Asymmetric frontal activation during episodic memory: what kind of specificity?

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Over the last decade functional brain imaging techniques, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), have become an important addition to the traditional lesion method in the long-standing effort to identify neural substrates of various cognitive functions. A major advantage of these techniques is that they allow study of the intact neural network subserving a specific process, thereby avoiding possible confounds associated with the study of damaged brains; for example, neural reorganization. In addition, it can be difficult, if not impossible, to make inferences based on lesion studies about the effect of the lesion on specific component processes. One example of this problem comes from the study of episodic memory[1]. Patients with medial temporal lobe lesions are known to be severely impaired on episodic memory tests, but it is not clear whether such a lesion is affecting the ability to properly encode and store new episodes or whether it is primarily compromising retrieval operations[2]. Functional neuroimaging can address this problem by allowing the separate study of encoding and retrieval processes.

In an early review of relevant PET studies, Tulving and colleagues noted that prefrontal brain regions were consistently involved in episodic memory[3]. Strikingly, activation patterns associated with encoding processes generally included left but not right prefrontal regions, whereas retrieval-related activations tended predominantly to involve right prefrontal regions. These results suggested that different neural systems mediate encoding and retrieval processes, and they formed the basis for the 'hemispheric encoding/retrieval asymmetry' (HERA) model. According to this model, left prefrontal cortex is differentially more involved in retrieval of information from semantic memory, and in simultaneously encoding novel aspects of the retrieved information into episodic memory, than is the right prefrontal cortex. The right prefrontal cortex is differentially more involved in episodic memory retrieval than is the left prefrontal cortex.

In a subsequent review[4], additional studies were considered. These included encoding tasks involving intentional learning – the studies covered in the initial review by Tulving *et al.*[3] involved incidental learning – and the left frontal asymmetric activation pattern was found to hold true for these intentional encoding tasks. Moreover, all the encoding studies in the initial review used verbal materials, and an important extension of the follow-up review was the inclusion of a study using non-verbal stimuli (faces). This study, in common with most of the other studies, was associated with left frontal activation, and it was concluded that 'because these studies, with a single exception (…), used verbal materials, it is not entirely clear whether the pattern would hold for other kinds of materials, but the fact that Grady and Haxby, and their colleagues, obtained left-frontal encoding activation with faces suggests that the pattern may turn out to be more general' (Ref. 4, p. 140). This interpretation has now been challenged by recent MRI findings reported by Kelley *et al.*[5]

In two experiments, Kelley *et al.* used functional MRI to study episodic memory encoding. In Experiment 1, the brain-activation pattern associated with encoding of (i) visual words, (ii) nameable line-drawn objects, and (iii) unfamiliar faces was compared with that associated with fixating a crosshair. Several interesting findings were observed but here we will focus on the findings that are of relevance to the HERA model. In keeping with HERA, word encoding in Experiment 1 involved activation in the left dorsal frontal cortex (near Brodmann area 6 or 44) and object encoding involved activation in a similar left frontal region. Additionally, object encoding was associated with increased activation in a posterior right frontal region, whereas face encoding involved activation of the right posterior frontal region only. In Experiment 2, identical encoding conditions were included, and the results from Experiment 1 were replicated. Subjects were also scanned during passive viewing of words, objects, and faces. These conditions produced a similar frontal activation pattern to the intentional conditions, but at a lower, statistically non-significant, level. Based on their findings, Kelley *et al.* suggested that multiple regions in frontal cortex allow encoding of different kinds of information and they argued that the involvement of right-sided areas, particularly during face encoding, is inconsistent with the HERA model.

These are significant findings, which advance our understanding of the neural network(s) subserving episodic memory encoding. What remains unclear, however, is whether the Kelley *et al.* findings really are invalidating the HERA model. For one thing, Kelley *et al.* did not scan subjects during retrieval, so nothing can be said about the relative contributions of left and right prefrontal cortex during encoding compared with retrieval. Secondly, it must be emphasized that the empirical regularity that defines HERA is based on a meta-analysis of data from different experiments and from different laboratories. HERA is an overall probabilistic *pattern*, not the outcome of a single experiment. In such patterns 'exceptions' to the general tendencies frequently occur, in that the outcome of a single study might not fit the pattern. In fact, at the time of the second review[4], several 'exceptions,' concerning both the encoding and the retrieval side of the model, were present and some tentative explanations were offered to account for these. Similarly, the Kelley *et al.* findings can be seen as yet another 'exception' to the general pattern, and because this study is one of few studies looking at encoding of non-verbal materials it is especially challenging to try to explain why this study, but not a previous one involving similar materials[6], found right- but not left-sided frontal activation.

It is quite possible, as alluded to by Kelley *et al.*, that one key factor is the type of encoding strategy. In the Kelley *et al.* study, the stimuli were presented at a fast rate, which presumably made it difficult for the subjects to make use of elaborate (verbally mediated)

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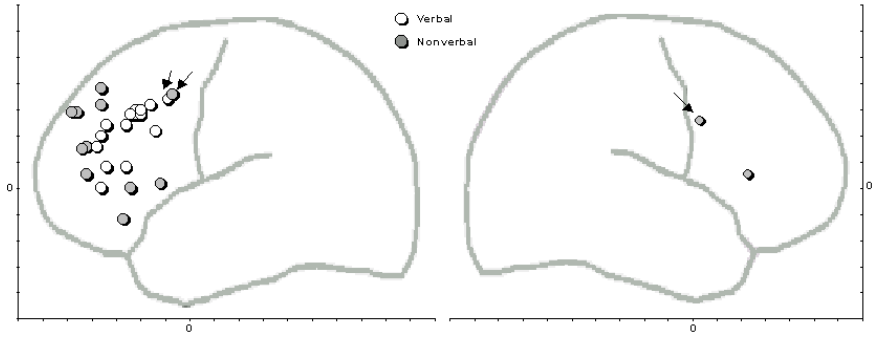

Fig. 1 Frontal cortical activation peaks from multiple neuroimaging studies of episodic memory encoding. Significant frontal activation peaks from studies involving intentional encoding of verbal[7,15–17] and non-verbal[6,14,18,19] information. The peaks from the first experiment by Kelley *et al.*[5] are indicated by arrows.

encoding strategies. If so, it is also possible that if the study were to be repeated, with an increased presentation time as the only difference, a left-sided activation might be observed for all types of materials. Importantly, though, it is quite likely that such left-sided activation would be located in a different region from that found to be associated with word- and object-encoding with the present design. It has been suggested that the dorsal posterior region observed by Kelley *et al.* is reflecting rote rehearsal/working memory processes, whereas a more anterior, inferior region reflects semantic processing[7].

In the context of specific localization of activations, it can further be noted that (bilateral) activation of the posterior frontal region has previously been associated with retrieval of complex pictures[8]. This study compared a recognition-memory condition involving mostly old (studied) items with a recognition condition involving mostly new (non-studied) items. In both conditions subjects were informed that the majority of items would be (either) old or new, and their task was to keep track of the minority items. In keeping with Kelley *et al.*, the result can be interpreted as showing that looking out for new items, and keeping track of them, leads to increased activity in posterior frontal cortex. More studies are needed to resolve whether the common activation of this region reflects a shared processing component. The important point here is that most encoding-related activations have been located anterior to the activations reported by Kelley *et al.* (Fig. 1).

In the follow-up review of HERA we noted that there was 'considerable variability in more precise localization of memory functions within the frontal regions' and that 'future research will reveal a much richer and more complex picture than HERA in its present form suggests' (Ref. 4, p. 145). Subsequent work has already begun, aimed at the elucidation of the specific contributions of distinct frontal regions to retrieval operations[9–12]. Similarly, as noted above, studies of encoding processes have pointed to dissociations between the involvement of left frontal regions[7], and recently different left frontal regions have been associated with semantic processing and intentional learning respectively[13]. The study by Kelley *et al.* adds important information to these previous studies by pointing to the relevance of materials and strategies in the hemispheric specificity of encoding-related processing. More investigations are needed to determine whether elaborate encoding of nonverbal information will consistently activate left prefrontal cortex as has repeatedly been demonstrated for verbal materials (Fig. 1), and, if found, what such activations signify[14].

To sum up: (1) Are the Kelley *et al.* findings important? Yes. They are very clear, and clearly important; (2) Do they invalidate HERA? No. It is logically impossible for the finding of a single experiment to invalidate a large pattern consisting of many findings; (3) Is the right-frontal activation to faces an 'exception' to HERA? Yes. It is definitely an exception to the pattern; (4) Did the exception come about because of the specific materials used, namely unfamiliar faces? It is possible that it did, but also possible that it was the combination of the materials and the particular encoding conditions that produced the results; (5) Are these results worth further study? Most definitely, including an extension of the design to retrieval conditions, in order to produce a more complete procedural fit with the paradigm that spawned HERA.

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