Research

Brain Activity During the Encoding, Retention, and Retrieval of Stimulus Representations

Greig I. de Zubicaray,¹ Katie McMahon, Stephen J. Wilson, and Santhi Muthiah

Centre for Magnetic Resonance, The University of Queensland, St. Lucia QLD 4072, Australia

Studies of delayed nonmatching-to-sample (DNMS) performance following lesions of the monkey cortex have revealed a critical circuit of brain regions involved in forming memories and retaining and retrieving stimulus representations. Using event-related functional magnetic resonance imaging (fMRI), we measured brain activity in 10 healthy human participants during performance of a trial-unique visual DNMS task using novel barcode stimuli. The event-related design enabled the identification of activity during the different phases of the task (encoding, retention, and retrieval). Several brain regions identified by monkey studies as being important for successful DNMS performance showed selective activity during the different phases, including the mediodorsal thalamic nucleus (encoding), ventrolateral prefrontal cortex (retention), and perirhinal cortex (retrieval). Regions showing sustained activity within trials included the ventromedial and dorsal prefrontal cortices and occipital cortex. The present study shows the utility of investigating performance on tasks derived from animal models to assist in the identification of brain regions involved in human recognition memory.

The delayed nonmatching-to-sample (DNMS) task has been used extensively in monkey studies to identify the brain regions involved in recognizing previously presented stimuli (Murray 2000; Zola et al. 2000). In a typical DNMS task, a monkey is presented with a trial-unique sample stimulus (e.g., a three-dimensional object) and, following a delay interval in which the sample is removed from sight, is allowed to choose between the sample and a novel stimulus item. A food reward is given for the choice of the novel item. Studies of DNMS performance following lesions of the monkey cortex have revealed a number of interconnected areas involved in the encoding, retention, and retrieval of stimulus representations within trials. This memory circuit consists principally of the ventromedial and ventrolateral prefrontal cortices, rhinal (entorhinal and perirhinal) cortex, thalamus, and area TE in the inferotemporal cortex (Kowalska et al. 1991; Meunier et al. 1997; Buffalo et al. 1999; Murray 2000). The hippocampus, located in the medial temporal cortex, might also be a component of this circuit. However, its precise role is currently the subject of debate (for an overview of this research, see Murray 2000; Zola et al. 2000).

In humans, researchers have increasingly used neuroimaging techniques to identify brain regions involved in recognition memory processes. These investigations have typically required participants to study a set of pattern, face, word, or picture stimuli and, after a delay, make recognition

memory judgements during scanning about studied and nonstudied items (Reber et al. 1998; Eldridge et al. 2000; Stark and Squire 2000a,b; Wiser et al. 2000). Other investigations have examined activity occurring solely during the encoding phase (Kelley et al. 1998; Fletcher et al. 2000; Otten et al. 2001). Relatively few studies have examined activity occurring during both encoding and retrieval or across the retention interval (Henson et al. 1999; McDermott et al. 1999). In addition, although these neuroimaging studies have revealed a number of human brain regions involved in recognition memory processes, the different stimuli and experimental methods used (e.g., verbally encoded picture and word items, set learning procedures) do not permit direct comparisons of results across species. Such comparisons can be useful because of the availability of animal models for recognition memory and the stronger causal inference afforded by lesioning relative to neuroimaging methods (Squire and Zola-Morgan 1983).

To facilitate comparisons with results from monkey studies, we used event-related functional magnetic resonance imaging (fMRI) and an analog of the trial-unique visual DNMS task using barcode stimuli to measure changes in neural activity during recognition memory processing of individual items in human participants. The event-related design allowed an examination of the transient hemodynamic responses to the different phases of the DNMS task on a trial-by-trial basis (Buckner 1998). Barcode stimuli were used as they comprise elementary visual attributes such as spatial frequency, orientation, and contrast (DeValois and DeValois 1990; Magnussen 2000). Although barcode stimuli are more difficult to discriminate than the three-dimensional objects usually presented to monkeys, they have the

¹Corresponding author.

E-MAIL greig.dezubicaray@cmr.uq.edu.au; FAX 617-3365-3833.

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advantage that they are less likely to be encoded verbally by humans. Participants were presented with a target barcode that they were required to encode, followed by a delay interval of 4, 6, or 8 sec during which they were required to retain the barcode in memory. After the delay interval, three barcodes, including the previously presented target and two novel nontarget barcodes, were presented, and the participants were instructed to select a novel item (nonmatching to sample) by making a button-press response. Each barcode stimulus contained three distinct arrays of bars and spaces, permitting the extent of the perceptual similarity of the novel items with the target barcode to be manipulated experimentally. On each trial, the two nontarget items differed from the target barcode by one and two of these arrays (i.e., by one-third and two-thirds of their content), enabling us to determine whether participants were using an explicit visual strategy based on the content of the barcode stimuli to perform the retrieval phase of the DNMS task (see Fig. 1). We predicted activity in a circuit of brain regions similar to that identified by the monkey lesion studies mentioned above.

RESULTS

Behavioral data collected during scanning showed that the participants performed ~90.9% of trials correctly (the 0.7% of trials in which participants failed to respond within 6 sec were omitted from subsequent analyses). Performance accuracy did not differ significantly as a function of delay

interval, $F(2, 414) = 0.04$, $P > 0.05$ (accuracy for trials with 4-, 6-, and 8-sec intervals was 90.6%, 91.4%, and 90.9%, respectively). Reaction times (RTs) for correctly performed trials also did not differ significantly as a function of delay interval, $F(2, 376) = 1.802$, $P > 0.05$ (mean RT $\pm$ SD for trials with 4-, 6-, and 8-sec intervals was 2.44 ± 0.94 , 2.66 ± 1.04 , and 2.65 ± 1.07 sec). On correctly performed trials, novel nontarget barcodes were selected with almost equal frequency, whether they differed from the target by one or two arrays (47.2% and 52.8%, respectively). There was also no significant difference in RTs for the type of barcode selected, $F(1, 377) = 0$, $P > 0.05$ (mean RT $\pm$ SD for one-array difference was 2.58 ± 0.97 sec; for two-array difference, 2.58 ± 1.07 sec), indicating that the participants were not consciously responding according to the magnitude of the perceptual difference of the barcode from the target. Finally, the interaction between barcode type and delay interval was also not significant $F(3, 375) = 1.21$, $P > 0.05$. The barcode selections were therefore combined for the fMRI analyses. The numbers of omitted and incorrect responses were considered insufficient to conduct analyses of these event types. The informal postscanning interview confirmed that none of the participants were consciously aware of the experimental manipulation of the array content of the barcodes. Most reported attempting to maintain an internal representation of the target across the delay intervals to compare with the barcodes presented during the nonmatching-to-sample phase.

The random effects analysis of the group fMRI data revealed significant blood oxygen level-dependent (BOLD) signal increases during both the sample presentation and nonmatching-to-sample phases. However, the comparisons of the 6- and 8-sec delays with the 4-sec delay interval failed to reveal significant delay-related changes in activation. We therefore combined the delay intervals and compared them with the baseline/intertrial interval (ITI) as per the sample presentation and nonmatching-to-sample phases.

Brain Regions Showing Activity During All Phases of the DNMS Task

Several cortical regions showed significant BOLD signal increases to correctly performed trials across all phases of the DNMS task relative to the baseline/ITI (see Tables 1–3, Figs. 2–4). These regions included the mid-dorsal lateral and medial lateral prefrontal cortices (areas 9/46 and frontopolar area 10) and occipital cortex (areas 18/19), although in the latter region the activity was less extensive during retrieval. The signal increases in these regions were broadly consistent in terms of their respective spatial locations across the different phases of the DNMS task, considering the resolution at which the fMRI data was acquired and the spatial smoothing applied for statistical inference across participants.

Figure 1 Sample barcode stimuli generated for a single trial of the delayed nonmatching-to-sample task. The target barcode plus two novel items differing from the target by one third and two thirds of their array content are shown on the *left*. The three distinct arrays of five bars and four spaces comprising each barcode are shown on the *right*. Ticks indicate arrays identical to those in the target barcode; crosses, dissimilar arrays.

Brain Regions Showing Activity Selectively During Sample Presentation (Encoding)

Activity occurred selectively during sample presentation in several cortical and subcortical regions (Table 1). The left dorsal medial frontal cortex showed significant activity in an area consistent with the recently proposed location of the human supplementary eye-field (see Tehovnik et al. 2000), as did the dorsal part of the lateral premotor cortex (area 6). Activity was also observed bilaterally in the thalamus, with the local maximum within the medial dorsal nucleus (Fig. 2, slice +12). Homologous signal increases were also observed in the caudate tail and lentiform nucleus in both hemispheres (Fig. 2, slice +16). Finally, the right cerebellum also showed significant activity.

Brain Regions Showing Activity Selectively During the Delay Intervals (Memory Retention)

Retention of newly encoded stimulus representations across the delay intervals (relative to the baseline/ITI) resulted in cortical signal increases selectively in the ventral lateral prefrontal cortex (area 47; Fig. 3, slice -8), and inferior parietal lobule (area 40) bilaterally (Table 2). Two regions showed activity in locations similar to that observed during the sample presentation phase: the dorsal part of the right lateral premotor cortex (area 6) and the left caudate tail. Additional selective activity was observed in the left brainstem.

Brain Regions Showing Activity Selectively During Nonmatching to Sample (Retrieval)

Signal increases during the nonmatching-to-sample (stimu-

lus recognition) phase were observed in several cortical and subcortical regions (Table 3). Activity was observed in the left middle frontal gyrus, in the vicinity of the recently proposed location of the “true” human frontal eye field (FEF; see Tehovnik et al. 2000) and in the medial anterior prefrontal cortex (around area 8). Posterior cortical activations were observed in the left inferior and right superior parietal lobules (areas 40 and 7, respectively) and right precuneus (area 7). A medial temporal lobe region located along the posterior lateral border of the parahippocampal gyrus (area 35) also showed signal increases (Fig. 4, slice -10). Although the resolution at which the fMRI data was acquired and the spatial smoothing applied for statistical inference across participants makes precise anatomical localization difficult, we consider it likely that this region is the rhinal (mainly perirhinal) cortex (Van Hoesen 1995). Finally, the left lateral dorsal nucleus of the thalamus and bilateral cerebellum also showed BOLD signal increases during this phase.

DISCUSSION

The present study identified brain activity during the performance of each phase of a trial-unique DNMS task (encoding, retention, and retrieval). We chose to examine brain activity during performance of the DNMS paradigm as it is a task that is regularly administered to monkeys to investigate recognition memory processes. In addition to discussing the present results in relation to relevant human neuroimaging and lesion investigations, we reasoned that it might be useful to compare them with the findings of comparable monkey lesion studies, although we acknowledge the difficulties inherent in transposing results across species (Squire and Zola-Morgan 1983; Tulving and Marcowitsch 1994). The information provided by animal models of recognition memory and the stronger (i.e., causal) inference afforded by lesioning relative to neuroimaging methods might therefore assist in the interpretation of important regions within our results.

Two different regions within the frontal lobe showed activity selectively during the encoding phase of the DNMS task. One of these, in the dorsal medial frontal cortex, corresponded to the recently proposed location of the human supplementary eye-field (Petit et al. 1998; Tehovnik et al. 2000). Imaging studies in humans have indicated that the human supplementary eye-field is involved in learning new tasks and is less dedicated to the execution of saccadic eye movements than is the more laterally FEF (Tehovnik et al. 2000). The second region was in the dorsal part of the lateral premotor cortex, which also showed less extensive activity during the retention phase. Previous imaging investigations of pattern encoding have reported similar premotor cortex activity, and it has been proposed that this activity may subserve short-term maintenance of visuospatial in-

Table 1. Signal Increases: Encoding (Sample Presentation)

Side	Cerebral region	Coordinates			
		<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>
L	Mid-dorsal lateral	10.06	-42	8	26
R	prefrontal cortex (BA 9/46)	4.89	48	12	28
L	Medial lateral prefrontal	4.68	-48	42	12
L	cortex (BA 10)	4.14	-32	62	12
L	Dorsal premotor cortex	5.77	-26	20	58
R	(BA 6)	5.70	38	6	60
L	Supplementary eye field	7.92	-6	16	50
L/R	Medial dorsal thalamus	5.51	0	-10	12
L	Caudate tail	4.77	-14	-4	14
R		6.16	16	-6	16
L	Lentiform nucleus	5.75	-18	16	-2
R		5.40	16	22	-8
R	Middle occipital gyrus (BA 19)	13.73	34	-86	18
R	Lingual gyrus (BA 18/19)	6.23	14	-66	4
R	Cerebellum	10.60	44	-70	-26

R, right hemisphere; L, left hemisphere; BA, Brodmann area.

Figure 2 Results from the group random effects analysis of the sample presentation/encoding phase superimposed on representative axial slices from the structural magnetic resonance imaging scan from a single subject in atlas space. PFC indicates prefrontal cortex; MD, medial dorsal nucleus; SEF, supplementary eye field.

formation (Iidaka et al. 2000). Our results are consistent with this interpretation.

The activity observed in the medial dorsal thalamus during the encoding phase is also consistent with the lesion data in monkeys and humans that indicate a role for this region of the thalamus in recognition memory (Aggleton and Brown 1999). Lesions of the medial dorsal nuclei in particular are reported to produce a severe amnesia in humans (Isaac et al. 1998), and the present results indicate that its involvement may be especially critical during memory formation. The caudate nucleus is generally considered to be involved in the learning of more gradually acquired visual discrimination tasks (i.e., visual habit formation; Teng et al. 2000), and lesions to the ventrocaudal neostriatum, including the caudate nucleus and lentiform nucleus, have been shown to not impair DNMS performance in monkeys (Fernandez-Ruiz et al. 2001). However, we found activity in these

neostriatal areas during the encoding phase of the DNMS task and less extensive activity (predominantly in the caudate tail) during the retention phase. Although this may indicate that the neostriatum in humans is capable of more rapid learning processes than those observed in monkeys, given the monkey lesion data, we consider this activity to represent a noncritical process (or processes) for successful DNMS performance.

Retention of newly encoded stimulus representations across the delay intervals produced selective activity in the ventrolateral prefrontal cortex and inferior parietal lobule in both hemispheres. Delay-related activity in the former region has been reported during delayed matching-to-sample (DMS) performance in human imaging experiments, leading researchers to hypothesize a role for this region in memory maintenance

(Rypma and D'Esposito 1999). However, in monkeys, lesions of the ventrolateral prefrontal cortex do not affect DMS performance at delays up to 8 sec (Rushworth et al.

Figure 3 Results from the group random effects analysis of the delay interval/retention phase superimposed on representative axial slices from the structural magnetic resonance imaging scan from a single subject in atlas space. PFC indicates prefrontal cortex.

Table 2. *Signal Increases: Retention (Delay Interval)*

Side	Cerebral region	Coordinates			
		<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>
L	Mid-dorsal lateral	8.07	-44	6	32
R	prefrontal cortex	5.58	42	8	32
R	(BA 9/46)	6.22	4	38	30
R		7.31	46	26	22
R	Dorsal premotor cortex	6.21	38	8	52
R	(BA 6)				
R	Medial lateral prefrontal	4.38	32	66	2
	cortex (BA 10)				
L	Ventral lateral prefrontal	4.20	-32	22	-4
R	cortex (BA 47)	10.91	38	28	-8
L	Caudate tail	4.90	-14	0	16
L	Inferior parietal lobule	8.94	-42	-40	54
R	(BA 40)	5.11	38	-48	54
R	Lingual gyrus (BA 18)	17.37	6	-96	-4
R	Superior occipital gyrus	12.05	34	-80	32
	(BA 19)				
L	Brainstem	6.19	-4	-24	-18

R, right hemisphere; L, left hemisphere; BA, Brodmann area.

1997). In addition, this region is considered to have a slightly different and selective role in DNMS performance in monkeys; namely, it contributes to the learning or relearning of the DNMS rule (Kowalska et al. 1991; Málkov&accute; et al. 2001). This suggests that the activity observed in the ventrolateral prefrontal cortex during the retention phase in the present study may represent, for example, activation of the nonmatching rule. The inferior parietal lobule showed significant activity during the retention phase and less extensive activity during retrieval, perhaps representing the focussing of attention on visual attributes of stimulus representations and/or reflecting a role for this structure in the retrieval operation of perceptual memory itself (DeValois and DeValois 1990; Greenlee et al. 2000). Projections from the inferior parietal lobule converge at the perirhinal cortex border, and it is thought that this convergence may contribute to the deficits in visual recognition memory resulting from lesions of the perirhinal cortex in the monkey (Ding et al. 2000).

When the different retention intervals (4 to 8 sec) were compared in the present study, no delay effect was found. This result contrasts with Elliott and Dolan's (1999) block-design fMRI study of DMS and DNMS performance, in which a delay effect was observed between blocks of trials with delay intervals of 5 and 15 sec. One possibility is that the delay intervals used here were too short to elicit differential delay effects (a maximum of 4-sec difference between intervals). As Elliott and Dolan (1999) suggested, there may be different memory systems involved in short (< 10 sec) versus long (> 10 sec) delays, with memory over brief delays relying on a short-term posticonic memory system and longer delays requiring conversion of visual representations

into more structural descriptions. The majority of participants reported attempting to maintain an internal representation of the target across the delay intervals to compare with the barcodes presented during the retrieval phase. In addition, they reported being unaware of the experimental manipulation of the array content of the barcode. This is consistent with a reliance on a short-term, low-level perceptual memory system to perform the task (DeValois and DeValois 1990; Magnussen 2000). Like Elliott and Dolan (1999), however, we did not find a significant difference in performance between the different delay intervals.

Retrieval of stimulus representations from memory resulted in selective activity along the lateral border of the parahippocampal gyrus (around area 35), corresponding to the location of the perirhinal cortex (Van Hoesen 1995). Lesions of the human perirhinal cortex are known to produce recognition memory impairments at delays of $\sim \geq 6$ sec (Buffalo et al. 1998), and there is considerable evidence from monkey-lesion studies confirming a critical role for this medial temporal lobe structure in recognition memory (Buffalo et al. 2000; Murray 2000). In addition, the perirhinal cortex is closely connected with the medial dorsal nucleus of the thalamus (Aggleton and Brown 1999). However, we did not observe any retrieval-related activity in the hippocampus, even at a more lenient significance threshold

Table 3. *Signal Increases: Retrieval (Nonmatching to Sample)*

Side	Cerebral region	Coordinates			
		<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>
R	Mid-dorsal lateral prefrontal cortex (BA 9/46)	7.83	42	36	36
R	Medial anterior prefrontal cortex (BA 8)	7.61	0	38	42
L	Frontal eye field	5.36	-50	20	40
L	Medial lateral	5.30	-14	52	10
R	prefrontal cortex (BA 10)	8.46	46	52	16
L	Lateral dorsal thalamus	7.28	-22	-32	10
R	Perirhinal cortex (BA 35)	4.51	18	-32	-10
R	Superior parietal lobule (BA 7)	7.12	40	-54	56
R	Precuneus (BA 7)	6.75	0	-68	58
L	Inferior parietal lobule (BA 40)	5.50	-38	-52	56
R	Superior occipital gyrus (BA 19)	5.53	34	-88	22
R	Cuneus (BA 18)	7.88	12	-98	20
L	Inferior occipital gyrus (BA 18)	5.57	-34	-82	-12
R	Cerebellum	8.59	38	-82	-20
R		5.82	2	-44	-4
L		8.57	-52	-66	-16

R, right hemisphere; L, left hemisphere; BA, Brodmann area.

Figure 4 Results from the group random effects analysis of the nonmatching to sample/retrieval phase superimposed on representative axial slices from the structural magnetic resonance imaging scan from a single subject in atlas space. PFC indicates prefrontal cortex; FEF, frontal eye field.

($P < 0.05$, uncorrected). This suggests that the recognition memory processes measured by the trial-unique barcode DNMS task do not differentially activate the hippocampus, at least at delays up to 8 sec. In contrast, Stark and Squire (2000a,b) reported significant retrieval-related hippocampal activity in their two-block design fMRI studies, and Eldridge et al. (2000) reported significant hippocampal activity during retrieval in their event-related fMRI study only when retrieval was associated with conscious recollection. These studies used lists of verbally encoded picture or word stimuli and much longer delays between encoding and retrieval (20 to 30 min). It should be noted that the evidence concerning the performance of patients with hippocampal lesions on visual DMS tasks is equivocal (Zola and Squire 1999; Holdstock et al. 2000), as is the evidence concerning the performance of monkeys with hippocampal lesions on the DNMS task (Murray 2000; Zola et al. 2000), and the precise role of this medial temporal lobe structure in simple recognition memory remains the subject of considerable debate (Aggleton and Brown 1999).

Additional selective activity during the retrieval phase was found in the medial anterior prefrontal cortex and in the putative location of the “true” human FEF (in the middle frontal gyrus; Tehovnik et al. 2000). Lesions to the medial anterior prefrontal cortex in monkeys are known to impair performance on conditional tasks requiring the selection of responses following presentation of a cue (Petrides 1987), and a recent fMRI study in humans found activity in this area as a result of the performance of fixed sequences that in-

involved acting after a delay (Koechlin et al. 2000). These processes are likely to have been engaged in each trial particularly during the nonmatching-to-sample phase. It seems reasonable to assume that the participants were performing saccadic eye movements during this phase to inspect the presented contents of the barcodes, thus accounting for the observed FEF activity. We cannot, however, rule out a role for the FEF in memory retrieval based on our results, although such a role seems unlikely (see Tehovnik et al. 2000).

Two prefrontal cortical regions and the occipital cortex showed sustained activity throughout all phases of the DNMS task. Of the two prefrontal regions, the mid-dorsolateral area (9/46) is hypothesized to have a specific role in assisting the encoding of infor-

mation through the application of associative or organizational strategies, based primarily on the results of human imaging studies (Kelley et al. 1998; McDermott et al. 1999; Fletcher et al. 2000; Iidaka et al. 2000). However, the dorsal prefrontal cortex is known to be unimportant for successful performance of the DNMS paradigm in monkeys (Bachevalier and Mishkin 1986). Consequently, this suggests that the sustained mid-dorsolateral activity observed in the present study may represent a noncritical process (Aggleton and Brown 1999). A possible explanation for this activity, also derived from the monkey literature, is that it represents the tracking or predicting of the probability of success over all phases of a trial, a more tonic function that may be closely related to attentional, arousal, or motivation level (Hasegawa et al. 2000).

The second prefrontal region that showed sustained activity within trials was the ventromedial prefrontal cortex (area 10, the frontal pole), a region previously established to be important for successful performance of DNMS tasks in monkeys (Meunier et al. 1997). It is hypothesized to participate in the same memory system as the perirhinal cortex and medial dorsal thalamic nucleus (Meunier et al. 1997). Unfortunately, there is little lesion evidence to either support or refute a similar role for this prefrontal region in humans (Aggleton and Brown 1999). fMRI studies of recognition memory in humans have tended to reveal retrieval-related activation in the frontal pole (area 10; Kelley et al. 1998; McDermott et al. 1999), and a recent positron emission tomography study also indicated a role for a more ven-

tral region (area 11) in encoding of visual information (Frey and Petrides 2000). We did not observe activation in the more ventral prefrontal cortex, although this may in part have been because of differences in magnetic susceptibility that result in partial signal losses around this region (Ojemann et al. 1997). Meunier et al. (1997) interpreted their results with monkeys as indicating the ventromedial prefrontal cortex may be involved in two types of interrelated memory processes: “memory across trials for the reward values of object classes (i.e., old versus new), and the other of memory within trials for the physical features and/or configurations of particular objects”, with the latter “the process that enables recognition of an object as familiar”. As participants were not rewarded on each trial of the present DNMS task, this latter process may account for the sustained activity observed in this prefrontal region within trials. An alternative explanation is that it might represent the suppression of responses to familiar stimuli, as proposed by Elliott and Dolan (1999). However, in monkeys, the impairment observed in trial-unique DNMS performance following lesions of the ventromedial prefrontal cortex does not appear to be a result of any special difficulty in suppressing responses within trials (Meunier et al. 1997).

Finally, the finding of activity in the occipital cortex (areas 18/19) during encoding, retention, and (less extensively) retrieval is consistent with the hypothesized existence of a low-level perceptual memory mechanism for visual attributes (e.g., spatial frequency, orientation, contrast) in the visual processing stream beyond V1 in humans (DeValois and DeValois 1990; Magnussen 2000) and with the results of a recent fMRI study of pattern recognition memory (Reber et al. 1998). We did not observe activation in anterior inferotemporal cortical area TE, a region frequently implicated in DNMS performance in monkey studies that used object stimuli (Murray 2000). However, evidence from similar studies indicates that extrastriate visual areas upstream of area TE (e.g., areas TEO and V4) are sufficient to process elementary visual stimuli such as the barcode stimuli used here (Buffalo et al. 1999, 2000; Gallant et al. 2000).

In conclusion, the present study has elucidated the brain regions involved in successful performance of a trial-unique DNMS task in humans. The event-related design enabled the identification of selective activity during the different phases of the task (encoding, retention, and retrieval). The results are consistent with the findings from human imaging and monkey lesion studies. In addition, the present study shows the utility of examining performance on tasks derived from animal models to assist in the identification of brain regions involved in human recognition memory.

MATERIALS AND METHODS

Participants

Ten right-handed participants (six males) took part in the study.

Mean age was 27.2 yr (SD = 5.6). No participant had a history of psychiatric or neurological disorder or of head trauma or substance abuse. Informed consent was gained from all participants before the commencement of the study. The study was conducted within the constraints of the ethical clearance from the Medical Research Ethics Committee of the University of Queensland for MRI experiments on humans at the Centre for Magnetic Resonance. Participants received a small gratuity and a magnetic resonance image of their brain for their involvement.

DNMS Paradigm

Participants were presented with a trial-unique target barcode stimulus in the middle of the screen for 4 sec, followed by a delay interval of 4, 6, or 8 sec (randomly ordered), during which they viewed a blank screen with a central fixation point (+) and were required to retain the target in memory. The variable delay intervals were included to minimize potential correlations (i.e., shared variance) between memory retention and transient recognition events (see Image Analysis below). Following the delay, three barcodes were presented side by side in the middle of the screen. These included the previously presented target as well as two novel nontarget barcodes (also trial unique). The positions of the target and nontarget stimuli varied randomly and were counterbalanced across trials. Participants were instructed to select a nontarget item by pressing one of three buttons corresponding to the positions of the barcodes on the screen. Response feedback was provided by highlighting the selected barcode in red for 250 msec. Selection time was limited to 6 sec, to allow an ITI of at least 12 sec for the BOLD response to return to baseline. If a response was not made within 6 sec, the items were removed from the screen and a null-response was recorded for the trial (a pilot study conducted outside of the scanner indicated that participants required up to 6 sec to initiate a response in the selection phase of the task). Response selection was followed by a blank screen with a fixation point presented for the period of the ITI. For both the delay and ITI periods during which a fixation point was displayed, participants were instructed to maintain their gaze on the crosshair. No further instructions were given for these periods.

Monochrome barcode stimuli were generated using the Code 39 alphanumeric bar code specification (also called three of nine). In this specification, a barcode consists of three distinct arrays of five bars and four spaces, with each array generated by an alphanumeric character. A bar or space is designated either wide or narrow, with three of the nine elements in any generated array being wide. Each barcode stimulus item consisted of three adjacently positioned arrays created from a set of 44 characters, with two additional narrow spaces inserted to separate them. Nontarget barcodes presented on each trial differed from the target by one and two arrays (see Fig. 1). The dimensions of the generated barcodes were ~70 pixels high by 105 pixels wide.

Before scanning, each participant underwent a practice session outside of the magnet to familiarize them with the task requirements. This involved presentation of three trials on a laptop computer consisting of one trial at each of the delay intervals. For the imaging sessions, barcode stimuli were generated via a computer and enlarged and back-projected onto a screen at the foot of the bore of the magnet. Participants viewed the screen through a mirror mounted at the top of the head coil. Two consecutive sessions were conducted, each consisting of a block of 21 trials. Responses and RTs were recorded by a computer. Following scanning, the participants were informally interviewed as to how they had performed the task.

Image Acquisition

Images were acquired using a 2 Tesla Bruker Medspec S200 system at the Centre for Magnetic Resonance, Brisbane. A quadrature Helmholtz head coil was used for RF reception. A total of 610 T_2^* -weighted gradient-echo echoplanar images depicting BOLD contrast (Ogawa et al. 1990) were acquired over two consecutive imaging runs in each of 21 planes parallel to the anterior-posterior commissure with echo time (TE) = 38 msec, repetition time (TR) = 2100 msec, 60° flip angle, in-plane resolution 3.44 mm and slice thickness 5 mm (zero gap). The first five image volumes from each imaging session were discarded to ensure that steady-state tissue magnetization was reached. Head movement was limited by a restraining band across the forehead and foam padding within the head coil. In the same session, a high-resolution three-dimensional T_1 image was acquired using an MP-RAGE sequence with inversion time (TI) 850 msec, TR 1300 msec, TE 5.2 msec, and slice resolution 0.9 mm³.

Image Analysis

Image processing and statistical analyses were performed using statistical parametric mapping software (SPM99; Wellcome Department of Cognitive Neurology, Queens Square, London). The time-series data were first sinc interpolated in time to correct for the interleaved fMRI acquisition sequence (Aguirre et al. 1998), then realigned to the first image of the series, and a mean image was created from the realigned data (Friston et al. 1995; Grooten et al. 2000). The high-resolution T_1 and mean T_2^* -weighted images were then spatially normalized via nonlinear basis functions to the T_1 and echoplanar template images, respectively, included in SPM99 (Ashburner and Friston 1999). These templates conform to the space defined by the International Consortium for Brain Mapping project (ICBM; National Institutes of Health P-20 grant) that closely approximates the stereotaxic space described in the atlas of Talairach and Tournoux (1988; Evans et al. 1994). The nonlinear transformations for the mean T_2^* -weighted images were subsequently applied to the realigned mean T_2^* -weighted time-series data. The normalized T_2^* -weighted data sets were then identically smoothed with a Gaussian filter (full width half maximum, 6 mm) to increase signal to noise and to accommodate variability in gyral anatomy and error of voxel displacement during normalization. A general linear model was applied to the signal intensity time-course of each voxel (Friston et al. 1995; Worsley and Friston 1995). The fixed-effects model included separate covariates consisting of synthetic hemodynamic response functions for transient BOLD responses to the stimulus presentation, delay intervals, and RTs during the nonmatching-to-sample phases of each correctly performed trial and its associated ITI (Josephs et al. 1997; Josephs and Henson 1999). Planned contrasts were then used to compare parameter estimates for the stimulus presentation and nonmatching-to-sample phases relative to baseline (ITI) for each participant. For the different delay intervals, the parameter estimates for the 6- and 8-sec intervals were each compared with the 4-sec interval for each participant. The resulting contrast images were entered into a one-tailed *t*-test in a group random effects analysis to permit inferences about phase effects across participants using a statistical threshold of $P < 0.005$ (uncorrected; Friston et al. 1999).

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