported here employs an adaptation of the von Restorff paradigm that allows it to be used both with human and nonhuman primates. The task could subsequently be used to compare performance in humans with either surgical or nonsurgical brain damage, and nonhuman primates with selective brain lesions, thereby providing converging sources of evidence that address the question of the neural basis of the memory-related processing afforded novel stimuli.

The first phase of the task consists of presentation of different individual two-dimensional visual objects (see Figure 1). The subsequent test phase is a delayed matching-to-sample (DMS) task where each of the objects presented in phase 1 are paired with a new object. In this second phase the task is to indicate (via a touch screen) which one of the pair of objects was presented in phase 1. Multiple phase 1 and phase 2 lists are presented, a proportion of which contain an isolate object, which appears in a different color from the other objects in that list. Over all subjects and sessions, half of the lists consist mainly of blue items with just one red (isolate) study item and foil and an equal number of lists consist mainly of red items with just one blue (isolate) item and foil. The design therefore allows a comparison of DMS error rate for novel (isolates) and nonnovel (homogenous) objects in the same list position. A von Restorff effect (or isolate memory advantage) is reflected in a lower error rate for isolate than for homogenous objects.

In this paper we build on a demonstration of reliable von Restorff effects in human and nonhuman primates by investigating the effects of selective brain lesions on the novelty effect. Three groups of monkeys underwent lesions of structures that are known to be important in memory processing and have also been implicated in novelty assessment. For each lesion group, abolition or attenuation of the von Restorff effect would indicate that the structures affected by surgical removal are important for the processing afforded novel stimuli in visual object recognition tasks. Of the three operated groups, the first had bilateral lesions of the amygdala and the fornix, which is the major output pathway of the hippocampus. The second group had disconnection lesions of the perirhinal cortex in one hemisphere and contralateral frontal cortex, and the third group had disconnection lesions of the magnocellular mediodorsal thalamus and contralateral frontal cortex. The logic of the disconnection procedure is that the pattern of lesions impair performance by preventing the intrahemispheric interaction necessary for the task the animal is required to do. This is achieved surgically by removing the commencement of a pathway in one hemisphere and the termination of that pathway in the contralateral hemisphere. This means that both hemispheres are then deprived of the interaction between the two areas. In a task requiring information about visual objects, the integrity of the perirhinal cortex is necessary for task performance because bilateral removal of this structure produces a large impariment in visual object DMS (Buckley, Gaffan, & Murray, 1997). Similarly, the prefrontal cortex is thought to be important in novelty processing, as discussed above. However, bilateral removal of the prefrontal cortex produces a wide range of impairments, making assessment of novelty processing impairments problematic. A disconnection method can therefore provide valuable information both about the role of prefronal cortex and its necessary interactions with other cortical areas.

RESULTS

Humans and Unoperated Monkeys

For the human and monkey groups two error rates were calculated: percentage errors for isolate stimuli and per-

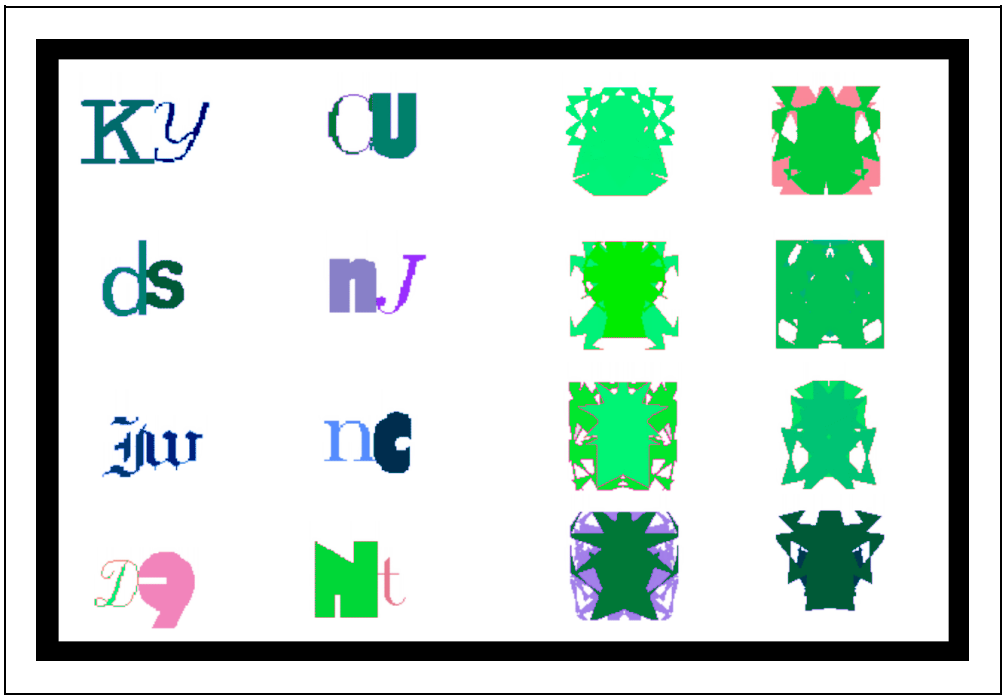

Figure 1. Left: Typographic stimuli. Top six examples are from the blue end of the color spectrum, the bottom two are from the red end. Right: Fractal stimuli. Top six examples are from the red end of the color spectrum, and the bottom two are from the blue end.

centage errors for homogenous stimuli at the same list position. From these percentage errors, the memory advantage for the isolates was calculated by subtraction of the error rate for isolates from the error rate for homogenous items (hereafter the *isolate memory advantage*). The size of this advantage for typographic and for fractal stimuli is shown in graph form in Figure 2, where it can be seen that although the size of the von Restorff effect is highly similar for typographic and for fractal stimuli in the normal monkeys, in the human group the isolate memory advantage is markedly larger for fractal than for typographic stimuli.

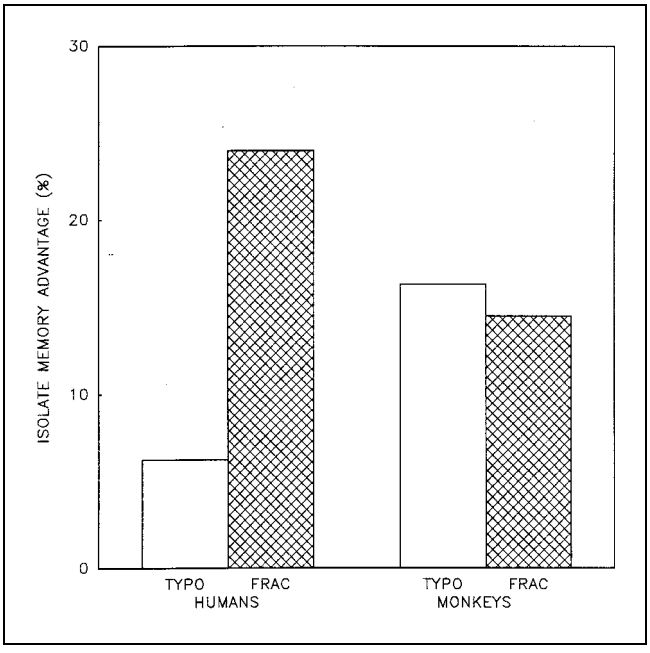

Figure 2. A comparison of the isolate memory advantage for monkey and human subjects, for typographic and fractal stimuli.

For the unoperated monkeys one-tailed t tests revealed that the isolate memory advantage was reliably above zero for both stimulus types (typographic: $t(2) = 6.63$, $p < 0.05$, fractal: $t(2) = 3.63$, $p < 0.05$), indicating better memory for isolates than for homogenous items. Direct comparison of the advantage scores for the two stimulus types revealed that they were not reliably different ($t < 1$).

For the human subjects a reliable isolate memory advantage was also observed for both stimulus types (typographic stimuli: $t(19) = 1.94$, $p < 0.05$; fractal stimuli: $t(19) = 10.01$, $p < 0.0005$, both one tailed). In addition, the size of the isolate memory advantage was reliably larger for the fractal than for the typographic stimuli ($t(38) = 4.35$, $p < 0.001$). For the human subjects, the size of the isolate memory advantage also did not vary according to whether the isolate/homogenous stimuli came from the red or blue end of the color spectrum ($t < 1$), indicating that the advantage is not a consequence of a particular color contrast. The percentage of errors made to isolate and homogenous stimuli for the humans and monkeys are shown in Table 1 (standard deviations for the human subjects are shown in brackets).

Pre- and Postoperative Memory in Monkeys

Figure 3 compares the isolate memory advantage for the unoperated monkeys and for the three lesion groups. The data are collapsed across stimulus type (fractal ver-

Table 1. Isolate Memory Advantage: Humans and Nonlesioned Nonhuman Primates

	Errors (%)		
Group	*Homogenous*	*Isolate*	*Advantage (%)*
Humans			
Typographic	13.5 (6.2)	7.3 (6.8)	+6.2
Fractal	29.9 (5.9)	5.9 (5.5)	+24.0
Mean humans	21.7	6.6	+15.1
Monkeys			
Typographic	34.9	18.7	+16.2
Fractal	28.1	13.6	+14.5
Mean monkeys	31.5	16.1	+15.4

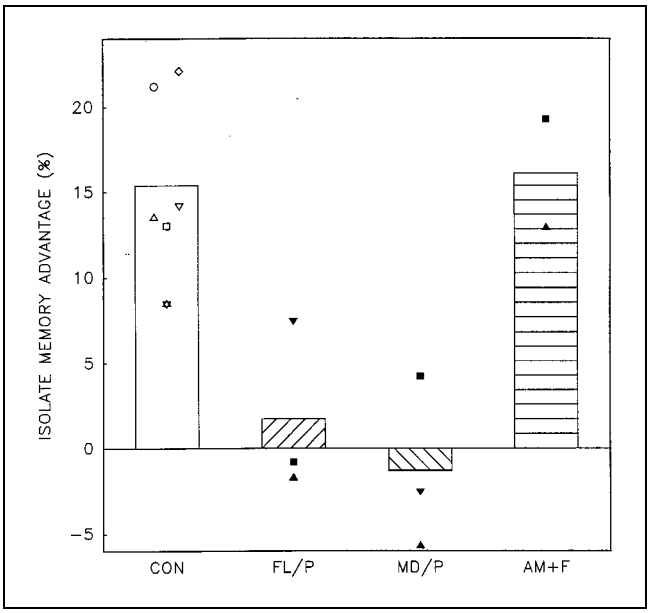

Figure 3. Isolate memory advantage for each of the monkey experimental groups. For open symbols, UNOP1 = triangle, UNOP2 = inverted triangle, UNOP3 = circle, UNOP4 = diamond, UNOP5 = star, and UNOP6 = square. For filled symbols, in each group animal 1 = triangle, animal 2 = square, animal 3 = inverted triangle.

sus typographic) because the isolate memory advantage for the control monkeys was equivalent for the two stimulus types. Figure 3 shows that although the size of the isolate memory advantage differs little for the unoperated and for the amygdala/fornix lesion groups, for the other two groups there is little evidence of an isolate memory advantage. This impression was confirmed by a series of statistical comparisons. An initial independent groups analysis of variance comparing the advantage scores for the four groups revealed a main effect of group ($F(3, 10) = 8.91$, $p < 0.005$). Planned pairwise comparisons between each lesion group and the unoperated group (using the pooled error term, see Snedecor & Cochran, 1967) indicated that whereas the amygdala and fornix lesioned group were not reliably different from unoperated monkeys ($t < 1$), the isolate memory advantage for the two groups FL/P and MD/P was reliably smaller (FL/P: $t(10) = 3.39, p < 0.005$; MD/P: $t(10) = 4.35, p < 0.001$). The percentage of errors of the individual monkeys in each lesion group for isolate and for homogenous stimuli are shown in Table 2.

A comparison of the unoperated animals with an animal with a unilateral perirhinal cortex ablation alone (MD/P3, postop 1 isolate memory advantage +14.2) and an animal with a unilateral prefrontal cortex ablation alone (FL/P1, postop 1 isolate memory advantage +17.7) indicated that in neither case did the unilateral lesion effect the size of the isolate memory advantage ($F < 1$ in both cases).

DISCUSSION

A robust von Restorff effect was observed in the unoperated monkeys and the human subjects, as revealed by a lower error rate for isolate than for homogenous stimuli (the *isolate memory advantage*). A robust isolate memory advantage was also found after bilateral amygdalectomy and fornix transection but was markedly attenuated in the two disconnection lesion groups—monkeys with disconnection of the perirhinal cortex from the prefrontal cortex and monkeys with disconnection of the perirhinal cortex from the magnocellular mediodorsal thalamus. The task is therefore one that can be used with both human and monkey subject populations. Consequently, it offers a useful tool for assessing

Table 2. Isolate Memory Advantage: Nonhuman Primates Postsurgery

	Errors (%)		
Monkey	*Homogenous*	*Isolate*	*Advantage (%)*
FL/P1	42.5	44.2	−1.7
FL/P2	39.2	40.0	−0.8
FL/P3	41.2	33.7	+7.5
Mean FL/P	41.0	39.3	+1.7
MD/P1	34.3	40.0	−5.7
MD/P2	44.7	40.5	+4.2
MD/P3	45.0	47.5	−2.5
Mean MD/P	41.3	42.6	−1.3
A + FX1	36.5	23.6	+12.9
A + FX2	29.6	10.3	+19.3
Mean A + FX	33.1	17.0	+16.1

novelty-related mnemonic processing in patients with brain damage. Of particular interest, in the light of the experimental findings reported here, would be the effects of performance on this task of lesions to particular areas of the prefrontal cortex or to circumscribed areas of the medial temporal lobe—for example, in epileptic patients who have undergone unilateral excisions of part of the medial temporal lobe.

One aspect of the data from the human subjects that is worthy of comment is the larger isolate memory advantage for fractal, rather than typographic, stimuli. This is probably due to the lower error rate for the homogenous typographic items (13.5 versus 29.9%, see Table 2), thereby reducing the maximum size of the isolate memory advantage for this stimulus set. The likely reason for the better memory for typographic than for fractal stimuli is that the typographic stimuli have a higher probability of being associated with a verbal label. Some support for this interpretation is provided by the fact that the unoperated monkeys revealed isolate memory advantages of equivalent magnitude for the two stimulus types. This finding reduces the likelihood that additional factors, such as possible differences in the complexity of the two stimulus types, are responsible for the larger isolate memory advantage for typographic than for fractal stimuli in the human subjects.

Whatever the explanation for the disparity between typographic and fractal stimuli, the disparity serves to emphasize the fact that the size of the isolate advantage is related to the overall level of memory for test items. In turn, this demands that consideration be given to the issue of equating performance in different groups. This is obviously of critical consideration when using patient populations, who may vary markedly from controls in their memory abilities. The approach employed for the monkey lesion groups described above, where performance for different animals was titrated by varying the list lengths used, is an example of one way in which performance can be equated. The extent to which this particular approach will be successful when comparing human subjects and human patients remains to be determined.

Bilateral Amygdalectomy and Fornix Transection

The fact that the isolate memory advantage remained after amygdala/fornix lesions indicates that these structures are not necessary for the memory advantage afforded novel stimuli in this modified von Restorff task. In addition, because the fornix is one of the principal outputs from the hippocampus, these findings suggest that hippocampally mediated novelty processing is not required for at least some aspects of novelty-related processing that support memory.

As previously noted (see "Introduction"), studies using various brain-monitoring methods (Knight, 1996; Tulving et al., 1994, 1996), as well as single-unit recording studies in awake behaving monkeys (Brown, 1996; Rolls et al., 1993), have indicated a role for the hippocampus in the processing of novelty. On the basis of these findings it has been proposed that the hippocampus forms part of a general novelty-processing network (Tulving et al., 1994). However, the fact that the isolate memory advantage survives bilateral amygdala/fornix lesions suggests that this view requires modification. Specifically, within the context of novelty processing that influences performance on visual-object recognition memory tasks, the hippocampus does not appear to be critical. However, this conclusion does not preclude hippocampal involvement in the processing of novelty. Rather, it emphasizes that it is important to consider the processing of novel information *in the context* of the type of information being processed. For example, the integrity of the hippocampus and its major output pathways may be critical for processing scene novelty and encoding information of that form into episodic memory.

Lesions Involving Perirhinal/Frontal Disconnection

The isolate memory advantage was markedly attenuated in animals with disconnection of the perirhinal cortex in the inferior temporal lobe from the prefrontal cortex. The surgical procedure in this group involved ablation of the perirhinal cortex in one hemisphere and ablation of the prefrontal cortex in the opposite hemisphere, thereby suggesting that the interaction between these structures *within the same hemisphere* (see "Introduction") is necessary to support the isolate memory advantage. A similar conclusion can be drawn from the finding that the magnocellular mediodorsal thalamus/perirhinal disconnection group showed an attenuated isolate memory advantage, because this area of thalamus has extensive afferent and efferent connections with prefrontal cortex.

The frontal lobes have been implicated in both novelty and memory processes (Knight 1984; Shimamura, Janowsky, & Squire, 1991; Tulving et al., 1996). PET studies have reported medial, orbito-frontal (Tulving et al., 1996) and dorsolateral prefrontal cortical activation (Dolan & Fletcher, 1997) when novel information is processed as part of a task. In each instance the frontal activity was explained as a "higher-level" form of strategic memory organization. In contrast, primate lesion studies have indicated a more direct role in memory tasks that involve novelty. Bachevalier and Mishkin (1986), and Meunier, Bachevalier, and Mishkin (1997) have shown that bilateral ablations of the ventral frontal cortex, and smaller lesions of the orbito-frontal cortex, cause significant impairments in recognition memory. However, the possibility must be considered that these impairments may be the result of some higher-level deficit rather than a deficit in memory processing per se.

Primate lesion studies have also indicated a critical role for the perirhinal cortex in visual recognition memory tasks (Buckley et al., 1997; Meunier, Bachevalier, Mishkin, & Murray, 1993), although recent evidence indicates that this region of the inferior temporal lobe may play a more general role in knowledge about visual objects (Buckley & Gaffan, 1997). Brown (1996) has argued that decremental changes in responses of neurons in the perirhinal cortex (which can be viewed as an index of stimulus novelty) are sufficient to solve a DMS task and that the time course of these changes is such that it can take no longer to generate the decrement in activity than it does to generate the second response itself. Consequently, Brown proposes that the influence of other structures such as the prefrontal cortex is unlikely to determine response changes in the perirhinal cortex.

These conclusions do not sit comfortably with the finding that perirhinal/frontal disconnection attenuates the isolate memory advantage because this lesion effect implicates the interaction between these structures in mediating at least one type of DMS memory performance. It is not entirely clear how to reconcile the apparent disparity between the lesion data and single-unit data. However, it is worthy of note that because the fast decrement in cell responses is a property of only some of the cells in the perirhinal cortex, it is possible that there are cell populations that show a decremental response and possess time courses more consistent with the view that frontal-perirhinal interactions support some types of DMS performance.

What functional role is the interaction between perirhinal and prefrontal cortex likely to play in the novelty assessment that underlies performance on the modified DMS task employed in this study? One possibility is that frontal modulation of perirhinal cortical activity varies with the novelty of a given stimulus. One form that this could take is if novelty assessment mediated by the frontal cortex influenced subsequent processing in the perirhinal cortex. This suggestion ascribes some form of novelty assessment role to the prefrontal cortex, a view that can be derived from the CHARM model of memory (Metcalfe, 1993), as well as from recent proposals about frontal cortical function based primarily on a critical review of neuropsychological and lesion study data (Wise, Murray, & Gerfen, 1996).

As previously described (see "Introduction"), in the CHARM model, memory encoding is modulated by an assessment of the similarity between new material and the contents of the memory store. The need for this form of modulation is demonstrated in terms of the computational demands imposed on the memory system, where in the absence of some form of novelty assessment the efficiency of the memory system declines markedly (Metcalfe, 1993). The model has also successfully predicted deficits in patients with damage to the frontal cortex on tests requiring feeling-of-knowing judgments and release from proactive interference (Metcalfe, 1993, 1994a, 1994b). Both of these tasks can be argued to require a form of novelty assessment. For feeling-of-knowing judgments, in the absence of specific memory for the relevant information, a general assessment of the relative novelty of a stimulus is assumed to underlie the ability to accurately predict when it will be possible to retrieve information from memory. In the case of release from proactive interference, the task requires an observation that the environment has changed—again, a form of novelty detection. This latter view of frontally mediated novelty-related processing is similar to that of Wise et al. (1996), who propose that the frontal cortex is particularly involved in supporting shifts away from a prevailing set or rule and in learning new behavior guiding rules. This function, in many circumstances, would require an observation that some aspect of the environment has changed.

Considering these observations in the light of the current findings, we can speculate that information about the novelty of an object in the perirhinal cortex must interact with novelty assessment and decision mechanisms in the prefrontal cortex to afford a memory advantage for novel stimuli. In addition, the findings from the magnocellular MD thalamus/perirhinal disconnection group suggest either that this route is essential for novelty information to be passed from perirhinal to frontal cortices or that this area of the thalamus is essential for other aspects of memory performance that are related to the processing of novel stimuli, possibly in the interaction between different frontal cortical regions.

Implications of the Present Results for Performance on DMS Tasks

The findings reported here also have implications for our understanding of how nonhuman primates solve the DMS task. The animals who formed the lesion groups here also acted as subjects in a DMS experiment that did not involve a differential novelty manipulation (Parker & Gaffan, 1998). Figure 4 shows their postoperative decrement in DMS performance at list position 2 (where the isolate was placed for the postoperative animals in the present experiment). Comparison of this measure with the results of their performance in the present experiment revealed that the animals who did not show a novelty advantage were also impaired in standard object recognition memory and that this observation was supported by a correlation of these two measures ($R(6) = 0.75$, $p < 0.05$). This evidence strongly supports the proposal that DMS is a task that depends heavily upon novelty detection. However, novelty detection may not be the only strategy available to the animals because both the FL/P and MD/P disconnection groups of Parker and Gaffan (1998, see Figure 4) were still able to perform the DMS task at levels reliably above chance. Because these animals did not show a novelty advantage, mne-

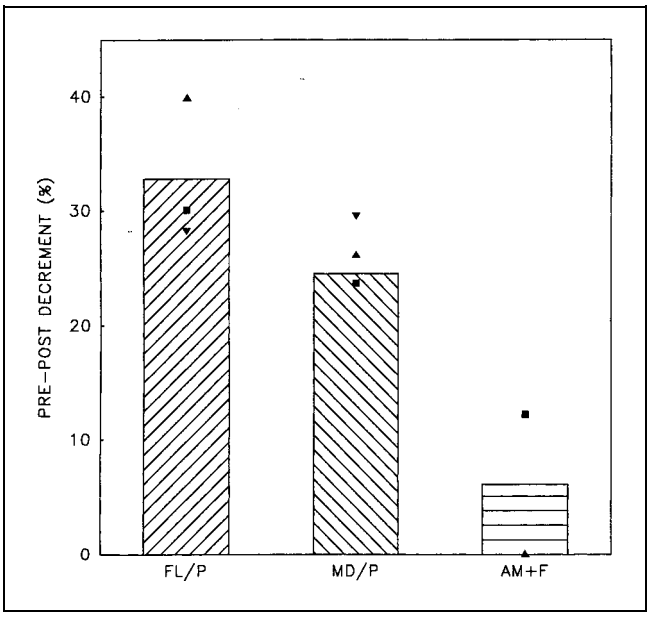

Figure 4. Postoperative decrement in DMS performance at list position 2 (equivalent to isolate or homogenous position) for the monkeys in the operated groups. Data from Parker and Gaffan (1998). Symbols as in Figure 3.

monic information unrelated to novelty may underlie their residual DMS performance. This form of proposal is consistent with the notion that recognition comprises two component processes, one based on familiarity judgments and the other based on the use of episodic (contextual) information about a prior experience with a given stimulus (Mandler, 1980).

CONCLUSIONS

We have demonstrated a robust von Restorff effect in human and nonhuman primates. The results from the three lesion groups permit two principal conclusions: (1) some forms of novelty-related mnemonic processing do not require the integrity of the amygdala and fornix, and (2) the integrity of the connection between the perirhinal and frontal cortices is critical for supporting enhanced visual object recognition memory performance as a function of stimulus novelty. The results are consistent with proposals that frontally mediated novelty detection mechanisms modulate the activity in the perirhinal cortex, which has been implicated in performance on DMS tasks. However, the results of the present experiments relate specifically to visual object recognition memory. It will be important to elucidate whether the isolate memory advantage seen here is the product of general novelty mechanisms or mechanisms that are specific to the type of information that is encoded into memory (in this case, visual object information). Disconnection of the frontal lobe from other medial temporal areas may selectively influence the processing of different types of novel information and the attendant mnemonic processing. An important focus for future experiments is to ascertain if isolate memory advantages for different forms of novel content (e.g., spatial information) depend on the interaction between different anatomical structures.

METHODS

Nonhuman Primates

Subjects

The subjects were nine male monkeys; seven were rhesus macaques (*Macaca mulatta*), and two were cynomolgus (*Macaca fascicularis*). At the time of their first surgery the rhesus weighed 5.4 kg on average, and the cynomolgus weighed 5.3 kg on average. Before taking part in this experiment, four were naive animals, and five had previously served as unoperated control animals in studies that used the same experimental equipment as the present study. Four animals were tested both pre- and postoperatively, four were tested only postoperatively, and one was tested only preoperatively because postoperative complications led to his withdrawal from the experiment. There were three surgical groups.

The first group (FL/P) was three rhesus. Each animal was operated on twice, once to remove the perirhinal cortex in one hemisphere and once to ablate the cortex of the frontal lobe in the contralateral hemisphere and to section the forebrain commissures. Animals FL/P1 and FL/P3 had right frontal ablation and forebrain commissurotomy as the first surgery. Animal FL/P2 had right perirhinal ablation as the first surgery.

The second group (MD/P) was three rhesus. Each animal was operated on twice, once to remove the peri-rhinal cortex in one hemisphere and once, in the contralateral hemisphere, to ablate the medial part of the mediodorsal nucleus of the thalamus unilaterally and partially to section the forebrain commissures. Animals MD/P2 and MD/P3 had mediodorsal thalamic ablation and commissurotomy in their first surgery: MD/P2 in the left hemisphere and MD/P3 in the right hemisphere. Animal MD/P1 had left perirhinal ablation as the first surgery.

The third group (A+F) was two cynomolgus. Each animal had two surgeries, in the same order, which were bilateral amygdalectomy and then bilateral fornix transection. On completion of behavioral testing both animals received bilateral perirhinal cortex ablation as part of a different experiment.

Surgery

Operations were carried out under aseptic conditions, and, after ketamine premedication, barbiturate anaesthesia was maintained until the end of surgery. In all cases a bone flap was raised over the area of the intended

ablation and the dura was cut. Ten to fourteen days were allowed for postoperative recovery before resumption of training. Fuller details of the surgical operations can be found in Parker and Gaffan (1998).

Perirhinal Cortex Ablation

The arch of the zygoma was removed and the temporal muscle was detached from the cranium and retracted. A bone flap was raised over the frontal and temporal lobe. The medial and posterior limits of the flap were in a crescent shape extending from within 5 mm of the midline at the brow to the posterior insertion of the zygomatic arch. The anterior limit of the flap was the brow and the orbit. Ventrally the flap extended from the posterior insertion of the zygomatic arch to the level of the superior temporal sulcus in the lateral wall of the temporal fossa anteriorly. The ventral anterior part of this bone opening was then extended with a rongeur ventrally into the wall of the temporal fossa to reach the base of the temporal fossa. The dura mater was cut to expose the dorsolateral frontal and lateral temporal lobes. The most anterior part of the rhinal sulcus was visualized by retracting the frontal lobe from the orbit with a brain spoon. The dorsal limit of the removal on the anterior face of the temporal pole was approximately 2 mm ventral to the lateral sulcus. A line of pia mater was cauterized, and the underlying cortex was removed by aspiration in the lateral bank of the anterior part of the rhinal sulcus and in the adjacent 2 mm of the cortex on the third temporal convolution. The monkey's head was then tilted to an angle of 120° from vertical, and the base of the temporal lobe was retracted from the floor of the temporal fossa with a brain spoon. The posterior tip of the first part of the ablation was identified visually and then extended in the lateral bank of the rhinal sulcus to the posterior tip of the sulcus, again removing 2 mm of laterally adjacent tissue. The dura mater was sewn and the wound closed in layers. The intended lesion is shown in Figure 5A.

Frontal Cortical Ablation and Forebrain Commissurotomy

The posterior limit of the frontal lesion was a line through the center of the precentral dimple from the most dorsal point on the lateral surface of the frontal lobe to the ventral surface, following a line parallel to the central sulcus and ventrally 1 to 2 mm posterior to the descending limb of the arcuate sulcus. The line then extended from the lip of the lateral sulcus along the posterior limit of the cortical surface of the orbital frontal lobe to the medial surface, followed the line of the corpus callosum anteriorly and ventrally, and then followed the boundary of the cortical surface until meeting the first point of cautery. The gray matter within all sulci was removed, leaving intact the white matter surrounding the striatum and the striatum itself. The intended lesion is shown in Figure 5B. A glass aspirator was used to transect the corpus callosum near the midline. The descending column of the fornix was gently retracted with a narrow brain spoon to enter the third ventricle. The anterior commissure was sectioned in the midline by electrocautery and aspiration.

Mediodorsal Thalamic Ablation, Body and Splenium of the Corpus Callosum Transection and Anterior Commissure Section

A glass aspirator was used to section the corpus callosum near the midline from the posterior limit of the splenium to the level of the interventricular foramen. The descending column of the fornix was gently retracted with a narrow brain spoon to enter the third ventricle. The anterior commissure was sectioned in the midline by electrocautery and aspiration. The splenium section was carried out 1 to 2 mm lateral from the midline to open the lateral ventricle between the fimbria-fornix and the splenium. The membrane covering the thalamus was cut in the midline by applying cautery to expose the posterior commissure, the third ventricle, and the posterior 5 mm of the midline thalamus. Next, the posterior 5 mm of the massa intermedia of the thalamus was cut in the midline with a glass aspirator. Tissue adjacent to the cut massa intermedia was removed unilaterally by aspiration with a metal aspirator. The dura was replaced over the cortex but not sewn.

Fornix Transection

The hemispheres were separated and the veins obscuring access to the corpus callosum were cauterized. A midline slit of approximately 5 to 10 mm in diameter was made through the corpus callosum using a glass sucker. The fornix was visualized just posterior to its descent along the superior boundary of the third ventricle and anterior to the massa intermedia of the thalamus and transected using a 20-gauge metal sucker with cautery.

Amygdalectomy

The medial temporal lobe was exposed by retracting the frontal lobe over the orbit of the eye. The pia mater was cauterized in an area approximately 5 mm in diameter on the medial surface of the temporal lobe, medial and superior to the rhinal sulcus. The amygdala and the periamygdaloid cortex medial to the amygdala were then ablated by aspiration through the defect in the pia mater. White matter of the temporal stem, and the lateral ventricle and anterior surface of the hippocampus, were visible boundaries of the ablation posteriorly, laterally and inferiorly.

Histology

After the conclusion of all behavioral experiments, the animals with ablations were sedated, deeply anaesthetized, and then perfused through the heart with saline solution (0.9%), which was followed by formal saline solution (10% formalin in 0.9% saline solution). The brains were blocked in the coronal stereotaxic plane posterior to the lesions, removed from the skull, allowed to sink in sucrose formalin solution (30% sucrose, 10% formalin), and then sectioned coronally at 50 μm on a freezing microtome. Every tenth section through the lesion area was stained with cresyl violet and mounted.

Figure 5 shows a representative set of sections of the perirhinal lesions. In the majority of cases the ablation was as intended, in that all included the entire anterior-posterior extent of the lateral bank of the rhinal sulcus. The cortex in the medial bank of the rhinal sulcus and the cortex medial to the sulcus were substantially intact. The lateral limit of the ablation was in every case on the inferior temporal gyrus, lateral to the rhinal sulcus, leaving the cortex in the anterior middle temporal sulcus intact. The posterior third of the ablation extended slightly more laterally in FL/P1 than intended, but by less than 1 mm. In all cases degeneration was visible in the white matter adjacent to the cortical removal. Although coronal sections are most appropriate for visualizing the main part of the ablation, the most anterior part of the ablation is difficult to interpret from the coronal sections through the temporal pole. However, inspection of the temporal pole before the brains were sectioned confirmed that the ablations had extended anteriorly and dorsally on the anterior face of the temporal pole to within 2 mm of the lateral sulcus, in the lateral bank of the most anterior part of the rhinal sulcus and in the laterally adjacent cortex, sparing the tissue medial to the rhinal sulcus.

Figure 5 shows representative sections through the frontal cortical ablations in animal FL/P1. In all cases there was a removal of the frontal cortex as intended and sparing of the primary motor area. In case FL/P1 there was slight sparing of the posterior part (approximately 5 mm anterior-to-posterior and 1.5 mm ventral-to-dorsal) of the ventromedial cortex. As can be seen in Figure 5C, the striatum and internal capsule are partially degenerated. In all of the animals this striatal damage was due to degeneration, not direct surgical damage.

Figure 6 shows the extent of the medial thalamic lesions in each of the animals in group MD/P. The sections from the brains were matched to a separately prepared set of sections of brains with normal mediodorsal thalamus in order to identify the cytoarchitectural limits of the lesions. The method used here is that which was fully described by Gaffan and Murray (1990). In all three cases there was substantial unilateral removal of the mediodorsal nucleus, magnocellular portion (MDmc), with minor sparing of MDmc and some damage

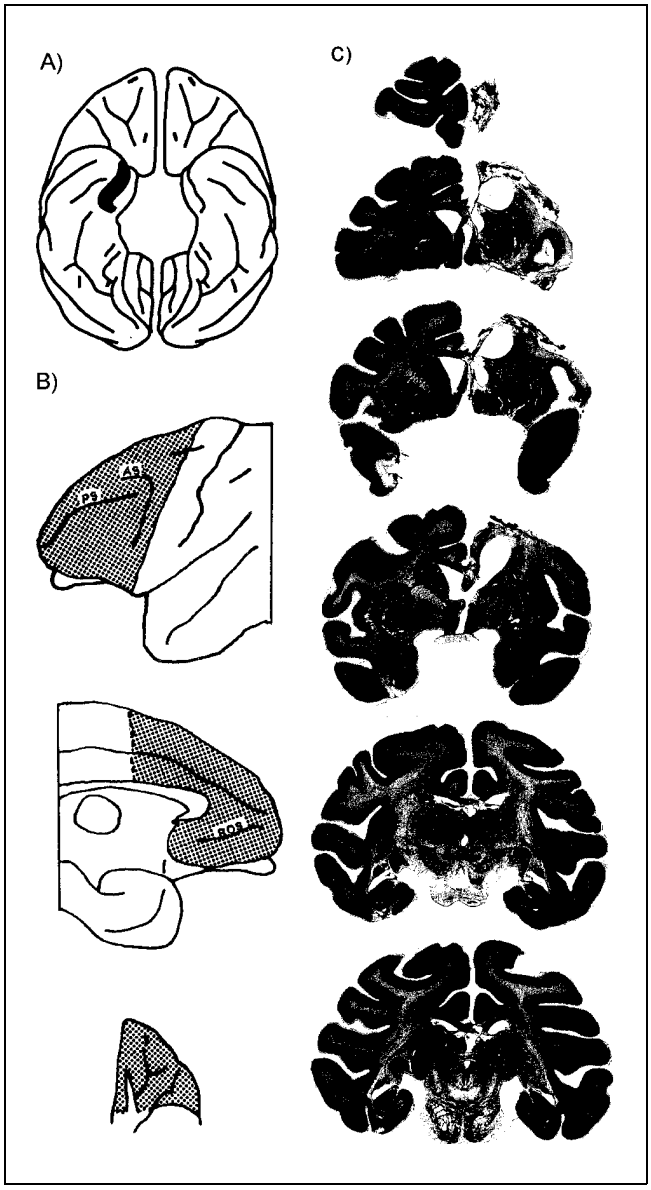

Figure 5. Intended lesions of the frontal lobe/perirhinal cortex disconnection group. The animals received perirhinal cortex ablation in one hemisphere, as outlined the ventral view in (A) and frontal cortical ablation in the contralateral hemisphere, the limits of which are shown from a lateral, medial, and ventral perspective in (B). In (C) a series of sections from animal FL/P1 illustrate the unilateral frontal and perirhinal cortex ablations. The sections run from anterior at the top to posterior at the bottom. Sections from the other animals were similar to these. See text for description of ablations.

to other structures. The initial removal of the posterior 5 mm of the massa intermedia of the thalamus in the midline had been largely as intended, except that subject MD/P1 showed slight unilateral damage to the anterior medial nucleus. In all three cases there was some damage to the reuniens nucleus, and in one case (MD/P2) central medial nucleus and parafascicular nucleus damage was seen in the midline. The second phase of the ablation, where tissue adjacent to the cut massa intermedia was removed unilaterally, was also largely successful

in all three animals. Two cases showed very little sparing of the MDmc, whereas the third (MD/P1) showed greater ventral sparing. There was also some unilateral damage to the parvocellular region of the MD in all three cases, but this was very small in extent in two animals (MD/P1 and MD/P2). In MD/P3 the damage extended into the paracentral nucleus and the posterior part of the ventral lateral nucleus. The three animals with mediodorsal thalamic lesions all had unilateral fornix damage, and some gliosis was observed in the fornix and fimbria. In MD/P1 and MD/P2 the fornix was deliberately transected ipsilateral to the MD lesion. In MD/P3 there was unintentional damage to the fornix contralateral to the MD lesion, sustained during the anterior commissure section.

Figure 7 shows representative sections from an animal from the A+F group. In both cases the fornix was successfully and completely transected and the amygdalae removed. Any damage to the cortex surrounding the amygdala was minimized by the choice of surgical approach. Instead, what can be seen as damage to the inferior temporal lobe is the result of a bilateral perirhinal cortex ablation that was performed subsequent to the present experiment.

Apparatus and Stimuli

The monkey sat in a wheeled transport cage in front of a touch screen (380 by 280 mm) and made choices between stimuli by reaching out between the bars of the cage (150 mm apart) and touching them. An automated pellet delivery system controlled by the computer delivered reward pellets into a food well (80 mm in diameter) positioned in front of and to the right of the monkey. Touches were registered by the computer and 190-mg of food pellets were delivered as rewards for correct

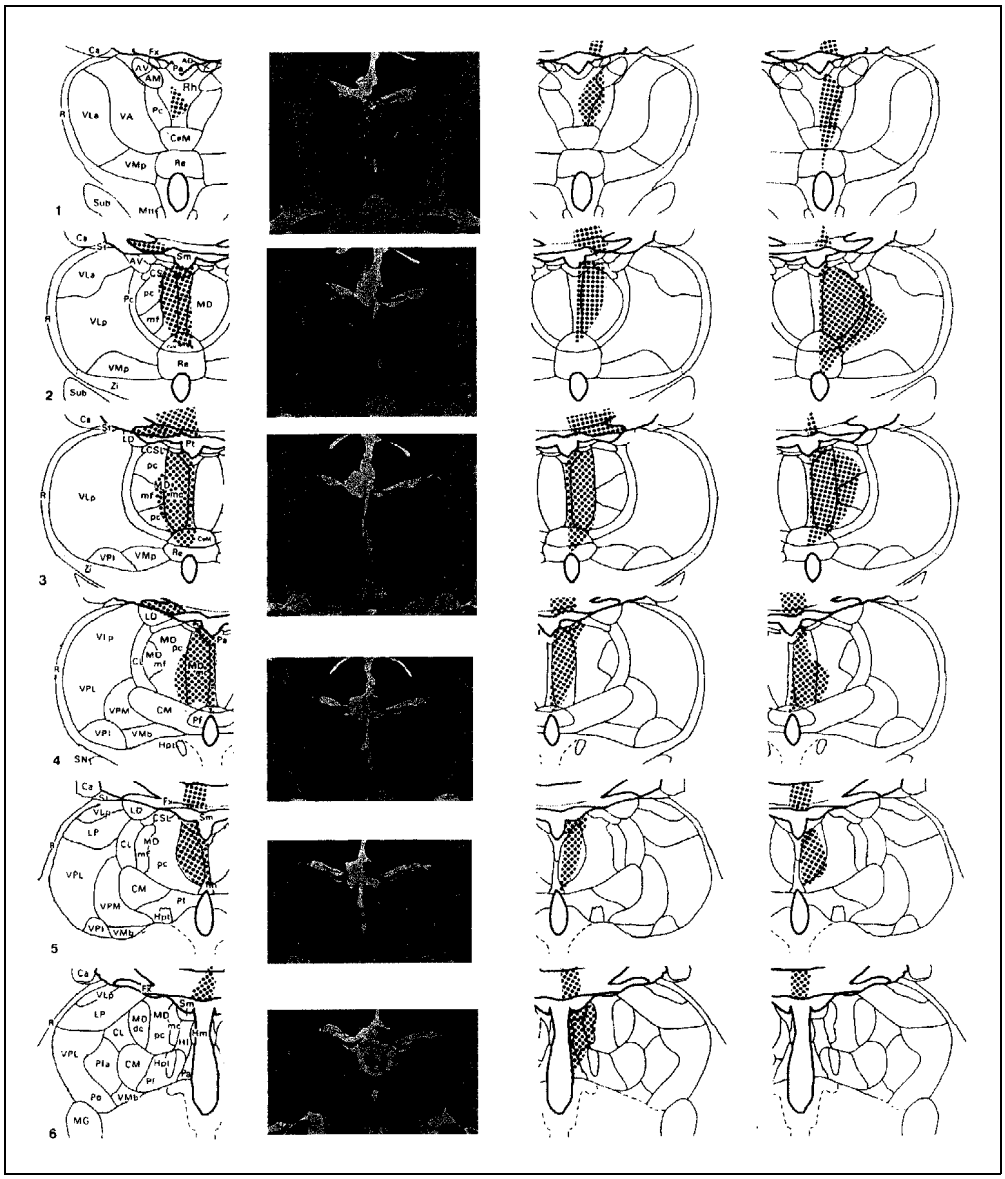

Figure 6. Columns 1, 3, and 4 illustrate the extent of the mediodorsal thalamic lesion in animals MD/P2, MD/P1, and MD/P3, from left to right. In column 2 are a series of sections from MD/P2.

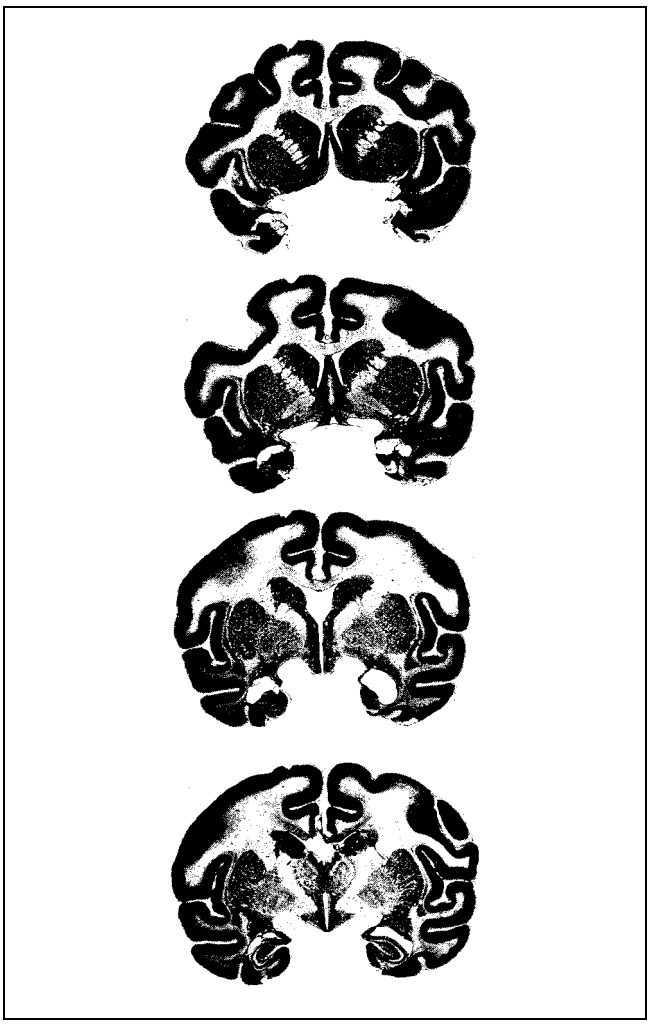

Figure 7. Sections from one animal (A+FX1) to illustrate the method of amygdalectomy and fornix transection. The sections run from anterior at the top to posterior at the bottom. Sections from the other animal were similar to these.

responses. An automated lunchbox was positioned in front of and to the left of the monkey. This opened at the end of a testing session, giving the animal access to its daily diet of proprietary primate pellets, nuts, raisins, and fruit. An infrared camera was positioned above the transport cage so that the monkey could be observed during the testing sessions. The apparatus was housed in an experimental cubicle that was dark apart from a 25-W incandescent lamp positioned so that there was no reflection on the touch screen, but the monkey was able to see into the food well and lunchbox when the screen was dark. The presentation of the visual stimuli on the touch screen was controlled by computer. The stimuli, examples of which can be seen in Figure 1, consisted of either two colored typographic characters abutted side by side (*typographic* stimuli) or two superimposed colored fractal polygons (*fractal* stimuli). Each stimulus was approximately 25 by 25 mm. For the typographic stimuli, each two characters were chosen at random from a set of 577. Fractal stimuli were generated by an algorithm that derived polygons by varying the parameters of size, axis of symmetry, and depth. Stimuli appeared in the center of the screen during the presentation phase of the experiment and 60 mm either side of the center during the test phase. Two color sets were used during the experiment, one with blue hues and the other with red ones. This was achieved by randomly selecting the values for the three elementary colors within two different specified ranges.

Procedure

The monkeys were pretrained to touch stimuli displayed on the screen and were then trained on DMS. The procedure and their performance data for this task appears elsewhere (Parker & Gaffan, 1998). They were then tested on von Restorff DMS as follows. During the presentation phase the subject was presented with a list of stimuli (for details of list length, see below), one after another, and was required to touch each stimulus as it appeared in the center of the screen. The stimulus disappeared 1 sec after the screen was touched and presentation of the next item occurred 5 sec later. The test phase commenced 5 sec after the end of the presentation phase. For each trial of the test list the subject was presented with a stimulus pair with one at the left and one at the right screen position (see "Methods"). Only one of each test pair matched an item from the presentation phase, and both were displayed in the color that the matched stimulus had been displayed in during the presentation phase. After the monkey had touched one of the stimuli, they both disappeared immediately from the screen. If the correct choice had been made, a reward pellet was delivered. The intertrial interval was 10 sec. The matching test stimuli were presented in reverse order compared to the presentation phase. That is, those stimuli presented last in the presentation phase were presented first in the test phase, and so on.

In accordance with von Restorff's original work, isolate items were always presented at the second list position unless list length was 2, in which case presentation was in list position 1. List length was adjusted for each animal such that all made between 60 and 80% correct responses to stimuli presented at the appropriate list position, but with shortest list length being 2. The probability of an isolate occurring in a list varied with list length, such that, on average, 1 in 100 stimuli were isolates. For example, for list length 5 an average of 1 in 20 lists contained an isolate, whereas for list length 10 an isolate occurred in 1 list in 10. The animals were required to satisfy a criterion of at least 100 correct responses per session and performed a series of sessions over consecutive days until each had received a total of 40 isolate items. Isolate stimuli were presented from the red and blue ends of the color spectrum in odd and even numbered sessions.

Humans

Subjects

Forty Oxford University students (25 males, 15 females) between the ages 18 and 23 years acted as subjects in the human experiment. They were assigned to one of two conditions, half to the *typographics* condition and half to the *fractals* condition.

Apparatus, Stimuli, and Procedure

The task was performed in an automated test apparatus, using the same computer-controlled touch-sensitive screens and the same stimuli and timings as for monkeys. Rather than dispensing a food pellet, the program indicated correct and incorrect responses by two different tone pitch sequences. List length for humans was always 20, piloting having determined that this list length effected acceptable error rates. Each subject took part in a single behavioral session, which ended when the subject had made 200 correct matches. Half of the human subjects were presented with isolate/homogenous stimuli from the red/blue end of the color space, whereas for the remainder the reverse was true. The maximum horizontal and vertical visual angles subtended by the screen display varied across subjects as each was required to sit within comfortable arm's reach of the touch screen. Assuming an average distance from the screen of 70 cm, the horizontal and vertical visual angles subtended by each stimulus were 2.05°. At 70 cm the visual angle subtended by the two stimuli presented side by side was 6.95°.

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