What does neuroimaging tell us about the role of prefrontal cortex in memory retrieval?

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The past five years have seen an outpouring of neuroimaging studies of memory — using both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These studies have convincingly demonstrated that neuroimaging can be used to study the functional anatomy of normal human memory and that neuroimaging can precisely localize memory related brain activations within small areas of cortex. To illustrate the application of neuroimaging in the study of memory, this review shows how several laboratories have produced data that converge on the notion that specific areas in the prefrontal cortex are active during long-term memory retrieval. Moreover, the data further suggest that distinct prefrontal brain areas might make differential contributions to different kinds of long-term memory retrieval.

Key words: neuroimaging / PET / fMRI / memory / prefrontal cortex / semantic memory / episodic memory / declarative memory

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Although the prefrontal cortex has long been accepted as an important brain region involved in short-term (working) memory,1,2 a flurry of recent neuroimaging studies (both PET and fMRI) have generated excitement about the possibility that the prefrontal cortex participates in a variety of memory processes — including long-term memory. The idea that areas in the frontal cortex contribute to human long-term memory performance has been suggested previously, based on neuropsychological studies.3,4 Neuroimaging studies, reporting prefrontal cortex activation during various long-term memory tasks, have focused interest on this possibility.5-11 In the following discussion, we will describe some of these findings and their implications. Since the most novel aspect of these studies has been the demonstration that specific prefrontal cortex regions participate in certain kinds of long-term memory retrieval, the discussion will focus on this area of memory research. For reviews of neuroimaging work on memory storage and working memory see refs 12 and 13.

The discussion is divided into two parts. The first section deals with conceptual considerations and how these relate to neuroimaging data. The remaining sections deal with recent neuroimaging findings and how these inform us about the role of the prefrontal cortex in memory retrieval.

Conceptual considerations

Important to a discussion of prefrontal contributions to memory functions are two ideas that have become well accepted in recent years, one in relation to the organization of the prefrontal cortex, and the other in relation to cognitive memory function.

With regard to prefrontal organization, it has become clear that multiple subregions exist within the larger area we label the prefrontal cortex. This has been demonstrated in the rhesus monkey by showing that localized prefrontal areas have distinct cytoarchitectonic structure, labeling patterns, physiological properties, and receive projections from other areas of cortex in a specific fashion.1,14-16 The multiple areas within monkey prefrontal cortex are likely to have distinct processing roles — a property that almost certainly extends to humans.

Already, human prefrontal cortex has been tentatively subdivided based on anatomy,17 and lesions to different regions of the prefrontal cortex are associated with distinct behavioral outcomes.1 Thus, it is essential that the human prefrontal cortex be treated as a region containing multiple areas. Our challenge, then, is to use neuroimaging to aid in identifying these individual areas, in determining their processing roles, and in understanding how their individual roles might collectively contribute to memory task performance.

Before attempting to use neuroimaging data in this manner, it is important to demonstrate the limits of...
neuroimaging to localize and resolve memory-related brain activations within subregions of the prefrontal cortex. Localization refers to the accuracy with which an activation can be placed in a specified space; resolution refers to the distance by which two regions of activation must be separated before they can be identified as separate responses.

Although many theoretical models and imaging data suggest the localization limits of neuroimaging data, we feel it is also important to demonstrate the empirical boundaries derived from data relevant to that presented in this review. For this demonstration, we turn to an instance in which nearly the same memory conditions were studied across three independent experiments.5 This study allowed us to observe independent subject-groups manifesting the same physiologic activation (Figure 1A). As can be seen, the localization of the responses across groups was remarkably consistent suggesting that current neuroimaging methods yield data that can be reliably localized to within 10 mm range across experiments.

Since it is equally essential to establish that neuroimaging can detect activations originating from

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**Figure 1.** Schematic diagrams show between subject-group and between task data in order to illustrate the ability of PET neuroimaging to reliably localize and resolve prefrontal brain activations. (A) Two activations, one in the left hemisphere (squares) and one in the right hemisphere (circles), are shown across three independent subject groups. Each symbol represents data from a single subject group. Across groups, the activations are reliably localized to small regions of prefrontal cortex. (B) Two functionally distinct areas of left prefrontal activation are shown that were reliably dissociated across tasks using PET. This level of resolution probably represents an upper boundary of the ability of functional neuroimaging to resolve activations originating from distinct prefrontal areas.
Table 1. Different kinds of memory retrieval discussed in this review

<table>
<thead>
<tr>
<th>Memory type</th>
<th>Other name</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic</td>
<td>Fact memory</td>
<td>Retrieval of foods that fit the category vegetable. Retrieval of the capital of France. Retrieval of words that begin with ‘L’.</td>
</tr>
<tr>
<td>Episodic</td>
<td>Event memory</td>
<td>Recollection of what article you read yesterday. Recollection of the vegetable you ate for dinner. Recollection of words presented on a study list.</td>
</tr>
</tbody>
</table>

Both semantic and episodic memories are types of conscious (or declarative) memories. They differ with regard to the type of information being retrieved. Retrieval of semantic memory involves accessing facts or pieces of information independently of where or when the information was learned. Episodic retrieval involves recollecting information that was learned and is associated with a specific point in time and context. Some researchers believe the two forms of memory are quite distinct while others believe they form a continuum with episodic memories relying on richer contextual information.

Distinct areas within the prefrontal cortex, evidence about the capability of neuroimaging to resolve separate activations within the frontal cortex is also important. The first evidence that neuroimaging can resolve multiple prefrontal areas comes from the observation that different experiments have reported activations that span nearly the entire volume of the prefrontal cortex — a region that is known to contain multiple areas. However, the variability across experiments represents an unknown combination of methodological and between-group factors that might cause variability unrelated to the participation of distinct anatomical areas.

To determine a more appropriate (and conservative) estimate of the ability of neuroimaging to distinguish among multiple prefrontal areas, it is necessary to systematically observe dissociations across prefrontal areas. This has been done in several instances and suggests a current upper limit to the resolution of neuroimaging at about 16 mm (Figure 1B). In humans this corresponds to the difference between the approximate locations of Brodmann's area 10 versus area 45, or between areas 44 and 47. Thus, there is every reason to believe that neuroimaging is capable of detecting distinct functional roles for multiple areas within the prefrontal cortex.

The second concept, related to cognitive aspects of memory function, is that multiple forms of memory exist. A complete description of current classification schemes, which are continuously being modified as more memory phenomena are elucidated, is well beyond the scope of this review (see ref 22). Nonetheless, a few brief examples are worth illustrating.

At the behavioral level, multiple forms of memory have been demonstrated by showing that acquisition and retention during different learning paradigms have distinct characteristics. For example, a distinction has been made between skill learning and conscious (or explicit) forms of memory. Learning to skillfully ride a bike takes months of practice and does not continuously require conscious retrieval of how to balance and move. On the other hand, learning to recognize a new face can take place in a single introduction and recognition of the face often brings to mind many aspects of the meeting such as the person's name.

A second distinction, which is important to this review (see Table 1), is between the recollection of general information (semantic or fact memory) and information associated with a specific event (episodic or event memory). Both semantic and episodic memories are considered examples of conscious memory because subjects are aware of the information being retrieved. Reciting a list of words beginning with the letter ‘L’ is an example of semantic memory because learned information is being retrieved but the context in which that information was learned is not accessed. Recollecting what you had for breakfast yesterday morning is an example of episodic memory because the specific source and the context associated with the learned information is required.

Importantly, several of these distinctions at the behavioral level have gained support at the biological level. Patients with amnesia can show selective impairment in conscious memory (both semantic and episodic) in comparison with preserved skill learning. These findings make clear that it is necessary to consider that different kinds of memory might be mediated by distinct brain pathways. In this regard, functional neuroimaging data from memory studies should be considered in terms of the kind of memory being addressed as well as the specific processes (e.g. encoding, storage, retrieval) involved. As will be seen, these behavioral distinctions have predicted some of the biological distinctions obtained from the neuroimaging data.
Recent neuroimaging findings

Numerous studies have observed prefrontal cortex activations during long-term memory tasks. Those studying semantic memory retrieval and episodic memory retrieval have been particularly reliable in producing robust prefrontal activations (semantic memory retrieval, refs 5,8,24-29; episodic memory retrieval, refs 5,9-11,30-34). These studies demonstrate convincingly that areas within the prefrontal cortex are active during tasks requiring retrieval from long-term memory. The current focus of the field has moved toward trying to understand which prefrontal brain areas are activated selectively during the different kinds of memory and what the processing roles of these areas might be.

As an initial step in this process, composite activations from a number of long-term memory tasks examining semantic and episodic memory retrieval are presented. The studies have also activated many areas outside of the prefrontal cortex indicating that multiple distributed areas are used to accomplish these tasks. However, for the purpose of this discussion, we focus only on the prefrontal activations (Figures 2 and 3). In addition, many other kinds of long-term memory retrieval have also been profitably studied using neuroimaging, sometimes revealing prefrontal activations (e.g. procedural memory, classical conditioning). Each of these kinds of memory could be discussed at length and are not included simply because of space limitations.

ACTIVATIONS DURING SEMANTIC MEMORY RETRIEVAL

Figure 2. Activations are shown for a number of neuroimaging studies that have examined subjects performing verbal semantic memory retrieval tasks. The activations are plotted on a horizontal brain section representing $Z = 12$ with all prefrontal activations falling $10\ mm$ above or below the $Z = 12$ plane included. The lateral view of the brain shows the approximate position of the horizontal section. The tasks include overtly retrieving verbs (circles 1 and 8);$^{25,27}$ silently retrieving words beginning with ‘F’ or ‘S’ (circle 2);$^{24}$ silently retrieving verbs (circle 3);$^{29}$ retrieval of whether words represent living objects (circle 4);$^{7}$ and overtly retrieving words from three-letter word beginnings (circles 5,6 and 7).$^{5}$ A region of common activation is reliably observed in the left-inferior prefrontal cortex.
Left-inferior prefrontal involvement in semantic memory retrieval

A number of studies involving the semantic retrieval of words, or information about words, have activated a cluster of areas within a region of the left-inferior prefrontal cortex (Figure 2). It seems reasonable to speculate that areas within this region might be used to access and maintain a representation of words during their retrieval — a demand common to all of the tasks. This idea is consistent with notions that have evolved from the study of speech production tasks. These studies have suggested that left prefrontal areas are used during more elaborate forms of production when words must be generated in a non-automatic or internally guided fashion. Perhaps all of these areas express a similar concept: left-inferior prefrontal cortex contributes to the access and/or representation of verbal information. The participation of the left inferior prefrontal cortex can occur within the context of word retrieval or with the goal of saying the word aloud.

Importantly, the role of this region seems to be at a higher level than simply controlling speech output as simple speech tasks have shown little or no activation here. The exact nature of the information operated on by this region is still unresolved but there is some suggestion that the information can be coded phonologically. Future experiments may find that there are multiple areas within this left-inferior prefrontal region which contain further functional subdivisions. Perhaps these areas will be found to represent different aspects of verbal information, or maybe even extend beyond verbal information.

ACTIVATIONS DURING EPISODIC MEMORY RETRIEVAL

Figure 3. Activations are shown for a number of neuroimaging studies that have examined subjects performing episodic memory retrieval tasks. The activations are plotted in the same way as Figure 2. The tasks include recall of words using three-letter word beginnings as cues (circles 1, 2, 3 and 10), recognition of faces by young subjects (circle 4), recognition of faces by old subjects (circle 5), recognition of auditory sentences (circle 6), paired-associate recall of pictures (circle 7), paired-associate recall of auditory words (circle 8), and yes/no recognition of words (circle 9). A region of common activation is reliably observed in right-anterior prefrontal cortex. This area(s) is often activated in addition to other prefrontal areas which are less consistent across tasks and might be related to the specific type of information being retrieved.
Table 2. Studies demonstrating activation of the left-inferior prefrontal cortex during tasks involving verbal semantic memory retrieval

<table>
<thead>
<tr>
<th>Circle number</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Target task</th>
<th>Reference task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-37</td>
<td>23</td>
<td>21</td>
<td>Verb generation</td>
<td>Noun repetition</td>
</tr>
<tr>
<td></td>
<td>-34</td>
<td>23</td>
<td>9</td>
<td>Generate words beginning with ‘F’</td>
<td>Word repetition</td>
</tr>
<tr>
<td>2</td>
<td>-43</td>
<td>29</td>
<td>20</td>
<td>Think of verbs</td>
<td>Rest</td>
</tr>
<tr>
<td>3</td>
<td>-38</td>
<td>28</td>
<td>16</td>
<td>Semantic decision</td>
<td>Orthographic decision</td>
</tr>
<tr>
<td>4</td>
<td>-37</td>
<td>20</td>
<td>9</td>
<td>Stem completion</td>
<td>Fixation</td>
</tr>
<tr>
<td>5</td>
<td>-40</td>
<td>18</td>
<td>15</td>
<td>Stem completion</td>
<td>Fixation</td>
</tr>
<tr>
<td>6</td>
<td>-40</td>
<td>20</td>
<td>17</td>
<td>Stem completion</td>
<td>Fixation</td>
</tr>
<tr>
<td>7</td>
<td>-43</td>
<td>28</td>
<td>13</td>
<td>Verb generation</td>
<td>Noun repetition</td>
</tr>
</tbody>
</table>

Listed are Talairach and Tournoux (1988) locations for each of the left-inferior prefrontal activations that are plotted in Figure 2. The studies are listed in relation to the number of the plotted circle in Figure 2. The target verbal semantic retrieval task that was studied and the reference (control) task used are listed in the right-most columns.

Already there is some evidence that areas in the more anterior region of the left prefrontal cortex, at or near Brodmann’s areas 46, 47 and/or 10, are activated during tasks requiring access to word meaning. This possibility is supported by studies which activate these anterior areas during tasks in which word meaning is accessed as a component of the information being retrieved. Gabrieli and colleagues have further shown that activation within a subset of these areas are sensitive to repeated retrieval of word meaning — which is often referred to as conceptual priming. Using fMRI, they found that left prefrontal areas active during retrieval of word meaning are less active the second time the same information is retrieved.

Given these findings, it might be the case that these anterior areas are recruited to maintain or control access to a second, higher-level of semantic information — which, in some instances, involves word meaning.

**Left-inferior prefrontal cortex is involved in other kinds of memory**

Given the tentative ideas about the role the left-inferior prefrontal cortex might be playing in semantic retrieval, it is not surprising that other kinds of memory tasks and memory processes activate this region. Some studies of verbal working memory have activated the left-inferior prefrontal cortex. Verbal working memory requires the maintenance and manipulation of words internally. This demand is inherent to the elaborate speech production and semantic retrieval tasks that have already been discussed.

Studies of tasks known to encourage storage of verbal material into episodic memory have also activated this area. This too is not surprising if one considers what the consequence of maintaining a word item might be. Representing words internally might be a partial source of memory traces leading to episodic long-term storage. That is, information represented within a pathway utilizing the left-inferior prefrontal cortex may be easily converted into a more enduring form. This idea is quite consistent with cognitive findings that have shown words generated by subjects (generation effect) or semantically elaborated on by subjects (levels of processing effect) are more likely to be remembered than those that are simply read aloud. In this regard, the process of retrieving word information from semantic memory (which activates the left-inferior prefrontal cortex) might simultaneously be storing knowledge of that retrieval event (or aiding in the storing of that knowledge) into episodic long-term memory. An interesting future question currently left unanswered is how these areas might interact with other brain areas thought to be important for memory storage, such as areas in the medial temporal lobe and other prefrontal areas.

**Episodic memory retrieval**

Almost all of the episodic retrieval tasks published to date have activated the right-anterior prefrontal cortex (Figure 3). This is in strong contrast to the more posterior left prefrontal activations that are discussed above in relation to semantic memory retrieval. Right prefrontal activation during episodic retrieval was initially observed in a series of studies using purely verbal materials but has been shown to generalize to the retrieval of faces, pictures, and another
Table 3. Studies demonstrating right-anterior prefrontal cortex activation during tasks involving episodic memory retrieval

<table>
<thead>
<tr>
<th>Circle number</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Target task</th>
<th>Reference task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>45</td>
<td>4</td>
<td>Stem-cued recall</td>
<td>Stem completion</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>50</td>
<td>9</td>
<td>Stem-cued recall</td>
<td>Stem completion</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>50</td>
<td>11</td>
<td>Stem-cued recall</td>
<td>Stem completion</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>54</td>
<td>4</td>
<td>Face recognition (Young subjects)</td>
<td>Face matching</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>52</td>
<td>8</td>
<td>Face recognition (Old subjects)</td>
<td>Face matching</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>44</td>
<td>12</td>
<td>Auditory recognition (all old sentences)</td>
<td>Auditory recognition (all new sentences)</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>47</td>
<td>16</td>
<td>Paired associate recall of pictures</td>
<td>Word repetition</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>47</td>
<td>18</td>
<td>Paired associate recall of words</td>
<td>Word repetition</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>44</td>
<td>10</td>
<td>Word recognition</td>
<td>Word reading</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>46</td>
<td>8</td>
<td>Stem-cued recall (Low recall version)</td>
<td>Stem completion</td>
</tr>
</tbody>
</table>

Listed are Talairach and Tournoux (1988) locations for each of the right-anterior prefrontal activations that are plotted in Figure 3. The studies are listed in relation to the number of the plotted circle in Figure 3. The target episodic retrieval task that was studied and the reference (control) task used are listed in the right-most columns. The consistency of the results is remarkable but it should be noted that at least two studies of episodic retrieval have not detected right-anterior prefrontal activation in the same area as the studies listed above, although both of these studies did detect right prefrontal activation in different areas.

Verbal task using auditory sentences. Various delay intervals between study and test have been used ranging from a few minutes to one-week, and the format of retrieval task has been yes/no recognition, forced choice recognition, perceptually cued recall, and paired associate recall. Old and young subjects and men and women (Buckner, unpublished observations) have independently demonstrated activation within this focal area during episodic retrieval.

The generality of this finding is remarkable and suggests that a process common to many episodic memory retrieval tasks is being facilitated by this right-anterior prefrontal region. The exact processing role this area plays in episodic retrieval is still unclear, but attempts to elucidate the role should pay careful attention to the localization of the activation. Current data suggest that the common activation is not across a distributed set of areas within the prefrontal cortex. Rather, all of these activations appear to be focused in a localized region in the anterior cortex.

The finding of right prefrontal activation across a wide range of episodic retrieval tasks, in the presence of the left prefrontal activations during episodic storage mentioned earlier, stimulated a model of hemispheric asymmetry in relation to prefrontal memory function. Tulving and colleagues suggested that the right prefrontal cortex is active more during episodic retrieval than is the left prefrontal cortex. This model helped greatly in drawing attention to the commonalities observed across the many laboratories studying these phenomena. However, the model is only minimally constrained in terms of prefrontal anatomy. As discussed above, prefrontal cortex is made up of multiple subregions. Given the reliability and resolution of our current neuroimaging techniques (Figure 1), we are already beyond classifying activation of prefrontal brain areas only in terms of which hemisphere they fall in. Moreover, posterior prefrontal areas, sometimes bilaterally, have been activated during episodic memory retrieval in addition to the right-anterior prefrontal area that has often been observed. This argues against a strict laterality hypothesis. Thus, although Tulving’s model was useful as an initial heuristic, recent data have suggested an even more specific set of hypotheses about which prefrontal areas are activated during episodic memory retrieval.

The observation of additional, and sometimes bilateral, prefrontal brain activations during episodic retrieval generates another set of interesting questions. The pattern of the posterior activations may be related to the kind of episodic information being retrieved. Purely verbal retrieval has activated posterior left frontal areas in addition to the right-anterior prefrontal area while face (pictorial) retrieval has exclusively activated right prefrontal areas while face (pictorial) retrieval has exclusively activated right prefrontal areas. Interestingly, a task requiring the paired associate recall of picture names (a task that demands both pictorial and verbal retrieval) has activated the posterior prefrontal cortex within the frontal operculum bilaterally. It will be interesting to see what emerges as more data are collected, but the notion that participation of certain prefrontal areas is dependent upon the kind of information being retrieved is consistent with, and predicted by, a great deal of non-human primate work.

An intriguing possibility is that the episodic memory tasks rely on multiple, distinct prefrontal areas to...
access the specific kind of information being retrieved. In addition to these areas, the common activation in right-anterior prefrontal cortex that has been reliably identified across laboratories may be more uniformly recruited to guide processes that generalize across episodic memory retrieval tasks.  

Whether this common area plays a role only in episodic memory retrieval remains an open question. Some have speculated that this area may be recruited to guide processes related to searching for information in memory and may be specific to episodic retrieval. Others have suggested its role is more general and involves relating information to a specific context — a prominent component of many episodic retrieval tasks but potentially relied on by other kinds of tasks as well. More data are needed to further resolve this issue, but it is noteworthy that in a period of a few years the field has already progressed from simply identifying prefrontal areas active during episodic retrieval to trying to determine their specific processing contributions.

Conclusions

Neuroimaging techniques have progressed to the point where they can reliably localize activations in the prefrontal cortex and can dissociate activations originating from functionally distinct areas. These technical accomplishments provide a foundation for using neuroimaging to aid in characterizing the prefrontal cortex’s role in memory function.

Progress has already been made in determining prefrontal areas that may play a role in long-term memory retrieval. An area in the left-inferior prefrontal cortex has been observed to be active across a wide range of tasks requiring subjects to retrieve words or information about words from semantic memory. Tasks requiring subjects to retrieve information from a specific study episode (episodic memory) have reliably activated the right-anterior prefrontal cortex in addition to more posterior prefrontal areas which vary across tasks. The functional identification and preliminary characterization of these two areas (left-inferior prefrontal cortex and right-anterior prefrontal cortex) in healthy normal subjects provides a clear demonstration of the utility of functional neuroimaging in the study of memory function.

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