Right Anterior Prefrontal Cortex Activation during Semantic Monitoring and Working Memory

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Areas of the adult human brain used for semantic monitoring were identified using positron emission tomography. For a series of tasks, subjects viewed a list of familiar English nouns and monitored the words for names of dangerous animals. The monitoring task used here also contained an instruction to keep track of the number or percentage of targets for report after the scan. Surface characteristics of the tasks such as stimulus rate, number of targets, and whether subjects were asked to count or estimate the number of targets were varied across multiple conditions within and between subjects. A passive word viewing condition was used as the control in all subjects. Reliable activations were identified in anterior and dorsal right prefrontal cortex [Brodmann areas (BA) 9 and 10] and left extrastriate cortex. The right prefrontal cortical locations are similar to areas that have been activated during many episodic memory tasks. This surprising finding led to a thorough review of the literature for examples of other activations within 16-mm vector distance of this right prefrontal area. Activations in the vicinity of right BA10 due to episodic memory retrieval, to various forms of working memory, and to miscellaneous tasks were found. The right prefrontal activations in the current experiment and the additional working memory and miscellaneous tasks demonstrate that, although right BA10 is routinely activated by episodic retrieval tasks, it is not uniquely activated by episodic retrieval tasks.

INTRODUCTION

Modern functional brain imaging with positron emission tomography (PET) and functional magnetic resonance imaging has provided a much expanded view of the neural systems underlying memory function in the normal human brain (for reviews see Ungerleider, 1995; Buckner and Petersen, 1996). Among the many findings has been the repeated demonstration of right prefrontal cortex involvement in episodic memory retrieval tasks (Andreasen et al., 1995; Buckner et al., 1995, 1996; Fletcher et al., 1995; Grady et al., 1995; Haxby et al., 1995; Rugg et al., 1996; Squire et al., 1992; Tulving et al., 1994a,b). In comparison, studies involving word comprehension and semantic retrieval have often not shown activation of these same areas of the right prefrontal cortex. Rather, word processing studies have been associated with left frontal activation (Binder et al., 1995, 1997; Buckner et al., 1995; Buckner and Tulving, 1995; Demb et al., 1995; Demonet et al., 1992; Frith et al., 1991; Kapur et al., 1994; Petersen et al., 1988, 1989; Petersen and Fiez, 1993; Price et al., 1994, 1996; Vandenberghe et al., 1996; Warburton et al., 1996; Wise et al., 1991). It should be noted that episodic retrieval tasks have often also activated these left prefrontal regions. Unlike word comprehension and semantic retrieval, episodic retrieval additionally activates areas within the right prefrontal cortex. This dichotomy has supported the hypothesis that specific areas of the right prefrontal cortex play a unique role in episodic memory retrieval (Tulving et al., 1994b).

It came as a surprise, in reviewing a semantic monitoring task previously reported by us (briefly mentioned in Petersen et al., 1989), to note prominent activation in right prefrontal regions, particularly in anterior right prefrontal cortex near Brodmann area (BA) 10. Activation of right BA10 in this task led us to a review of the literature for activations within 16-mm vector distance. Activations in this area were found in studies of episodic and working memory, as well as other miscellaneous tasks that do not fall easily into one of these two categories. Our findings serve as a note of caution in interpreting too literally the role of the right prefrontal cortex in episodic memory retrieval. Right anterior prefrontal cortex is clearly activated by many episodic retrieval tasks, but the critical processing demands it subserves are most likely shared by a set of tasks extending beyond episodic retrieval.

SEMANTIC MONITORING STUDY

Healthy normal subjects were recruited from the Washington University community. A total of 11 strongly

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right-handed subjects, 7 female, ranged in age from 18 to 39 years (mean 24.1, SD 6.2). Across these 11 subjects five different versions of the semantic monitoring tasks were performed (Table 1). During each of these tasks the subjects viewed words presented one at a time and were instructed to decide whether, in their judgment, they represented the name of a dangerous animal. Words for all tasks appeared in uppercase on a computer monitor in white on a black background, approximately 12 in. from the subject's face. The monitor was placed approximately 12 in. from the subject's face. The subjects were instructed to fixate on the crosshair throughout the tasks. Each word remained on the screen for 150 ms.

Three of the five tasks were done with a word presentation rate of 60 words per minute (slow condition) and two of the tasks were done at a word presentation rate of 120 words per minute (fast condition). Three of the five tasks were done with word lists containing 50% targets (many condition) and two of the tasks were done with word lists containing 2.5% targets (few condition). In two of the tasks, subjects were asked to count silently the number of targets (counting condition) and in three of the tasks the subjects were asked to make a gross estimate (i.e., a percentage) of the number of targets (estimating condition).

The control task consisted of passively viewing a list of words which contained no names of dangerous animals. There was a slow and fast rate for the control condition which matched the stimulus presentation rate of the task conditions. There was also a fixation point control for some subjects.

All emission and transmission scans were obtained on a PETT VI tomograph (Ter-Pogossian et al., 1982; Yamamoto et al., 1982) and the scanning techniques used have been described extensively elsewhere (Fox et al., 1987; Mintun et al., 1989; Petersen et al., 1988).

To isolate changes in blood flow due to semantic monitoring, difference images were made by subtracting the passive word control scans from the semantic monitoring scans. All subtractions were screened for subject movement. Scan pairs with noticeable movement artifact were eliminated from further data analysis. A total of 23 movement-free pairs were obtained from 11 subjects (Table 1). Subjects were divided into two groups. One group (the hypothesis-generating group) was used to create an image from which regional responses could be selected for analysis. A second group (the hypothesis-testing group) was used to test the reliability of these regional responses (Hunton et al., 1996). Attempting a within-subjects design, we tried to balance the two groups for task variable. We were not entirely successful in achieving this because only one control scan was available for each subject and movement artifacts were not consistent across subjects.

The hypothesis-generating group contained 7 subjects with a total of 9 scan pairs. Only voxels which were sampled in all of the subjects were included in the final image. The maxima in the image were located using a peak search algorithm (Mintun et al., 1989). The top 10 maxima were selected for further testing. These points were used as seed points to center a 12-mm-diameter sphere in the individual scans of the hypothesis testing group (11 subjects with 14 scan pairs). A one-sample, upper-tail t test was then performed weighing the data equally for each subject's contribution.

Of the 10 peaks of activation identified in the hypothesis-generating data for semantic monitoring minus

<table>
<thead>
<tr>
<th>Activation tasks</th>
<th>Control tasks</th>
<th>Hypothesis generating Sub</th>
<th>Hypothesis testing Sub</th>
<th>Total</th>
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<tr>
<td>Sem Mon&lt;sup&gt;a&lt;/sup&gt; + Est&lt;sup&gt;b&lt;/sup&gt;, Many&lt;sup&gt;c&lt;/sup&gt;, Slow&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>1</td>
<td>2, 5</td>
<td>3</td>
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<td>1, 3, 4</td>
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<td>Passive word, Slow</td>
<td>2</td>
<td>5, 6</td>
<td>3</td>
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<td>Passive word, Fast</td>
<td>7, 10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>8, 9, 10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>5</td>
</tr>
<tr>
<td>Sem Mon&lt;sup&gt;a&lt;/sup&gt; + Est&lt;sup&gt;b&lt;/sup&gt;, Few&lt;sup&gt;f&lt;/sup&gt;, Fast&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Passive word, Fast</td>
<td>9&lt;sup&gt;h&lt;/sup&gt;, 10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>7, 9, 10&lt;sup&gt;h&lt;/sup&gt;, 11</td>
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<tr>
<td>Total</td>
<td>9</td>
<td>14</td>
<td>23</td>
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</table>

Note. The subjects used in the subtraction pairs in the hypothesis-generating group and hypothesis-testing group are shown.

<sup>a</sup> Semantic monitoring.
<sup>b</sup> Estimating.
<sup>c</sup> Many targets (50%).
<sup>d</sup> Slow rate (60 words/min).
<sup>e</sup> Counting.
<sup>f</sup> Few targets (2.5%).
<sup>g</sup> Fast rate (120 words/min).
<sup>h</sup> Different subtraction pairs.
passive word control, three replicated (Table 2). Two of the peaks were in the right prefrontal cortex and one was in the left extrastriate cortex. The most robust change was in the anterior right prefrontal cortex in the vicinity of right BA10 (Fig. 1).

Two additional subtraction images were assessed: semantic monitoring minus fixation and passive word control minus fixation. This was done because of the absence of a response in the left frontal operculum in the semantic monitoring tasks minus the passive word control. Previous studies involving semantic retrieval have reported activation of left frontal cortex (Binder et al., 1995, 1997; Buckner et al., 1995; Buckner and Tulving, 1995; Demb et al., 1995; Demonet et al., 1992; Frith et al., 1991; Kapur et al., 1994; Petersen et al., 1988, 1989; Petersen and Fiez, 1993; Price et al., 1994, 1995).

<table>
<thead>
<tr>
<th>Region name</th>
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<th>Hypothesis-testing results</th>
<th>Combined image</th>
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<td>25 61 6 2.774</td>
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<td>2.233 0.02</td>
<td>33 35 32 2.503</td>
</tr>
<tr>
<td>L occipital, BA 18</td>
<td>-25 -83 6</td>
<td>2.254 0.02</td>
<td>-27 -81 6 2.601</td>
</tr>
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</table>

Note. BA, Brodmann area.

* In the atlas of Talairach and Tournoux, 1988.

**TABLE 2**

Regions of Significant Activation in Semantic Monitoring Minus Passive Word Control

<table>
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<tr>
<th>Region name</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>P</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>R sup front, BA 10</td>
<td>27</td>
<td>59</td>
<td>6</td>
<td>3.685</td>
<td>0.01</td>
<td>25</td>
<td>61</td>
<td>6</td>
<td>2.774</td>
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<tr>
<td>R front, BA 9</td>
<td>33</td>
<td>35</td>
<td>34</td>
<td>2.233</td>
<td>0.02</td>
<td>33</td>
<td>35</td>
<td>32</td>
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<td>6</td>
<td>2.601</td>
</tr>
</tbody>
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Note. BA, Brodmann area.

* In the atlas of Talairach and Tournoux, 1988.

**FIG. 1.** Sagittal section of a normalized PET blood flow difference image at x = 25 mm (Talairach, 1988), showing an increase in right anterior frontal cortex (BA10) in Semantic monitoring minus Passive word control (n = 11). The gray scale bar represents increases in blood flow quantified in PET counts.
1996; Van den Bergh et al., 1996; Warburton et al., 1996; Wise et al., 1991) and its absence in our data was puzzling. We identified a region of interest on the basis of previously published responses in the left frontal operculum in semantic monitoring tasks (Buckner et al., 1995). The largest increase in each of the two images was in left frontal operculum within 11-mm vector distance of this previously reported response and within 3 mm of each other. Thus the apparent lack of a response in the semantic monitoring minus passive word control was due to an increase in the passive word control. Presumably subjects covertly performed the monitoring task instead of passively viewing words.

The right BA10 location found in the semantic monitoring minus passive word control subtraction was surprisingly close to the location described across many studies of episodic retrieval (Andreasen et al., 1995; Buckner et al., 1995, 1996; Grady et al., 1995; Schacter et al., 1996; Squire et al., 1992; Rugg et al., 1996; Tulving et al., 1994a,b) and led us to do a directed review of activations found at or near this location.

**REVIEW**

The majority of episodic, but not semantic, memory retrieval studies have indeed shown right dorsolateral prefrontal cortex activation at or near right Brodmann area 10 (Table 3, Fig. 2). Activations have occurred for long-term word (Buckner et al., 1995, 1996; Schacter et al., 1996; Squire et al., 1992), sentence (Tulving et al., 1994a), picture (Buckner et al., 1996), and face (Grady et al., 1995) retrieval tasks. They have occurred for memory delays of several minutes (Buckner et al., 1995, 1996; Squire et al., 1992) and of a day (Tulving et al., 1994a). They have occurred for tasks of auditory word recognition (Buckner et al., 1995), auditory sentence recognition (Tulving et al., 1994a), cued stem recall (Buckner et al., 1995; Schacter et al., 1996; Squire et al., 1992), and forced-choice recognition (Grady et al., 1995) (see Table 3, Fig. 2, squares). This has led to the hypothesis that this area of cortex contributes in a unique way to episodic memory retrieval (Tulving et al., 1994b).

However, there is no apparent episodic memory retrieval demand in the semantic monitoring tasks. The semantic task consisted of monitoring a series of words for dangerous animals. In addition subjects were asked to keep track of the number of targets. This was done either by counting or by estimating, both of which presumably require specific manipulation and maintenance within working memory.

Prefrontal cortex in general has frequently been
assigned an important role in working memory\(^1\) (Goldman-Rakic, 1987; Fuster, 1989; Goldman-Rakic and Friedman, 1991; Frith et al., 1991; Jonides et al., 1993; Paulesu et al., 1993a,b; Petrides et al., 1993; Goldman-Rakic, 1994; Raichle, 1994; Fiez et al., 1996). This prompted us to ask the obvious question, has right Brodmann area 10 activation been observed in studies employing working memory? Many studies of working memory report activation in right Brodmann area 10 (Table 3, Fig. 2, triangles). These include object (Bonda et al., 1995), spatial (Owen et al., 1996), and verbal (Grasby et al., 1993, 1995; Petrides et al., 1993) working memory tasks. Bonda et al. (1995) showed an activation in this area in a task in which subjects familiarized themselves with eight photos of various hand postures. Seven of these photographs were shown during the PET scan and subjects had to report which one was missing. Haxby et al. (1996) showed a similar activation for an object working memory task of a delayed match to sample face recognition.

Owen et al. (1996) showed activation in this area for spatial monitoring tasks which involved touching 8 or 12 red circles until 1 turned blue and to continue this process until each circle had turned blue and back to red again. Once a circle had turned blue it was not to be touched again in a given sequence. The same activation was not seen when subjects had to remember the location of 3 circles presented 1 at a time and then touch those three locations from a choice of eight. Nor was it activated when subjects viewed 8 red circles, 5 of which sequentially turned blue then back to red and subjects touched the five locations which had turned blue. Third, it was not activated when subjects learned a fixed random sequence for touching 8 red circles.

Grasby et al. (1993) showed an activation in this area

\(^1\) It is inherently difficult to classify complex cognitive tasks into a single global category such as "working memory." In a strict sense, many tasks place demands on working memory, including the tasks labeled here as semantic and episodic retrieval. Our use of "working memory" therefore only reflects a broad category and describes tasks that have placed explicit demands on working memory and, for the most part, have lacked or controlled for demands related to semantic and episodic retrieval.

FIG. 2. Diagrammatic representation of foci found in literature search for BA10 (see Table 3). The circle represents the present experiment. The x coordinate is the mean for all of the studies with BA10 activation listed in Table 3. The horizontal line represents the z axis and the vertical line represents the y axis for the center of the response in the present experiment.
when subjects heard 15 words and had to immediately recall them but not for the same task using a word list of 5. Grasby et al. (1995) showed a similar activation for the same task in a group of placebo-treated subjects but not in subjects that received scopolamine. Petrides et al. (1993) showed an activation in this area when subjects listened to a list of numbers between 1 and 10 in which one number was omitted and then reported the missing number. It was not seen when subjects generated their own random list of the numbers 1 through 10, being careful not to use any number twice.

To further confound our understanding of right BA10, several working memory studies do not report activation in this region (Fiez et al., 1996; Paulesu et al., 1993a,b; Smith et al., 1995).

In addition, several miscellaneous studies demonstrating significant activation in this area of right BA10 were found (see Table 3, Fig. 2, diamonds). This included a study by Decety et al. (1994) showing several activations within a 16-mm vector distance of our right BA10 point. These activations occurred when subjects imagined themselves grasping with their right hand objects viewed through a three-dimensional virtual reality system. Kosslyn et al. (1994) showed activation in this area when subjects viewed line drawings of objects in familiar representations and heard a name. Half of the time the name matched the picture. A yes/no response was required for each object/name pair. This was compared to abstract line drawings of similar shapes coupled with a word, but no response was required. No activation was seen when the pictures were viewed from unusual angles under otherwise similar conditions. Silbersweig et al. (1993) showed a decrease in activation in this area when sentence monitoring was compared to a control condition in which subjects were told to monitor for sentences but none were presented. Whether this should be viewed as an increase in right BA10 in the control condition or a decrease in the activation condition is uncertain.

One obvious question that arises is whether the area in the right frontal cortex reported in studies of episodic memory retrieval, working memory, and these miscellaneous conditions (Table 3) is, in fact, the same area we observe active in our experiments. To answer this question we took the coordinates for the right frontal focus of activation from each of the studies in which it was observed (Table 3) and asked whether a spherical region 12 mm in diameter centered on these coordinates replicates in our data. The answer (Table 3) would appear to be yes.

Thus, based on currently available information from functional activation studies in normal adult humans it is not possible to say what the exact role of this area of the right prefrontal cortex is. There may be even smaller subsets of this area used for different tasks but this cannot be resolved with current data. Future studies with careful task analysis will be needed to sort out the role(s) of this area. Additionally, the study of patients with focal lesions confined to the area of interest could prove invaluable (Swick and Knight, 1996). Studies of such patients based upon tasks known to activate this area would serve to enlighten us as to its role in neural information processing. Our findings and our review of the literature do suggest that, while anterior prefrontal cortex is often activated during episodic retrieval tasks, it is also activated by a class of tasks that fall outside the domain of episodic retrieval.

Our eventual understanding of the processing role or roles of this area will have to accommodate both why it consistently participates in episodic retrieval tasks as well as how its processing contribution sometimes generalizes to tasks without obvious demands on episodic memory retrieval.

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REFERENCES


