PERGAMON

Neuropsychologia 40 (2002) 2420–2437

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

# Evidence for asymmetric frontal-lobe involvement in episodic memory from functional magnetic resonance imaging and patients with unilateral frontal-lobe excisions

Andy C.H. Lee [a,b,*], Trevor W. Robbins [b], Stephen Smith [c], Gemma A. Calvert [c], Irene Tracey [c], Paul Matthews [c], Adrian M. Owen [a]

[a] *MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK*
[b] *Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK*
[c] *Functional Magnetic Resonance Imaging of the Brain Centre (FMRIB), John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, UK*

Received 3 September 2001; received in revised form 17 May 2002; accepted 22 May 2002

**Abstract**

Recently, there has been considerable debate regarding the involvement of the left and right prefrontal cortices in the encoding and retrieval of episodic memory. In a previous PET study, we found that the use of easily verbalisable material may lead to activation predominantly in the left lateral frontal cortex whilst the use of non-easily verbalisable material may lead to activation predominantly in the right lateral frontal cortex, in both cases irrespective of encoding and retrieval processes. In order to replicate and extend these findings, the same task was modified for use with *f*MRI. Six healthy volunteers were scanned while encoding and then recalling stimuli that either emphasised visual or verbal processes. It was found that, in comparison to a baseline condition, the encoding of visual stimuli led to a bilateral activation of the prefrontal cortex whilst the encoding of verbal stimuli led to a preferential activation of the left prefrontal cortex. An effect of stimulus type was less evident during retrieval, with both visual and verbal stimuli leading to bilateral prefrontal cortex activation. Overall, encoding and retrieval activated similar regions of the prefrontal cortex suggesting that these areas mediate processes that are fundamental to both aspects of memory. To extend these findings further, the tasks used in the *f*MRI study were used to assess a group of patients with unilateral frontal lesions and a group of healthy control volunteers. The patients were significantly impaired compared to the healthy volunteers, although no significant differences were found in performance between the right- and left-sided lesioned patients. This result suggests that the memory-related asymmetries observed during functional neuroimaging studies may not be critical for task performance.


*Keywords:* Neuroimaging; Encoding; Retrieval; Lateralisation; Prefrontal cortex

## 1. Introduction

A common distinction made in the cognitive neuropsychology of memory is that between semantic memory, which refers to people's general knowledge of the world and episodic memory, which refers to the conscious recollection of personal experiences [58,59]. Although autobiographical memories (personally experienced episodes from one's past life) are most clearly synonymous with Tulving's original conception of episodic memory, most studies have used recall and recognition of recently studied material or 'new learning' as a vehicle for investigating episodic memory.

One model of episodic memory that has risen out of the human functional neuroimaging literature suggests that the left prefrontal cortex is predominantly involved in episodic memory encoding whilst the right prefrontal cortex is predominantly involved in episodic memory retrieval, irrespective of the type of information (e.g. verbal versus non-verbal) involved [20,38,50,60,61]. More recently, however, evidence has emerged to suggest that the left–right encoding–retrieval asymmetry model may not be an adequate framework for understanding the role of the human prefrontal cortex in episodic memory. In fact, given the known dominance of left hemisphere regions in language processes [28,31] a number of investigators have suggested that it is the involvement of verbally mediated mnemonic strategies, rather than encoding–retrieval processes, which determines the relative involvement of the left and right prefrontal cortices during episodic memory processes ([21,23,25,39,62]; for review, see [24]). For example, Owen et al. [42] suggested that subjects may preferentially use verbal strategies while encoding

* Corresponding author. Tel.: +44-1223-355294.
*E-mail address:* andy.lee@mrc-cbu.cam.ac.uk (A.C.H. Lee).

0028-3932/02/$ – see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0028-3932(02)00081-7

episodic information (whether that information is ostensibly verbal or not) and these strategies may be less critical for efficient retrieval. Thus, memorisation of *visual* information is frequently accompanied by subvocal verbal repetition of the to-be-remembered material. In contrast, if subjects are required to choose between two stimuli, one of which they have seen previously, verbalisation is not necessarily required for visual recognition to occur. Similarly, in studies where verbal material is employed, encoding often requires the subjects to repeat and/or learn a series of words, thereby emphasizing subvocal or vocal articulation and rehearsal. In contrast, retrieval of those same words, particularly when tested through free recall may be mediated by a combination of verbal, semantic and visual retrieval strategies.

In a previous study, we used Positron Emission Tomography (PET) to scan healthy volunteers while they encoded and then recalled stimuli that either emphasised visual or verbal processes (for full details, see [23]). Verbal stimuli led to activation predominantly in the left prefrontal cortex while visual stimuli led to activation predominantly in the right prefrontal cortex, in both cases, irrespective of encoding or retrieval processes. Whilst these results cast some doubt over the left–right encoding–retrieval asymmetry model of episodic memory, a number of methodological factors precluded more definite conclusions being drawn. First, a restriction on the number of PET scans allowed (imposed by radiation guidelines) precluded the use of a 'low-level' baseline condition in that study. Consequently, encoding conditions were always compared directly to retrieval conditions, and thus activation common to both of these processes would have been 'subtracted out' during the statistical analysis. Second, the use of a 90 s PET acquisition period required that each trial had to be repeated three times during the retrieval tasks. One consequence of this was that subjects' choices became increasingly automated during the course of each scan, irrespective of their accuracy. A reduction in activation observed during the retrieval tasks was one possible consequence of this (for further discussion, see [23]).

To extend the findings from the earlier PET study and to address these concerns, the same encoding and retrieval tasks were adapted for use with 3 T functional magnetic resonance imaging (*f*MRI), which also provides greater spatial and temporal resolution than PET. Two control conditions were designed to serve as baseline comparisons for the encoding and retrieval tasks. Given the results of the PET study, it was predicted that similar regions of the lateral frontal cortex would be involved in the encoding and retrieval tasks. In addition, it was hypothesised that the verbal tasks would lead to greater activation of the left prefrontal cortex whilst the visual tasks would lead to greater activation of the right prefrontal cortex, in both cases, irrespective of encoding or retrieval.

Although functional neuroimaging can identify which cortical and subcortical regions are involved in a particular process, it cannot reveal how *critical* any specific region is to that process. In a parallel study, therefore, the same tasks were adapted for testing patients with unilateral damage to the frontal cortex and comparisons were made with healthy control subjects. Given the predictions of the left–right encoding–retrieval asymmetry model, one might reasonably expect to observe a dissociation of encoding and retrieval deficits in patients with left or right unilateral prefrontal cortical excisions, respectively. This, however, does not appear to have been the case to date; past studies have suggested that unilateral prefrontal patients are not disproportionately impaired at either memory encoding or retrieval [27,51,52,55]. There is, however, some evidence to suggest that left- and right-sided frontal-lobe patients are differentially impaired at verbal and non-verbal memory tasks (e.g. [44]). On this basis and given the results of the previous PET study, it was predicted that left and right frontal patients would be disproportionately impaired at the verbal and non-verbal episodic memory tasks, respectively.

## 2. Study 1—*f*MRI study

### 2.1. Methods

#### 2.1.1. Subjects

Six right-handed healthy subjects (three male, three female) were scanned. The age of the subjects varied between 23 and 50 years (mean age = 37 years). The study received ethical approval from the Central Oxford Research Ethics Committee.

#### 2.1.2. Image acquisition and data analysis

Scanning was carried out at the Functional Magnetic Resonance Imaging of the Brain Centre (FMRIB), Oxford, UK on a 3 T MRI system driven by a Varian Unity Inova console and equipped with an Oxford Magnet Technology magnet, a Siemens body gradient coil and a bird-cage radio-frequency head coil. Two four-dimensional datasets were acquired for each subject, one for the visual tasks and one for the verbal tasks. Each dataset consisted of three experimental blocks of 160 s (480 s in total) and the onset of each experimental block was triggered using the FMRIB Stimulus Presentation Software version 1.2 (FSPS, FMRIB, Oxford, UK). Stimuli were presented via a projector on a white screen located at the foot end of the scanner bed, and the subjects could view this screen by wearing a pair of prism spectacles during scanning. Subjects' responses were made using two specified buttons ('left' and 'right') on a four-button response box held in the right hand and were recorded via FSPS. For functional data, an echo planar imaging (EPI) pulse sequence was implemented to acquire T2*-weighted image volumes with blood oxygen level dependent (BOLD) contrast. Each volume consisted of 17 mm × 7 mm slices with a TR of 2.5 s (TE = 28 ms). A T1 structural scan (32 mm × 7 mm slices) was also acquired for each subject. Foam padding was utilised to immobilise subjects within the MRI head coil.