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Note

Differential activation of ventrolateral prefrontal cortex during working memory retrieval

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Abstract

Brain imaging studies have suggested a predominant involvement of prefrontal areas during retrieval of information from working memory (WM). This study used event-related functional magnetic resonance imaging to assess the gradual recruitment of brain areas during verbal WM-retrieval with a parametrically varied modified version of the Sternberg Item Recognition Paradigm. In particular, we were interested in activation differences during retrieval of negative and positive probes. Fifteen subjects performed a WM-task which required the retrieval of a probe letter from a set of a maximum of three letters. The analysis of the retrieval period regardless of probe type revealed bilateral VLPFC activation during retrieval from a single remembered item. These initially activated regions showed a gradual activation increase of left VLPFC (BA 47) and anterior PFC (BA 10) as well as and bilateral DLPFC (BA 9) with increasing retrieval demand, i.e. during retrieval of two and three previously remembered letters. The comparison of negative and positive probes (non-targets versus targets) revealed greater activity in VLPFC (BA 47) in response to negative than to positive probes. These findings demonstrate that ventral areas of prefrontal cortex seem to be differentially engaged during the discrimination of a non-target from a previously manipulated set.

Keywords: Working memory; Prefrontal cortex; Retrieval; BA47; fMRI; Target; Non-target

1. Introduction

The concept of working memory (WM) refers to the ability of transient storage and manipulation of information held on-line for further usage in related cognitive processes or for goal-directed behavioral guidance (Baddeley, 1996, 2003). Both anatomical tracing and functional neuroimaging studies demonstrated that the prefrontal cortex (PFC) is crucial for mediating WM-functions (D'Esposito, Postle, & Rypma, 2000; Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971; Goldman-Rakic, 1990; Walter et al., 2003; Wolf & Walter, 2005); for a meta-analysis see (Owen, McMillan, Laird, & Bullmore, 2005; Wager & Smith, 2003). Previous studies have tested several WM-models, including prefrontal organization by material type (Funahashi, Bruce, & Goldman-Rakic, 1993; Wilson, Scalaidhe, & Goldman-Rakic, 1993) or by the type of cognitive process (Petrides, 1994). However, studies using functional magnetic resonance imaging (fMRI) have challenged these concepts. Thus, lateral PFC is clearly recruited during a variety of different cognitive processes that are engaged during the performance of a whole range of WM-tasks, including encoding, maintenance, manipulation and updating of information (Wager & Smith, 2003). While most studies have analyzed PFC activation during the delay period, there is less evidence concerning PFC function during WM-retrieval (D'Esposito et al., 2000; Habeck et al., 2005; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Leung, Gore, & Goldman-Rakic, 2005). Baddeley (1986) considered the relationship between WM and retrieval from long-term memory by acknowledging the differential role of phonological processes during successful retrieval. The neuronal correlates of these processes may involve predominantly ventral PFC-regions (at or near BAs 44/6, 45 and 47) in elaborating on verbal information, including remembering and retrieval (Buckner & Wheeler, 2001).

Event-related fMRI studies of WM-retrieval have implied differential contributions of both ventro- (VLPFC) and dorsolateral prefrontal cortex (DLPFC). For instance, DLPFC has

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been associated with scanning of information, VLPFC with inhibitory functions and selection (D'Esposito et al., 2000). At present, parametric variations of the amount of information during WM-retrieval have been less extensively studied (but see Habeck et al., 2005). Sufficiently parametrized designs can yield additional information concerning differential PFC-activation with increasing target discrimination load. Recently, Leung et al. (2005) have demonstrated differential activation of anterior PFC (BA 10) during the recognition stage of a spatial WM-task, indicating that this region may show greater activity in response to negative probes (non-targets) than positive probes (targets). These results support the concept of differential prefrontal engagement during decision process in WM-retrieval, possibly depending on target features.

We have recently shown prefrontostriatal recruitment with increasing load during the delay period of a verbal WM-task (Wolf & Walter, 2005). In this report, we chose to reanalyze this data, addressing the issue of parametric recruitment of lateral prefrontal areas with increasing retrieval demand. Furthermore, we investigated differential activation effects during parametric retrieval of targets versus non-targets. Previous event-related fMRI studies of WM-retrieval have shown contributions of both ventral and dorsal PFC during WM-retrieval (D'Esposito et al., 2000), VLPFC-activation being consistently found at low WM-load levels (Lee, Robbins, & Owen, 2000). Thus, we hypothesized VLPFC-activation during low-level retrieval and increasing DLPFC-activation with increasing retrieval demand. Moreover, we hypothesized that VLPFC-function would show increasing retrieval-related activation, since recent evidence indicates that VLPFC function may be modulated in a load-dependent manner during the probe period (Habeck et al., 2005). The second aim of the study was to show that VLPFC activation is not solely modulated by 'retrieval load' in general but may depend on selection and discrimination processes that differ between probe features.

2. Materials and methods

2.1. Subjects

We studied fifteen right handed healthy subjects (8 m, 7 f; mean age = 28.13 ± 4.17 years; educational level = 12.0 ± 1.5 education years), recruited from the University of Ulm campus, after having been screened to assure only the inclusion of participants without a history of major head trauma, significant neurological or psychiatric disorder or substance abuse or dependence within the past 6 months. The project was approved by the local Ethics Committee and all subjects gave written informed consent prior to participation.

2.2. Cognitive task procedure

The cognitive activation task has been described elsewhere in full detail (Wolf & Walter, 2005). During a stimulus period of 1500 ms, three capital grey letters were presented on a black screen. For a brief period of 500 ms, either one, two or all letters could turn bright depending on randomization (Fig. 1). Starting from these letters, subjects were instructed to memorize only the letter(s) which directly followed in the alphabet ("manipulated set"); see Fig. 1 for an example of a single trial. In the probe period of 2000 ms a lower-case letter was presented and subjects had to indicate whether this letter was or was not part of the "manipulated set". Probes consisted of both targets and non-targets (positive or negative probes, respectively), i.e. of probes which either had to be

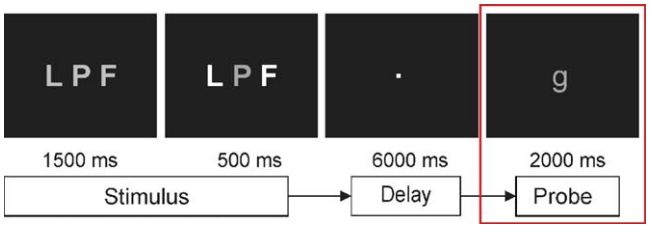

Fig. 1. Activation paradigm, shown for Load2. In this example, the letters L and F turned bright, and subjects had to subsequently memorize the letters M and G ("manipulated set"). The probe-letter g is a part of the previously manipulated set, i.e. a positive probe/target. Red rectangle: *period-of-interest* for fMRI. See also text for further details.

accepted or rejected from the "manipulated set". Probe-selection included an equal number of positive and negative probes which had to be retrieved from a set of one to three letters ('Load' 1–3). The control condition consisted of three grey X's calling for a stereotype button press during the presentation of a small x in the probe period, thus forming a motor task without mnemonic requirements.

2.3. Data acquisition

Data were acquired using a 1.5 T Magnetom VISION (Siemens, Erlangen, Germany) whole-body MRI system equipped with a standard head volume coil. T2*-weighted images were obtained using echo-planar imaging in an axial orientation (TR = 2400 ms, TE = 40 ms, FoV 192 mm, 64 × 64 matrix, 24 slices, slice thickness 4 mm, gap 2 mm). Stimuli were presented via LCD video goggles (Resonance Technologies, Northridge, CA) and both reaction times and accuracy indices were recorded. Head movement was minimized using padded ear phones. The fMRI-protocol was a rapid event-related design with a pseudorandomized time-jitter of 1.5 ± 0.5 TR inter-trial-interval. Trial duration was 10 s + 2.4–4.8 s. Stimuli were pseudorandomized and counterbalanced for the relative appearance frequency of each letter per load, highlighted position or target. Each condition was associated with a balanced number of target and non-target probe-letters. The experimental design avoided the appearance of recent negative trials in order to prevent proactive interference during retrieval (Jonides et al., 1998). Subjects performed three sessions, each including 28 trials (7 trials per condition), comprising 164 volumes (492 volumes in total). The first 8 volumes of each session were discarded to allow for equilibration effects.

2.4. Data analysis

2.4.1. Behavioral data analysis

Performance was recorded as percentage of correct responses (accuracy) during target and non-target trials, reaction times (RT) of the correct trials are reported in ms. Additionally, accuracy and RT were calculated for target and non-target conditions. Significant changes in performance and RT with increasing load were assessed separately using a repeated-measures analysis of variance (MANOVA) followed by Scheffé's Test post hoc. Differences between target and non-target conditions were assessed using paired *t*-tests.

2.4.2. fMRI data analysis

Functional data analyses were carried out with SPM2 (Wellcome Department of Cognitive Neurology, London) implemented in MATLAB 6.0 (MathWorks, Natick, MA). The functional images were first subject of slice-timing and correction of motion artifacts, then spatially normalized to the SPM2 EPI standard template of 3 mm × 3 mm × 3 mm voxels. These images were spatially smoothed with a 9-mm full width at half maximum isotropic Gaussian kernel. Analyses were performed within the framework of the General Linear Model in SPM2 (Friston, Holmes, Worsley et al., 1995; Friston, Holmes, Poline et al., 1995) using the canonical-hrf-function as a predictor in order to estimate the hemodynamic response function of each event. For single-subject analyses, only correct trials were included after removal of incorrect and omitted probes. We modelled stimulus and delay periods as one regressor, thus obtaining a lower degree of event-correlation relatively to the retrieval period. Omitted and false trials were pooled and used as individual regressor of no interest for each subject.