NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 39 (2008) 857 – 872

Delayed match to object or place: An event-related fMRI study of short-term stimulus maintenance and the role of stimulus pre-exposure

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Received 25 May 2007; revised 25 August 2007; accepted 12 September 2007
Available online 21 September 2007

Recent delayed matching studies have demonstrated that maintaining trial-unique stimuli in working memory modulates activity in temporal lobe structures. In contrast, most previous studies that focused on the role of the prefrontal cortex (PFC) used familiar stimuli. We combined fMRI with a delayed-match-to-sample (DMS) task in humans that allowed us to manipulate stimulus pre-exposure (trial-unique vs. familiar objects) and stimulus domain (object vs. location). A visually guided saccade task was used to localize the frontal eye fields (FEF). We addressed two questions: First, we examined whether delay-period activity within PFC regions was more strongly engaged when stimuli were familiar (pre-exposed) than when they were not seen previously (trial-unique). Second, we examined the role of regions within the PFC in object vs. location working memory. Subjects were instructed to remember one stimulus domain while ignoring the other over an 8-s delay period. Object-specific delay-period activity was greatest in the posterior orbitofrontal cortex (OFC) bilaterally, and was stronger for familiar than trial-unique objects. In addition, consistent with previous findings, right posterior superior frontal sulcus, and the FEF were specifically active during the delay period of the location DMS task. These activations outside FEF were not related to saccadic eye movements. In contrast to previous reports, object-specific delay activity was more prominent in the posterior OFC than in the ventrolateral PFC, and was found to be greater for familiar than for trial-unique objects. These results suggest a critical role for the orbitofrontal cortex for maintaining object information in working memory.

Keywords: Orbitofrontal cortex; Frontal eye fields; Dorsolateral prefrontal cortex; Superior frontal sulcus; Match-to-sample; Working memory

Introduction

Sustained activity in prefrontal (PFC) neurons during delayed match to sample tasks has been regarded as the neural correlate of memory maintenance (Fuster and Alexander, 1971; Kubota and Niki, 1971; Fuster, 1973; Rosenkilde et al., 1981; Quintana et al., 1988, see Fuster, 1991, for review). While most fMRI and animal studies investigating the role of the PFC in visual working memory have used a small set of highly familiar stimuli (Courtney et al., 1997; Rao et al., 1997; Postle and D'Esposito, 1999a; Postle et al., 2000b; Sala et al., 2003), those studies that used working memory paradigms with novel or trial-unique stimuli have focused on the medial temporal lobes (Gaffan, 1974; Zola-Morgan et al., 1989; Gaffan and Murray, 1992; Zola-Morgan et al., 1993; Alvarez et al., 1994; Eacott et al., 1994; Ranganath and D'Esposito, 2001; Schon et al., 2004). Using fMRI, we have previously shown that 2-back working memory performance with trial-unique visual stimuli recruited the medial temporal lobes, whereas 2-back working memory performance with a small set of familiar visual stimuli recruited the prefrontal cortex (Stern et al., 2001). Based on this finding, it is possible that the PFC may be recruited only when pre-exposed (i.e., highly familiar) objects, but not when trial-unique objects need to be maintained in working memory. Specifically, one candidate may be the dorsolateral PFC (DLPFC) that has been implicated in executive control functions.

Executive functions of the DLPFC include online monitoring and manipulation of information held in working memory regardless of stimulus material (Petrides, 1995; Owen et al., 1996; Owen et al., 1999; D'Esposito et al., 1999; Curtis et al., 2000; Stern et al., 2000; Stern et al., 2001; Pochon et al., 2001). Other studies have shown that both DLPFC and ventrolateral PFC (VLPFC) are recruited when executive processes related to short-term storage are needed (Rypma et al., 1999; Stern et al., 2001; Barde and Thompson-Schill, 2002; Glahn et al., 2002; Rypma et al., 2002; Veltman et al., 2003).

Another candidate for monitoring task relevant information may be the orbitofrontal cortex (OFC). In the rat, the OFC is

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter
doi:10.1016/j.neuroimage.2007.09.023

necessary for delayed non-matching of odor stimuli drawn from a small stimulus set but not when the stimulus set is large (Otto and Eichenbaum, 1992). In monkeys, the OFC, together with the VLPFC, has been shown to be important for selecting behaviorally relevant stimuli (Rushworth et al., 2005). A PET study using a 1-back continuous picture recognition paradigm in humans indicated that while initial learning activated the MTL, posterior medial orbitofrontal cortex activity was evident in subsequent runs in which previously seen pictures increasingly recurred (Schnider et al., 2000). This condition would require close monitoring of the currently relevant stimulus in the face of interference. Successful interference resolution has been shown to activate two cortical networks, one involving the VLPFC, and a secondary one involving the orbitofrontal cortex (Caplan et al., 2006). Thus, another potential candidate within the PFC may be the mid-VLPFC, as recent event-related fMRI (Stern et al., 2001; Henson et al., 2002; Badre and Wagner, 2005; Caplan et al., 2006, see Jonides and Nee, 2006 for review) and rTMS studies (Feredoes et al., 2006) have shown that the left VLPFC supports interference resolution.

In addition to sustained activity in dorsolateral and ventrolateral prefrontal cortex, delay-dependent activity has also been observed in the frontal eye fields (FEF) in monkeys (Funahashi et al., 1989; Gaymard et al., 1999; Umeno and Goldberg, 2001; Sommer and Wurtz, 2001), and in humans (Sweeney et al., 1996; Brown et al., 2004; Curtis et al., 2004; Leung et al., 2004; Linden et al., 2003; Postle et al., 2004; Mohr et al., 2006). Delay-period activity in the FEF has been attributed to the maintenance of a prospective motor code or maintenance of a saccadic plan (Wurtz et al., 2001; Curtis et al., 2004, 2005; Curtis and D'Esposito, 2006), and to covert spatial attention (Kastner et al., 1999, see Pessoa et al., 2003, for review). Findings from monkey lesion (Sommer and Tehovnik, 1997), and human neuropsychological (Pierrot-Deseilligny et al., 1993) studies also demonstrate a role of the FEF in spatial working memory.

Delay-dependent activity in the posterior superior frontal sulcus (SFS) has been observed specifically for short-term maintenance of spatial information in humans (Courtney et al., 1998; Rowe et al., 2000; Rowe and Passingham, 2001; Glahn et al., 2002; Sala et al., 2003; Slotnick, 2005, but see Postle, 2005) and in a homologous region in the monkey (Chafee and Goldman-Rakic, 1998; Rainer et al., 1998a; Inoue et al., 2004). In both humans and monkeys, this spatial-specific delay-period activity was posterior and superior to the DLPFC, and distinct from and just anterior to the FEF. However, some studies found that activation in this region is not limited to short-term maintenance of spatial information (Jha and McCarthy, 2000; Postle et al., 2000a; Zurowski et al., 2002), or that activity in this region is related to saccadic eye movements (Postle et al., 2000a; Brown et al., 2004).

Based on monkey neurophysiological recording data, activity in the mid-DLPFC has also been attributed specifically to the short-term maintenance of spatial information, whereas the ventrolateral PFC has been implicated in the short-term maintenance of nonspatial information (Funahashi et al., 1989; Wilson et al., 1993). However, there is very little support for this domain-specific specialization as most neuroimaging studies (D'Esposito et al., 1998; Owen et al., 1998; Postle and D'Esposito, 1999a; Postle et al., 2000b; Nystrom et al., 2000) and single-unit recording studies (Rao et al., 1997; Rainer et al., 1998a; Rainer et al., 1998b; Ferrera et al., 1999) were unable to find such segregation.

This study addressed two questions: First, are there regions within the PFC that are more strongly engaged when stimuli are pre-exposed (i.e., highly familiar) than when they are not previously encountered (i.e., trial-unique)? Possible candidates include DLPFC, OFC, and VLPFC. Second, are the FEF, the posterior SFS, and the DLPFC preferentially recruited for short-term maintenance of locations, and is the VLPFC preferentially recruited for maintenance of objects? If so, can activity in these regions (outside FEF) be distinguished from saccadic eye movement-related activity in the FEF? We addressed these questions by combining fMRI with a DMS task that allowed us to manipulate the stimulus type simultaneously on two dimensions: stimulus domain (object vs. its location) and stimulus pre-exposure (trial-unique vs. familiar objects), and added a visually guided saccadic eye movement task.

Materials and methods

Subjects

Seventeen subjects (8 males and 9 females, mean age 21.29± 3.72 years, age range 18–30 years) were recruited from the student population at Boston University. All subjects were screened for MR compatibility, and subjects with a history or current condition of neurological or psychiatric illness were excluded. Vision was normal or corrected-to-normal. All subjects gave written informed consent to participate in this study in a manner approved by the Partners Human Research Committee of the Massachusetts General Hospital and by the Boston University Charles River Institutional Review Board.

Stimuli

The stimuli for this experiment consisted of 3.8 cm×3.8 cm digital color pictures of birds and fish on a uniform gray background, and 10 spatial locations around a central fixation dot (see Fig. 1A).

Familiar objects

Approximately 20 min before the beginning of the functional scans, subjects saw a set of 5 birds and 5 fish on the center of a computer screen five times for 4 s each in a randomized order to familiarize themselves with the familiar stimulus set.

Trial-unique objects

All other stimuli (birds and fish) were not pre-exposed to the subjects and were trial-unique. Trial-unique stimuli were randomly selected from a set of 63 pictures of birds and 73 pictures of fish. Across all runs, a stimulus from the trial-unique set would be seen twice only in the case of a DMS match trial.

After stimulus familiarization, all subjects received detailed instructions on a computer screen and practiced the object and location tasks before scanning.

Tasks and procedures

There were four tasks: spatial DMS, object DMS, spatial control task, and object control task (Fig. 1A). Subjects performed both object and location DMS tasks with either familiar, previously exposed objects or trial-unique, not previously exposed objects. Tasks differed only in instruction. During each DMS trial, subjects saw a picture of a bird or a fish in one of ten possible locations (sample presentation) and a central fixation dot for 2 s. Then, the sample stimulus disappeared and the screen remained black except for a central fixation dot for 8 s. At the end of the delay, the subject saw a stimulus in one of the ten locations for 2 s (probe