Decreased activity in inferotemporal cortex during explicit memory: dissociating priming, novelty detection, and recognition

Jonas Persson,[CA] Reza Habib[1] and Lars Nyberg

Umeå University, Department of Psychology, 901 87, Umeå, Sweden; [1]Rotman Research Institute of Baycrest Centre, University of Toronto, 3560 Bathurst Street, Toronto, Ontario, M6A 2E1, Canada

[CA]Corresponding Author: jonas.persson@psy.umu.se

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Studies of non-human primates have shown that activity in inferotemporal (IT) brain regions decrease over repeated stimulus exposure, a phenomenon known as repetition suppression. In the present study, repetition suppression was examined during recognition of personally experienced events (explicit memory). Brain activity was measured while subjects encoded and subsequently recognized scenic pictures. First, two recognition conditions were compared; one that mainly included familiar pictures and one that mainly included novel pictures. Responses derived from this contrast may reflect recognition memory, perceptual priming, or novelty detection. To test specifically for responses associated with recognition memory, subjects encoded a new set of pictures followed by two recognition tests. All test pictures had been presented during the course of the experiment, and the subjects identified pictures that appeared in the second encoding list. Since all pictures were familiar, repetition suppression was specifically associated with recognition memory. In the first contrast, relative change in brain activity was observed in inferotemporal, extrastriate, and hippocampal regions during recognition of familiar versus novel pictures. In the second contrast, decreased activity in IT cortex was found. The location of this region overlapped with that for the region identified in the first contrast, and a conjunction analysis showed that reduced activity in left IT cortex was common to both contrasts. These results suggest that repetition suppression in IT cortex reflects recognition memory, and that such a response is not a simple function of stimulus repetition but can be modulated by top-down processing. *NeuroReport* 13:2181–2185 © 2002 Lippincott Williams & Wilkins.

Key words: Activity decreases; Episodic memory; Inferotemporal cortex (IT); Positron emission tomography (PET); Recognition memory; Repetition suppression

INTRODUCTION

Single-cell recordings in non-human primates have shown that the activity of neurons in inferotemporal (IT) regions is maximal when novel stimuli are presented, and that the activation decreases when a stimulus becomes more familiar [1,2]. This phenomenon is known as repetition suppression. In most previous studies on repetition suppression a delayed matching-to-sample (DMS) task has been used. In the DMS task, a test stimulus is presented and the subject must indicate whether the test stimulus matches a previously shown target stimulus. Holding the target stimulus in memory has a temporary effect on many IT neurons, as shown by a reduced response in neuronal firing. Thus, IT decreases in activity may carry information regarding relative familiarity of a stimulus and thus reflect recognition memory.

In humans, functional neuroimaging has been used to study brain activity associated with the DMS task [3]. A reduced response in left IT cortex was found when unfamiliar compared to familiar abstract patterns were contrasted. Decreased activity associated with processing of novel *vs* repeated items has also been observed for other memory tasks [4]. One example is priming, that is, the facilitation in the processing or identification of a stimulus as a consequence of prior exposure to it. Conceptual priming has been associated with reduced activity in regions of the prefrontal cortex [5], whereas perceptual priming has been associated with decreased activity in extrastriate cortex [6]. Another example is studies of explicit (episodic) memory, that is, memory for personally experienced events. Less activation has consistently been observed in studies where retrieval of novel and familiar information have been contrasted [7,8]. Such decreases have been observed in medial temporal lobe areas (MTL), but decreases have also been found in IT cortex [9]. In a multistudy analysis of five PET experiments, Habib and Lepage [9] used a multivariate statistical approach to identify brain regions that were less active during recognition of familiar relative to novel information. They found that regions in lateral temporal cortex, including the IT cortex, and MTL were less activated by familiar stimuli. This result may be interpreted as showing that episodic recognition is asso-

ciated with decreased regional activity. However, as noted by Habib and Lepage [9], these responses may also be related to perceptual priming or detection of novel items. Evidence for MTL involvement in novelty detection has been found in studies on patients with focal brain damage [10], single cell recordings in non-human primates [11], and neuroimaging studies [8].

Thus, previous neuroimaging studies do not differentiate between decreases in brain activity associated with recognition memory and responses related to priming or novelty detection. This study was explicitly designed to separate between responses related to novelty detection, perceptual priming, and recognition memory. Regional cerebral blood flow (rCBF) was measured while subjects decided (yes/no recognition) whether scenic pictures had been encoded or not. Of main interest was whether specific regions show a reduced response when items are recognized based on their familiarity, and also whether recognition of a visual target among equally familiar distracter items is associated with reduced regional activity.

MATERIALS AND METHODS

Participants: Eight young right-handed adults (five females, age range 19–29 years) with no history of neurological or psychiatric illness performed six experimental conditions during PET scanning. Subjects were paid for their participation. The study was approved by The Joint Baycrest Centre/University of Toronto Research Ethics and Scientific Review Commmitee, and written informed consent was obtained from all participants.

Materials: Seven conditions were included in the experiment, one baseline condition, two encoding conditions and four retrieval conditions. In baseline, a coloured square surrounded by a black frame was presented on a coloured background. In half of the items, the square was the same colour as the background. In the encoding and retrieval conditions, items consisted of scenic pictures representing animals, vegetation, coastlines, and water. Each list in the seven conditions contained 30 items, 20 of which were presented within the 60 s scanning window. In the first two retrieval conditions, items were either new (distracters) or had been presented in the first encoding list (targets). In the second two retrieval conditions, items were either presented as distracters or targets in the first two retrieval conditions (distracters), or presented in the second encoding list (targets). In all recognition conditions, a mixture of eight new/old items were presented before the scanning window to prevent subjects from forming strategies.

Procedure: All tasks were presented on a computer screen. Each item in each of the six conditions was presented for 2.5 s (ISI = 0.5 s). The experimental protocol is summarized in Fig. 1. In baseline (1), coloured squares surrounded by a black frame were presented on a coloured background. The subjects were instructed to indicate if the square presented in the middle of the screen had the same colour as the background or not. In the encoding conditions (2,5) subjects were instructed to memorize as many of the pictures as possible for a subsequent memory test. No scanning was made during the second encoding list (5). In the recognition conditions, subjects were instructed to indicate if the picture had been presented in the encoding list (3,4), or to indicate if the picture had been presented in the second encoding list (6,7). For each picture, subjects responded by pressing a mouse button. The order of conditions, except for the second encoding list (5), was counterbalanced across subjects.

Data acquisition and analysis: PET was performed using a GEMS Scanditronix (Uppsala) PC-2048 head scanner. An i.v. bolus of 30 mCi ^{15}O-labeled water was given in the subjects' left forearm vein for each 60 s acquisition scan, SPM99 (www.fil.ion.bpmf.ac.uk/spm/) implemented in Matlab (Mathworks Inc. Sherborn, MA, USA) was used for image pre-processing. Following realignment of all images to the subjects' first scan, images were transformed into a standard space [12]. As a final pre-processing stage images were smoothed using a 10 mm FWHM isotropic Gaussian kernel.

Before presenting the analyses a few things should be noted. To isolate brain regions where activity decreased during recognition of a familiar item compared to recognition of a novel item, a series of analyses were specified (see 1–3 below). It should be noted that what is defined as increases or decreases in pairwise contrasts depend on how the contrasts are set up. The contrast of main interest here was between recognition of novel and familiar items. Brain regions that show relatively higher activity in this contrast may signal increased activity during processing of novel information or decreased activity during processing of familiar information. Based on previous findings (see Introduction), findings of relatively higher MTL activity during recognition of novel items was interpreted as increases related to novelty detection, findings of relatively decreased occipital activity was interpreted as decreases related to perceptual priming, and findings of relatively decreased IT activity was interpreted as decreases related to explicit recognition memory.

(1) The first analysis involved contrasting recognition of novel and familiar items (Fig. 1a). Resulting changes in rCBF may reflect decreases associated with priming, decreases associated with recognition or increases related to novelty detection. (2) A second analysis involved contrasting familiar distracter and target items (Fig. 1b). This analysis specifically revealed decreases associated with recognition memory; responses related to priming and novelty detection were eliminated since all items were familiar. (3) A conjunction analysis [13] was used to identify responses that were common to contrasts 1 and 2 (Fig. 1c). (4) Finally, the two retrieval conditions in which subjects were instructed to recognize familiar target pictures among familiar distracter pictures (6 and 7) where contrasted with the two retrieval conditions where subjects were instructed to identify familiar target pictures among novel distracter pictures (3 and 4). This contrast reveals activations associated with selection and monitoring of whether an item was presented in a specific study list or not.

Based on previous findings of altered regional activity during processing of novel versus familiar information, responses in IT cortex, medial temporal cortex, and in extrastriate cortex were *a priori* defined to be of interest. The

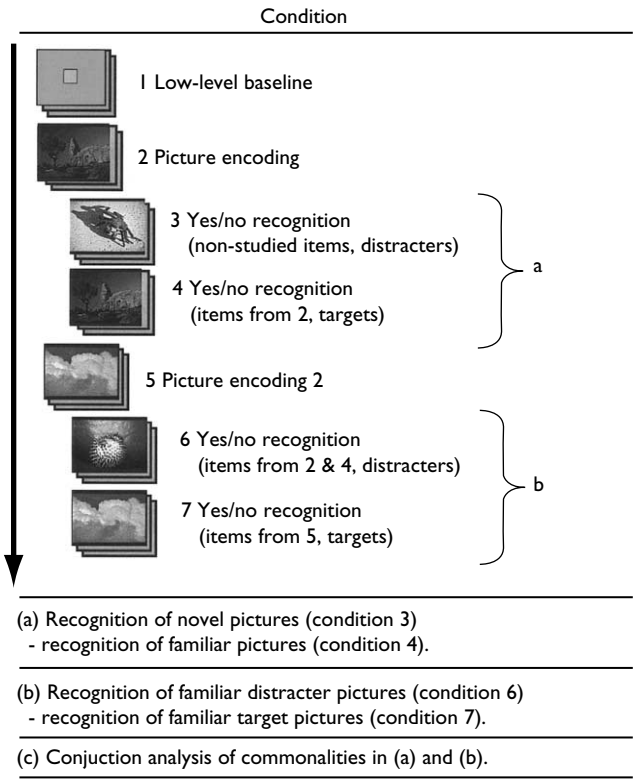

Fig. 1. Experimental protocol and strategy for data analysis. Icons are examples of the pictures that were used as stimuli. (**a**) Contrast 1: Increases associated with novelty, decreases associated with perceptual priming, and decreases associated with recognition memory. (**b**) Contrast 2: Decreases associated with recognition memory. (**c**) Conjunction analysis of commonalities in contrasts 1 and 2.

threshold for statistical significance in these regions was $p < 0.005$ (uncorrected). For all other regional responses, a threshold of $p < 0.05$ corrected was used.

RESULTS

Behavioral data: The mean proportion of false alarms (yes responses) during conditions 3 and 6 (20 distracters, 0 targets) was 5.71 and 3.75, respectively. The mean proportion of yes responses (hits) in conditions 4 and 7 (0 distracters, 20 targets) were 90.63 and 90.00 respectively.

Imaging data: In the first contrast of novel and familiar items, changes in rCBF were found in left IT cortex, left MTL, and right dorsal occipital cortex (Fig. 2, top left). In the second contrast of familiar distracters with familiar targets, a change in rCBF was observed in left IT cortex (Fig. 2, top right). The conjunction analysis identified decreases common to contrasts 1 and 2. It was found that decreased activity in left IT cortex was common to both contrasts (Fig. 2, bottom left). In the fourth contrast, retrieval conditions involving a higher degree of selection/monitoring were associated with increased activation in left ventrolateral PFC (Fig. 2, bottom right).

DISCUSSION

Decreases in IT cortex during recognition memory have been found in neuroimaging studies, but the functional significance of these decreases has remained unclear. This is because in previous studies it has been difficult to dissociate responses related to novelty detection, recognition memory, and perceptual priming. In the present study we addressed the question whether decreases in IT cortex are specifically associated with recognition memory.

In our first analysis, recognition of novel and familiar stimuli were contrasted. Changes in rCBF were found in the left MTL, right extrastriate cortex, and left IT cortex. Relatively increased MTL activity during processing of novel compared to familiar stimuli has been found in several neuroimaging studies [7,8]. These responses have been attributed to processes involved in detecting novel items; they are not restricted to encoding tasks but appear in any encounter with novel stimuli. Support for MTL involvement in novelty detection also comes from ERP recordings in patients with hippocampal lesions [10]. Normally, about 300 ms after presentation of a novel item, a positive ERP signal can be detected from the subject's scalp. It has been suggested that this signal is reflecting processes associated with novelty processes in the brain [14]. However, in patients with hippocampal lesions, this novelty-related signal is not observed, indicating that MTL is involved in the process of novelty detection [10]. The specific site of activation in the present experiment was in parahippocampal gyrus rather than hippocampus proper. This is in good agreement with a suggested dissociation between hippocampal and parahippocampal responses [15,16]. This suggestion is based on findings that responses in parahippocampal gyrus decrease as a stimulus becomes familiar in much the same way as in the IT cortex, whereas hippocampal responses increase as a function of increasing familiarity [16].

Extrastriate cortical regions have in previous neuroimaging studies showed decreased activity during presentation of familiar *vs* novel items [17,18], a decrease that has been attributed to perceptual priming. Our observation of decreased activity in right extrastriate cortex during recognition of familiar relative to novel pictures is consistent with this account.

Our observation of a decreased response in IT cortex when novel and familiar stimuli were contrasted closely overlaps with a previous finding of decreased activity during a DMS task [3]. This decrease may also correspond to the mnemonic suppression of the activity of single neurons in IT cortex following stimulus repetition that has been found in studies of non-human primates [1,2]. Related suppression effects were also found in an recent fMRI study using the DMS task [19]. These findings show that stimulus selective IT neurons decrease their activity in many different tasks. Hence, our finding of decreased IT-cortex activity during recognition of familiar items does not provide strong evidence that this response is related to explicit (episodic) remembering. However, the results of the second analysis provided more conclusive evidence.

In the second analysis, a decrease in IT cortex was found in the contrast of familiar distracters and familiar targets. This result is noteworthy since all pictures in this contrast had been presented previously and subjects had to selectively respond to those pictures that they remembered

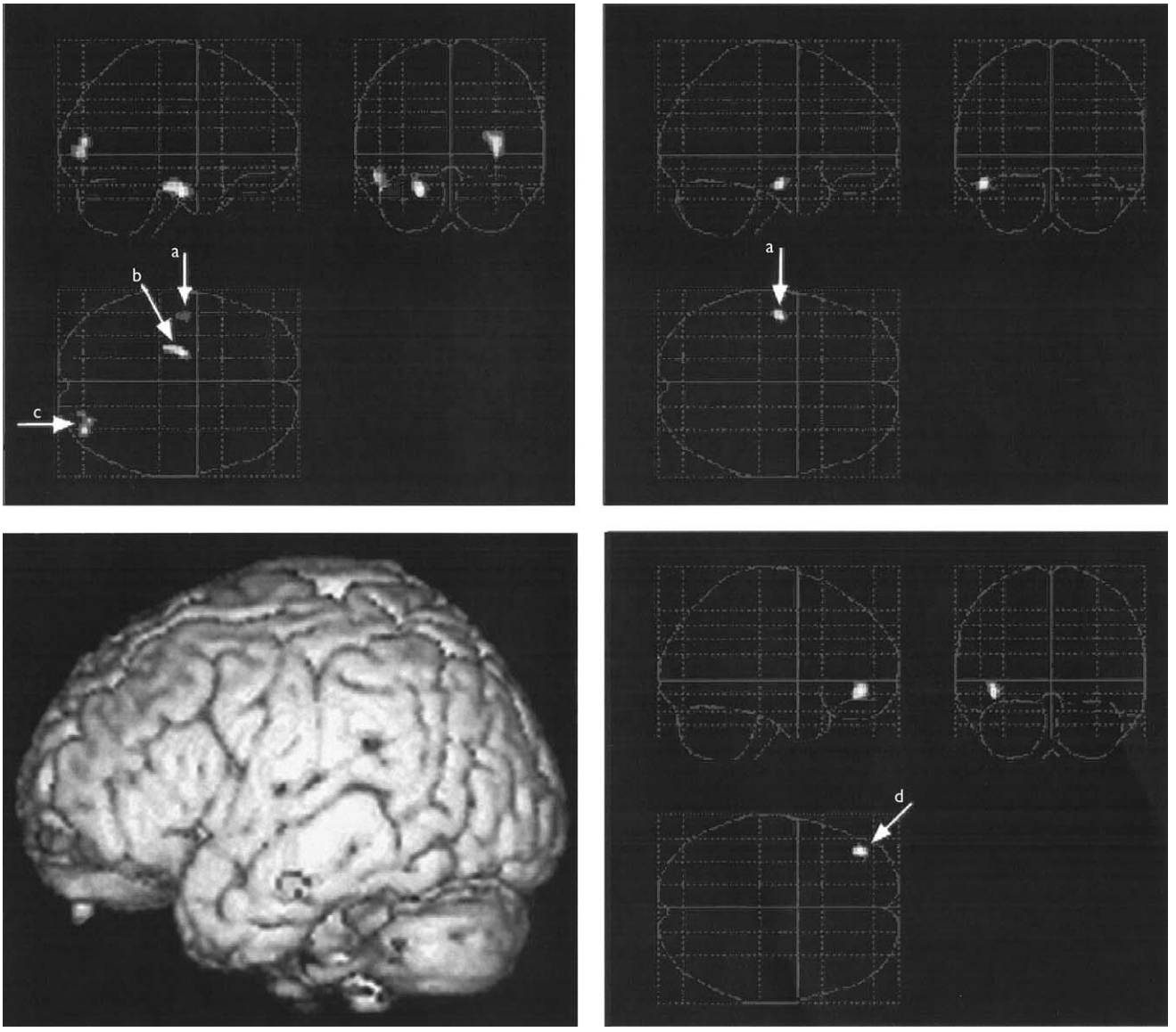

Fig. 2. Top left: Brain regions showing decreased activity during recognition of targets compared to distracters. (**a**) left IT cortex (Brodmann area 20; x, y, z, = −48, −14, −22; Z = 2.61), (**b**) left MTL (Brodmann area 36; −22, −12, −26; Z = 3.63), (**c**) right extrastriate cortex (Brodmann area 19; 34, −80,10; Z = 3.17). The image was thresholded at $p < 0.01$ (uncorrected). Top right: Decreased activity in IT cortex (**a**) during recognition of targets compared to familiar distracters in the second contrast (Brodmann area 20; x, y, z, = −48, −12, −20; Z = 3.65). The image was thresholded at $p < 0.01$ (uncorrected). Bottom left: decreased activity in IT cortex (Brodmann area 20, −48, −14, −22; Z = 4.09) related to recognition memory (from the conjunction analysis). The response is rendered on a brain volume that has been transformed into standardized space. The image was thresholded at $p < 0.0005$ (uncorrrected). Bottom right: increased activity in left ventrolateral prefrontal cortex (Brodmann area 10/47; −42, 46, −6; Z = 5.38). The image was thresholded at $p < 0.005$ (corrected).

from the second study list. As a result, observations of altered regional activity could not be related to novelty detection or perceptual priming, and no changes in activity in the MTL and extrastriate cortex were observed in the second analysis. The fact that reductions in IT cortex still were found argues against an interpretation of this response in terms of automatic processes related to stimulus repetition. Instead, our results suggest that reduced IT cortex activity is not only related to familiarity-based recognition but also to higher-order recollective memory judgements. By this view, IT responses may be modulated by top-down processes.

With regard to top-down mediation of IT neurons, enhanced activation in prefrontal areas has been associated with detection of behaviorally relevant target stimuli [2]. Several studies have also explicitly examined interactions between IT cortex and prefrontal cortex [20,21]. These studies suggest that PFC is related to the mnemonic functions of IT cortex. In one study [21] monkeys were trained to associate a cue with a choice stimulus. During the test phase, activation in IT cortex was recorded while the animal responded to cue stimuli by releasing a lever when correct choice stimuli were presented. By severing connecting fibers between IT cortices in each hemisphere, each IT

cortex only received bottom-up input from the contralateral visual field. Despite this, it was observed that IT neurons that did not receive visual input were activated during stimulus presentation. This activation reflected top-down control from PFC; when PFC connections were lesioned to eliminate feedback, activity in IT-cortex was reduced and task performance was disrupted. Furthermore, results from functional neuroimaging associate increased activation in frontal areas with memory tasks that require a high degree of strategic processes (for a review see [22]), and enhanced responses were found in prefrontal, but not inferotemporal, regions during a working memory task in which subjects responded to specific target items [19].

Thus, there is much evidence that frontally mediated top-down processes are recruited when there is high demand on stimulus specificity, such as recognizing a target from a specific study list among other equally familiar distracters. This was tested in the comparison of the last two recognition tasks, when the subjects decided if the items had been part of the second encoding list, with the first two recognition tasks, when familiarity-based responding was sufficient. This contrast revealed increased activity in left ventrolateral frontal cortex. Interestingly, in a previous neuroimaging study, left VLFC activity was associated with selecting a proper response according to specific task requirements [23]. Although no formal test of PFC–IT interaction was made, our observation of increased activation in left VLFC when there is a demand for high specificity in responses point to VLFC as a candidate region involved in modulation of activity in IT cortex.

Given that reduced activity in IT cortex is related to deciding whether items are familiar in a given context, a crucial question is what such reductions signify. It has been suggested that reduced IT activity reflects a tuned representation [24]. Our observation of reduced activity in the comparison of familiar distracters with familiar targets is not compatible with this suggestion. In this contrast, all items should be of equal familiarity and all should have a representation, which is supported by the behavioral data. An alternative possibility is that specific representations are activated depending on the task demands, and when a test stimulus is presented that matches an activated representation an activity decrease in specific brain regions follows. In a DMS task, the target stimulus is likely actively maintained during the presentation of intervening items, and the same should be true for tests of working memory [19]. In tests of episodic memory, the process of directing one's attention towards a previous study event may involve activation of representations from that event, and when a target subsequently is presented during the test the interaction between the activated mental representation and the target could lead to a reduction of activity. Although speculative, such interactions between activated representations and test stimuli could account for the data from a range of tasks.

Taken together, the present analyses associate reduced activity in IT cortex with explicit (episodic) remembering and we have suggested that IT-cortex activity is top-down modulated according to current task demands. Indeed, in most experiments on humans where reduced IT-cortex activity has been observed, the stimuli had varying degrees of pre-experimental familiarity (e.g. words) [25]. Still, subjects can recognize items as familiar in the experimental context with accompanying reductions in IT-cortex activity. This process, too, implies a certain level of top-down modulation since pre-experimental variations in stimulus familiarity should be disregarded.

CONCLUSION

This study aimed at investigating decreases in inferotemporal (IT) cortex associated with episodic recognition memory of pictures. Decreased activity in IT cortex was observed when subjects could base their responses on stimulus familiarity. Decreased activity in IT cortex was also found when subjects recognized familiar target items among equally familiar distracter items. We therefore conclude that matching effects in IT cortex during long-term explicit/episodic memory is based on an interaction between stimulus repetition and higher-order cognitive processes.

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