Comparison of Brain Activation during Word Retrieval Done Silently and Aloud Using fMRI

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Using functional MRI we compared the patterns of activation in an effortful word retrieval task (stem completion) performed both silently and aloud. The silent and overt conditions showed expected differences in activation magnitude in regions such as primary motor cortex. Some regions, such as frontal operculum and dorsolateral frontal cortex, showed similar activation magnitude across conditions. Thalamus was more active on the left in both conditions and showed a symmetric drop in activity in the silent compared with the overt condition. Putamen was also more active in the overt condition and showed a larger decrease in activity on the right than on the left in the silent compared with the overt condition. Thus it appears that silent and overt performance of this task engage the thalamus and putamen in different ways. © 2000 Academic Press

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INTRODUCTION

Functional MRI (fMRI) is increasingly being used to study the organization of the brain structures involved in cognitive tasks. In order to study language, it is important to include speech production among the tasks used. This has proven to be a difficult problem due to the marked sensitivity of MRI scanning to movement associated with talking. To date, very few fMRI studies of overt speech production have been published (McCarthy et al., 1993; Yetkin et al., 1995; Small et al., 1996; Birn et al., 1998). We have

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recently used fMRI to study an effortful speech production task performed both aloud and silently in the same subjects and obtained images with reliable sites of activation at multiple cortical locations as well as in thalamus and putamen. Though this was primarily a methodological study, the activation elicited in the subcortical structures and the relationship of these activations to the task manipulation are relevant to the role of these structures in language function.

Subcortical structures are heavily involved in the processing of motor and sensory tasks. However, their role in language processes is less well established. The proposition that they play a role in the motor aspects of language is easily accepted. However, the question of whether they play a role in the nonmotor aspects of language and the nature of that role is the subject of considerably more debate. Though the presence of language dysfunction has been reported after thalamic and striatocapsular hemorrhages and infarcts, not all investigators agree on the interpretation. While some attribute the language deficits directly to the lesions seen in subcortical structures, others attribute the observed deficits to subtle ischemic injury to overlying cerebral cortex or to fibers of passage which course through the injured region (Nadeau & Crosson, 1997). Studies using SPECT to assess regional cerebral blood flow have, in fact, shown decreased blood flow in the left middle cerebral artery territory overlying subcortical lesions associated with aphasia (Weiller et al., 1993; Okuda et al., 1994). One of the major underlying difficulties with studies in brain-injured patients is the difficulty in precisely identifying the structures damaged by the lesion or which one of the multiple damaged structures is responsible for the observed deficits.

Another experimental approach which may be useful in elucidating the role of subcortical structures in language is the use of functional imaging techniques (PET and fMRI) in normal subjects. These techniques involve the measurement of regional changes in cerebral blood flow or oxygenation which are known to occur in association with local changes in brain activity (Fox & Raichle, 1984). Despite the large number of imaging studies done to date, only a small number have reported activations in subcortical structures during performance of language tasks (Friston et al., 1993; Demonet et al., 1994a, 1994b; Price et al., 1994; Warburton et al., 1996; Baker et al., 1997; Ojemann et al., 1998). Some authors have attributed the activity to articulatory loops involved in the task (Demonet et al., 1994a, 1994b; Paulesu et al., 1997), to primary sensory stimulation (Warburton et al., 1996), or to subcortical involvement in language and verbal memory (Ojemann et al., 1998).

In this paper we report strong activations of subcortical structures during an effortful word retrieval task and we discuss their significance in light of current knowledge on the physiology of subcortical structures.
METHODS

Participants

Five right-handed subjects [ages 18 to 34 (mean of 26), three female, two male] whose native language was English were recruited through advertisements at the undergraduate and medical campuses of Washington University. They were reimbursed at a rate of $25 per hour. Informed consent was obtained after approval of the Washington University Human Studies Committee.

Imaging Apparatus and Technique

At the beginning of the session subjects lay supine with the head resting in a foam pad inside the standard Siemens head coil. This pad was contoured to fit into the head coil on one side and to accommodate the shape of the back of the head on the other. A thermoplastic mask using the materials, size, and preparation previously used at this laboratory for PET studies was then fitted to the face to limit subject head movement (Fox, Perlmutter, & Raichle, 1985). A new method was devised to fix the mask in place. This consisted of removing the standard sliding side head braces from their tracks in the head coil and replacing them with specially fashioned lucite mask clamps which held the mask in place. Subjects were also reminded of the need to keep their head as still as possible, even while speaking.

Images were obtained using the Siemens MAGNETOM vision 1.5 T system (Erlangen, Germany) with the standard head coil. Anatomical images were obtained after automatic shimming using a sagittal MPRAGE (Mugler & Brookeman, 1990) sequence (TE = 4 ms, TR = 9 ms, TI = 300 ms, flip angle = 12°, 80 slices, 2 × 2 × 2 mm voxels). From this image, the anterior commissure–posterior commissure (AC–PC) plane was identified and functional imaging was performed parallel to this plane. Functional images were collected using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (TR = 2364 ms, T2* evolution time = 50 ms, α = 90°, 8-mm slices, in-plane resolution 3.75 × 3.75 mm). Each “run” of data acquisition consisted of 124 whole brain EPI acquisitions (frames). The first frame of each run was used for anatomical image information, while each frame from the fourth on was considered steady state and used for functional imaging.

Stimulus Presentation and Procedure

The experimental task was a word stem completion task which has been studied previously with functional imaging (Squire et al., 1992; Buckner et al., 1995; Ojemann et al., 1998). Three letter strings, or “word stems,” were visually presented one at a time under a crosshair fixation point. Subjects were asked to think of a word which began with each word stem which appeared on the screen. A large set of word stems was necessary to provide enough stimuli for this experiment. In total, 375 unique word stems, which were available from another study (Ojemann et al., 1998), were used. Each word stem could be used to create at least five unique English words with a frequency of greater than one per million (Kucera & Francis, 1967). In half the scans, subjects were asked to say the word out loud. In the other half of the scans, subjects were asked to say the words silently to themselves, without moving their lips.

Stimuli were presented through a Power Macintosh 7100 computer (Apple Computer), projected through a Sharp LCD projector (640 × 480 pixel resolution) onto a screen behind the subject’s head. The subject was able to see this screen through a mirror placed on the head coil. Stimuli were displayed in black 24-point bold Geneva font in capital letters on a white background. At the start of each run, a centrally placed visual crosshair, subtending a visual...
angle of 0.26° was put up in the center of the screen as a target for visual fixation. Subjects were instructed to stare at this fixation point for the duration of the scan. The run was then started and stimulus presentation began after 21.3 s (at the beginning of the 10th EPI acquisition). The word stems subtended a visual angle of about 0.5° per letter (width) and were displayed 1.3° directly below the fixation point (measured to the midpoint of a letter). The stimulus duration was 150 ms. During the interstimulus interval, subjects continued to attend to the crosshair in the center of the field of view.

In order to ensure a predictable relationship between fMRI frames and stimulus presentation, interstimulus intervals were always multiples of the TR used for EPI scanning (about 2.4 s, see Imaging Apparatus and Technique, above) and presented immediately after an electronic synchronization pulse sent from the scanner at the beginning of each whole brain EPI acquisition (frame). For this study we used an "event-related" approach to stimulus presentation and analysis rather than a simpler block-design paradigm (Dale & Buckner, 1997). The specific interstimulus intervals were chosen because of methodological concerns not to be discussed here. Three types of stimulus presentation paradigms were used. The first had a fixed interstimulus interval with presentation once every 16.5 s (seven EPI acquisitions), and 16 stimuli per run. The other two types of runs had variable interstimulus intervals. Stimulus presentation in these runs was arranged by designating two trial types: stem completion trials (stem presentation for 150 ms followed by crosshair fixation) and equally long fixation only trials. The trial lengths were 2.4 s long for one type of run and 4.7 s long for another type. Equal numbers of these trial types were pseudorandomly ordered such that each trial type was equally likely to be followed by itself or the other trial type. Two more types of runs were created in this way: (1) runs with variable interstimulus intervals ranging from 4.7 to 23.6 s, with 28 stimuli per run and, (2) runs with variable interstimulus intervals ranging from 2.4 to 11.8 s, with 56 stimuli per run. Each subject performed 4 runs of stem completion with each stimulus presentation paradigm, 2 silently and 2 aloud, resulting in a total of 375 stimuli. The stimuli were rerandomized into new blocks after every two subjects. The same ordering of types of stimulus presentation blocks were used for each pair of subjects, but each block was run once silently and once overtly across every pair of subjects. Thus each stimulus was represented in both conditions.

Each 124-frame run underwent several automated processing steps, including removal of a single pixel spike caused by signal offset, minimization of differences in slice intensity caused by interleaved slice acquisition, realignment within and across runs using a rigid-body rotation and translation correction, and slice-based normalization to correct for artifactual fluctuations in signal intensity (see Ojemann et al., 1998).

Analysis

Localization of significantly activated pixels. To determine the location of significant changes in MRI signal related to the behavioral task, each fMRI run was analyzed using an application of the general linear model (Friston et al., 1995; Worsley & Friston, 1995). Although independently implemented, the basic estimation algorithm is the same as that used in the statistical parametric mapping package (SPM). The data were not smoothed prior to calculation of \( z \) statistics and correction for multiple comparisons (Ollinger, 1997).

Single-run \( z \) images were averaged across subjects (Ojemann et al., 1998) in the atlas space of Talairach and Tournoux (1988). This was accomplished through a number of steps which have been described recently (Ojemann et al., 1997). Averaged statistical images were created for the overt and silent conditions, collapsing the data from the various stimulus presentation paradigms together, across subjects. The resulting statistical images represent a total of 30 run of stem completion each.

Comparison of activated regions within and across conditions. The hemodynamic response seen with BOLD contrast has a well-defined delay relative to the onset of the behavioral task, with a peak at 4 to 6 s (Bandettini et al., 1992; Malonek & Grinvald, 1996) and a return to
baseline after about 14 s (Buckner et al., 1996). Given that each EPI scan through the brain (frame) takes about 2.4 s, the full hemodynamic response to a particular event would take about seven of our measurements (or time points) to characterize from beginning to end. This represents a time course for a response and the most prominent effects in a responding voxel would be visible at about the third and fourth measurements. Thus time is an important factor in assessing a response since even a voxel which is responding to an event would not do so at all time points. To evaluate the magnitude of the signal response to our stimulus at various locations, magnitude images were created representing, in each voxel, the percentage of change in signal from baseline at every time point after stimulus presentation, averaged over all the stimuli for that run. Thus each magnitude image was actually composed of seven images, one for each time point. These magnitude images were averaged within subject separately for each condition (silent and overt).

To compare magnitudes at particular locations across the two conditions, regions of interest were selected from the statistical images obtained using the general linear model. To avoid selecting points which would be biased toward a particular condition, regions were selected from a statistical image comprising activation sites from both conditions combined. These regions were then applied to the magnitude estimate images in each subject and the values obtained were averaged across subjects (one value per subject at each time point). The resulting time course estimates were then compared within subjects across conditions and locations using repeated measures analysis of variance, with time, condition, and hemisphere as factors (SuperANOVA, Abacus Concepts, Berkeley, CA). Because of the characteristic time course of the fMRI signal response, any region which was found to be active through our application of the general linear model should show an effect of time in this analysis. The main question here was to determine whether there were interactions of time and other factors, indicating differences in signal response between conditions or hemispheres.

RESULTS

Localization of Significantly Activated Pixels

Table 1 and Fig. 1 provide a summary of the most prominent sites of activation. It should be noted from Fig. 1 that the images are largely free of artifact. It has been reported that there are often large artifacts associated with mouth movements during fMRI studies (Yetkin et al., 1995). The current results may be due to our use of an event-related paradigm (Birn et al., 1998), careful head fixation, or a combination of these factors.

At the cortical level, the patterns of activation sites for the two conditions show some of the differences one might expect. Strong bilateral activation in superior temporal gyrus, at or near primary auditory cortex (Fig. 1E), can be seen in the overt version of the task, whereas there is no significant activation in the superior temporal gyrus in the silent condition. Also, very reliable activation can be seen in bilateral motor cortex in the overt condition (Fig. 1A, bottom). Interestingly, there also appears to be a less prominent but reliable activation in motor cortex during the silent condition (Figure 1A, top; Table 1).

In contrast, there are a number of cortical regions which appear to be very prominently activated in both conditions. For instance, activations can be seen in dorsolateral frontal cortex (Fig. 1B) and in frontal opercular cortex, overlapping the insula (Fig. 1F), in very similar locations in both conditions.
TABLE 1
Summary of Areas of Activation in Averaged Statistical Images across Five Subjects in Each Condition

<table>
<thead>
<tr>
<th>Region (BA)</th>
<th>Overt</th>
<th>Covert</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coordinate</td>
<td>z score</td>
</tr>
<tr>
<td>Cortical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial frontal(6)</td>
<td>$-1,1,52$</td>
<td>$13.7$</td>
</tr>
<tr>
<td>Left motor(4)</td>
<td>$-49, -15,34$</td>
<td>$12.6$</td>
</tr>
<tr>
<td>Right motor(4)</td>
<td>$45, -11,36$</td>
<td>$11.8$</td>
</tr>
<tr>
<td>Right motor(4)</td>
<td>$53, -7,42$</td>
<td>$10.2$</td>
</tr>
<tr>
<td>Right superior temporal(42)</td>
<td>$49, -21,8$</td>
<td>$8.7$</td>
</tr>
<tr>
<td>Left superior temporal(42)</td>
<td>$-53, -25,8$</td>
<td>$8.5$</td>
</tr>
<tr>
<td>Left dorsolateral frontal(44/6)</td>
<td>$-43,5,28$</td>
<td>$8$</td>
</tr>
<tr>
<td>Right dorsolateral frontal(44/6)</td>
<td>$43,9,26$</td>
<td>$7.8$</td>
</tr>
<tr>
<td>Left frontal operculum</td>
<td>$-29,21,6$</td>
<td>$7.6$</td>
</tr>
<tr>
<td>Right frontal operculum</td>
<td>$35,19, -2$</td>
<td>$4.8$</td>
</tr>
<tr>
<td>Right parietal(7)</td>
<td>$25, -57,46$</td>
<td>$8.6$</td>
</tr>
<tr>
<td>Left parietal(7)</td>
<td>$-29, -53,46$</td>
<td>$7.1$</td>
</tr>
<tr>
<td>Subcortical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left thalamus</td>
<td>$-9,21,8$</td>
<td>$9.6$</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>$7, -17,6$</td>
<td>$9.2$</td>
</tr>
<tr>
<td>Left putamen</td>
<td>$-23,1, -2$</td>
<td>$8.1$</td>
</tr>
<tr>
<td>Right putamen</td>
<td>$23, -5,8$</td>
<td>$8$</td>
</tr>
</tbody>
</table>

*a* BA, Brodmann’s area, approximate location.
*b* Coordinates refer to the stereotaxic coordinates in the system of Talairach and Tournoux (1988). The locations were identified by superimposing the activation images on an averaged anatomical MRI representing all five subjects transformed into Talairach space.

Subcortical regions appear to be active in both conditions as well. Thalamic sites of activation can be seen in approximately similar locations in both the silent and overt conditions (Fig. 1C). The location of these sites of thalamic activation are at the border or mediodorsal and ventrolateral nuclei (Table 1). Regions in putamen (Fig. 1D) are very reliably activated in the overt condition, but no pixels in the putamen passed our statistical threshold for activation in the silent condition.

Comparison of Activated Regions within and across Conditions

In order to more closely examine the behavior of the activated regions, we estimated the magnitude of activation at these regions for each subject in each condition and compared the average magnitudes between conditions using repeated measures analysis of variance. Regions were selected from a combined silent–overt statistical image. Analysis of variance was performed with hemisphere, condition (silent or aloud), and time point as factors (see Methods for a further explanation of time points). As is discussed under Methods, time is an important factor in this analysis. All regions show main...
FIG. 1. Axial sections through an average anatomical MRI from five subjects. The averaged, thresholded statistical maps (z scores, indicated by the color scale in the lower right) showing regional activation are superimposed for each condition. The vertical coordinate (Z) represents the distance, in millimeters, from the anterior commissure–posterior commissure plane of a given axial section. Left hemisphere is on the left. (A) Primary motor cortex, (B) dorsolateral frontal cortex, (C) thalamus, (D) putamen, (E) superior temporal gyrus, (F) frontal operculum. Motor cortex activation (A) in the silent condition is less apparent than that in the overt, but reaches statistical significance.

effects of time, confirming that there were significant responses to the events in question. The goal of this analysis was to assess differences in signal response across conditions and regions. Table 2 summarizes the analyses performed which are discussed below.

Figure 2 shows the magnitude of the MRI signal in motor cortex during successive frames occurring after the stimulus. The difference in response magnitude between the two conditions is highly significant [a significant interaction between condition and time; \( F(6,24) = 17.81, p < .0001 \)] yet there is no interaction among hemisphere, condition, and time \( (F < 1) \), indicating that the left and right motor cortex regions showed similar levels of signal response in each condition.

Figures 3 and 4 show the response magnitudes in bilateral frontal opercular and bilateral dorsolateral frontal cortex in both conditions. The activation magnitudes are not significantly different across conditions in either region. In dorsolateral frontal cortex, however, there is a significant interaction between hemisphere and time \( [F(6,24) = 4.70, p = .003] \), reflecting the stronger activation on the left. There is no significant interaction among hemisphere, condition, and time \( [F(6,24) = 1.78, p = .145] \), indicating that
TABLE 2
Summary of Analyses Performed on Activated Regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Effect</th>
<th>Degrees of freedom</th>
<th>F value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left/right motor</td>
<td>Condition × time</td>
<td>(6,24)</td>
<td>17.81</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Hemisphere × time</td>
<td>(6,24)</td>
<td>0.82</td>
<td>0.569</td>
</tr>
<tr>
<td></td>
<td>Condition × hemisphere × time</td>
<td>(6,24)</td>
<td>0.37</td>
<td>0.892</td>
</tr>
<tr>
<td>Left/right DLF</td>
<td>Condition × time</td>
<td>(6,24)</td>
<td>0.70</td>
<td>0.651</td>
</tr>
<tr>
<td></td>
<td>Hemisphere × time</td>
<td>(6,24)</td>
<td>4.70</td>
<td>0.003*</td>
</tr>
<tr>
<td></td>
<td>Condition × hemisphere × time</td>
<td>(6,24)</td>
<td>1.78</td>
<td>0.145</td>
</tr>
<tr>
<td>Left/right FOP</td>
<td>Condition × time</td>
<td>(6,24)</td>
<td>0.25</td>
<td>0.953</td>
</tr>
<tr>
<td></td>
<td>Hemisphere × time</td>
<td>(6,24)</td>
<td>1.94</td>
<td>0.115</td>
</tr>
<tr>
<td></td>
<td>Condition × hemisphere × time</td>
<td>(6,24)</td>
<td>1.10</td>
<td>0.390</td>
</tr>
<tr>
<td>Left/right thalamus</td>
<td>Condition × time</td>
<td>(6,24)</td>
<td>8.05</td>
<td>0.0001*</td>
</tr>
<tr>
<td></td>
<td>Hemisphere × time</td>
<td>(6,24)</td>
<td>4.61</td>
<td>0.003*</td>
</tr>
<tr>
<td></td>
<td>Condition × hemisphere × time</td>
<td>(6,24)</td>
<td>1.50</td>
<td>0.222</td>
</tr>
<tr>
<td>Left/right putamen</td>
<td>Condition × time</td>
<td>(6,24)</td>
<td>5.17</td>
<td>0.0015*</td>
</tr>
<tr>
<td></td>
<td>Hemisphere × time</td>
<td>(6,24)</td>
<td>6.95</td>
<td>0.0002*</td>
</tr>
<tr>
<td></td>
<td>Condition × hemisphere × time</td>
<td>(6,24)</td>
<td>3.22</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

*DLF, dorsolateral frontal cortex; FOP, frontal operculum.

<table>
<thead>
<tr>
<th>Region</th>
<th>Effect</th>
<th>Degrees of freedom</th>
<th>F value</th>
<th>p value</th>
</tr>
</thead>
</table>
|              | Condition × overt performance = overt or covert performance of the task. Hemisphere = the same region on the left or right. A significant interaction with time indicates that the MRI response curves are different across a given variable (i.e., overt vs. silent and/or left vs. right).

This interaction implies that the left/right asymmetry seen in the covert condition is different in the overt condition, consistent with Fig. 6, where no left/right asymmetry is evident in the putamen for the overt condition.

*Denotes statistically significant effect.

FIG. 2. MRI signal response during successive time points after each stimulus, averaged within and across subjects. Each time point represents one whole brain volume acquisition, which requires 2.4 s. Signal is in units of percentage of change from baseline. (a) Left motor cortex response in overt and covert conditions; (b) right motor cortex response, both conditions. The differences across conditions were highly significant by ANOVA (condition × time). There was no difference in the magnitude of activation between hemispheres.
this asymmetric activation occurs in both silent and overt conditions. The frontal opercular regions sampled do not show a significant interaction between condition and time \((F < 1)\) nor between hemisphere and time \([F(6,24) = 1.1, p = .39]\).

Thalamic structures (Fig. 1C) are active in both conditions but, as shown in Fig. 5, the magnitude of activation is smaller in the silent condition on both sides. ANOVA confirms a highly significant interaction between condition and time \([F(6,24) = 8.05, p < .0001]\) for the thalamus. There is also a significant interaction between hemisphere and time \([F(6,24) = 4.61, p = .003]\), reflecting the higher thalamic activation on the left. There is no

**FIG. 3.** Signal response in the frontal operculum for both conditions (see legend, Fig. 2). (a) Left frontal operculum response in overt and covert conditions; (b) right frontal operculum response, both conditions. Both curves show a significant effect of time, but response magnitude showed no interaction with condition or hemisphere.

**FIG. 4.** Signal response in the dorsolateral frontal cortex for both conditions (see legend, Fig. 2). (a) Left dorsolateral frontal response in overt and covert conditions; (b) right dorsolateral frontal response, both conditions. Response magnitude over time showed no interaction with condition, but there was a difference in the magnitude of activation across hemispheres (hemisphere × time interaction).
interaction among hemisphere, condition, and time \[ F(6,24) = 1.5, p = .22 \], indicating that the left and right activated thalamic regions do not show different relative changes in activation level across task conditions.

Figure 6 shows the pattern of activation in putamen. On both sides, the level of activation is higher in the overt than the silent condition. This effect is highly significant, as demonstrated by the interaction between condition and time \[ F(6,24) = 5.17, p = .0015 \]. Whereas there appears to be some response in the silent condition on the left, there is virtually no response in

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**FIG. 5.** Signal response in the thalamus bilaterally (see legend, Fig. 2). (a) left thalamus; (b) right thalamus. Response magnitude showed a significant interaction with both condition and hemisphere, but there was no interaction between time, condition, and hemisphere indicating the left/right asymmetry was similar in both overt and covert tasks.

**FIG. 6.** Signal response in the putamen bilaterally (see legend, Fig. 2). (a) left putamen; (b) right putamen. There was a significant effect of condition (condition × time interaction) and a significant interaction of hemisphere × condition × time, indicating that the left/right differences changed between covert and overt task performance. This appears to be due to nearly equal left and right putamen activity in the overt task with lower, but preserved, left putamen activity in the covert task without preservation of right putamen activity.
the right putamen during the silent condition (Fig. 6). A significant interaction among hemisphere, condition, and time [$F(6,24) = 3.22, p = .018$] exists for putamen, confirming a different effect of condition in the left putamen than on the right. There is also a highly significant interaction between hemisphere and time [$F(6,24) = 6.95, p = .0002$]. Inspection of the time curves would suggest that this effect mostly reflects the interhemispheric difference in putamenal activation in the covert condition, as the level of activation on the two sides in the overt condition appears roughly the same. Posthoc analysis revealed this to be the case.

**DISCUSSION**

A comparison of the stem completion task performed silently and aloud showed some expected differences in regions such as primary motor cortex and superior temporal gyrus (at or near primary auditory cortex), reflecting the differences in motor demands and sensory stimulation. Similar activation magnitudes across condition were seen in areas such as frontal operculum and dorsolateral frontal cortex, presumably reflecting the nonmotor aspects of this word retrieval task. These regions have been activated before in silent word retrieval tasks with PET (Wise et al., 1991; Buckner et al., 1995) and fMRI (Ojemann et al., 1998).

The activity in the putamen displays an intriguing pattern. The strong bilateral activation in putamen, well in excess of that seen in the covert condition, along with motor cortex activation in the overt condition well in excess of the magnitude of activation in the covert condition, is consistent with the role of the lenticular nuclear structures in motor functioning.

The presence of weak bilateral motor cortex activity in the silent condition suggests the possibility that the subjects may have been ‘‘subvocalizing’’ in some way, making subtle lip or laryngeal movements of which they may have been unaware. Because of logistical problems associated with MRI scanning we were unable to observe or otherwise monitor the subjects’ mouths in this experiment and one may validly assert that without electromyographic recordings from mouth and larynx this question cannot be adequately addressed.

Despite the potential confound of subvocalization and the activation of motor cortex in the silent condition, the asymmetry in the putamenal activity is not consistent with a straightforward ‘‘motor’’ explanation of this nature. If both putamen are functioning only in control of movement, then one would expect their fMRI signals to respond to the change in motor task demands in the same fashion, since control of mouth movements should require equal contributions from the motor systems of both hemispheres. In support of this, we may observe that the small amount of motor cortex activation seen in the covert condition is seen bilaterally (Fig. 1A, top), with no significant interaction between the MRI response magnitude across time and hemispheres nor among the factors time, hemisphere, and condition (Table 2).
On the other hand, there are some data which suggest that striatothalamic output, often characterized as primarily motor, is segregated into pathways which connect to differing cortical structures, some of which have nonmotor functions. Such output has been found in cebus monkeys originating in globus pallidus interna, synapsing in the ventrolateral, ventral-anterior, and mediodorsal nuclei of the thalamus, and terminating in dorsolateral prefrontal cortex, an area characterized as having nonmotor functions (Middleton & Strick, 1994). The pallidal neurons labeled in this pathway were in a different location than those which sent output to primary motor cortex, though they were in very close proximity. The existence of such connections does not explain how or when they are used, but does allow for the possibility that subcortical neurons adjacent to those involved more directly in motor function can be involved in higher order processes, including those used for the stem completion task. It is thus worth noting that structures in dorsolateral frontal cortex (at the border between Brodman's areas 44 and 6) were strongly activated in both the silent and the overt conditions. It is possible that the putamenal activation in the overt condition represents activity of two different neuronal populations communicating with motor and prefrontal cortex, with the stronger or more widespread activity of the motor control neurons dominating the image in the overt condition. In the silent condition, the residual activation may be related to the neuronal population communicating with dorsolateral frontal cortex.

It is possible that both the small motor activations and the putamenal activation in the silent condition represent a higher order process and that no actual movement is occurring. Previous neuroimaging studies of motor operations with careful subject monitoring have shown activation of primary motor cortex in a motor planning phase, prior to motor output (Kawashima, Roland, & O'Sullivan, 1994). Our data would imply that the putamen, though symmetrically involved in motor output, is asymmetrically involved in such higher order processes, at least for word production tasks such as stem completion. One previous series of imaging studies has linked left putamenal activation to articulatory factors (Klein et al., 1994). In those studies, left putamenal activation was associated with production of words in a second language regardless of whether the words were repeated or retrieved from an auditory cue. It was proposed that the increased difficulty with expression in a second language was the crucial factor. Whether the putamenal activation was related to difficulty at the planning stage or at the execution stage would be impossible to discriminate from these studies since all tasks were performed aloud. Left putamenal activation has also been found in a word memorization task in the absence of motor cortex activation (Demonet et al., 1994a). The putamenal activation was attributed to articulatory factors in the memorization process.

The presence of bilateral thalamic activation at the same location in both the silent and overt conditions is interesting. In light of persistent motor cortex
activation in the silent condition, the most parsimonious explanation would again involve subvocalization during this task. Again, the alternative explanations advanced for the putaminal activations, higher order processing, and parallel motor and nonmotor pathways can be applied to thalamus as well. The fact that the thalamic activation is in either the mediodorsal or ventrolateral nucleus is relevant, as these are the same thalamic sites labeled in the nonhuman primates studied by Middleton and Strick (discussed above). The asymmetry in the thalamic activity (left greater than right) is interesting in light of the fact that dorsolateral frontal cortex also showed more activity in the left hemisphere (significant effect of side, both locations, see Table 2). Thalamic activity can partially be accounted for by the activity in motor cortex but motor cortex activation would not account for the asymmetry of thalamic activation. As was suggested for the putamenal activations, it is possible to explain these results as an additive effect of two populations, one involved in motor processing and communicating with motor cortex and the other in higher order processing and communicating with dorsolateral frontal cortex. Nevertheless, it is not possible from the available data to reject the subvocalization argument in favor of an explanation involving higher order processing.

Although fMRI studies of overt speech are uncommon, a large number of functional imaging studies have investigated language function. Early studies looking at various types of word generation tasks made no note of any subcortical activation despite the fact that the tasks included oral (Petersen et al., 1988; Frith et al., 1991) or manual (Wise et al., 1991; Demonet et al., 1992) motor output. Subsequently, a number of studies using language tasks have demonstrated subcortical activations. For instance, bilateral thalamic activation has been found during monitoring of auditory letter strings for a particular sequence of phonemes compared to detection of a single phoneme (Demonet et al., 1994b) and for passive, silent viewing of words when compared to viewing false fonts (Price et al., 1994). Thalamic activation has also been found in studies using language tasks similar to those described here, such as silently generating verb or noun associates for visually presented nouns (Warburton et al., 1996) and generation of words based on semantic or phonemic cues both aloud (Friston et al., 1993; Baker et al., 1997) and silently (Paulesu et al., 1997; Ojemann et al., 1998). It is difficult to reconcile all the studies given that, in some cases, identical tasks do not reveal the same results (Warburton et al., 1996). However, imaging studies across centers has shown a high degree of reproducibility in thalamic activation (Ojemann et al., 1998). Looking across the studies which show thalamic activation in language tasks, the most common reported site of activation is in the mediodorsal nucleus. Activations in the ventrolateral nucleus or on the border between the mediodorsal and ventrolateral nuclei are also commonly seen. More posterior activations in the pulvinar have also been reported (Paulesu et al., 1997). These results are consistent with our own data, which show activation at the mediodorsal/ventrolateral border with and without overt
motor output. Putamenal or lenticular activations have also been described in some of these studies (Demonet et al., 1994a; Warburton et al., 1996; Ojemann et al., 1998). Our study is unique in directly comparing the silent and overt verbal fluency tasks within subjects.

The fact that these activations were found in a word retrieval task similar to clinical assessments of verbal fluency is interesting. Mega and Alexander (1994) described the “core” deficit in cases of limited striatocapsular infarction as a deficit primarily in verbal fluency. The typical thalamic aphasia has been described as a deficit in naming and verbal fluency with good comprehension and repetition (Nadeau & Crosson, 1997). Difficulty with verbal fluency has also been described in a small series of patients after implantation of pallidal stimulating devices (Troster et al., 1997). It is not clear from this study whether such deficits were limited to left-sided pallidal stimulation. Mild deficits in verbal fluency were also the only neuropsychological deficits found in a recent study of patients after pallidotomy (Scott et al., 1998). The majority of patients in this study who had verbal fluency deficits had either unilateral left or bilateral pallidotomy, though at least one patient with a right pallidotomy displayed a deficit in verbal fluency. The fact that the left putamen maintains some level of activity even in the silent version of a verbal fluency task suggests that clinical deficits in verbal fluency seen after natural and surgical lenticular injury may in part be related to impaired functioning of task components at higher order processing levels, rather than at purely motor levels of processing, at least on the left. The asymmetry in thalamic and putaminal activation (left greater than right) is also consistent with the clinical data indicating that language difficulties arising from subcortical lesions involving putamen occur predominantly with left-sided lesions (Weiller et al., 1993; Mega & Alexander, 1994; Chung et al., 1996).

With respect to thalamic involvement in this task, it may be noted that deficits in word retrieval have also been noted with thalamic stimulation (Ojemann et al., 1971; Ojemann & Ward, 1971; reviewed by Johnson & Ojemann, this issue), primarily in ventrolateral nucleus. Consistent with the high levels of activation seen in our patients in the overt task, thalamic stimulation on either side could produce speech arrest. However, as Johnson and Ojemann point out, the stimulation data indicate that language-specific effects, such as misnaming, can only be produced after left-sided stimulation. Again, the asymmetry in thalamic activation in the stem completion task is consistent with these stimulation data.

Because these results are from a larger set of studies looking at various methodological issues, the set of data available for this analysis is relatively small. The size of this dataset does not allow for analysis of certain issues, such as possible differences across genders. In these data, no significant differences in activation were found across gender. It is also possible that some effects not seen, such as an interaction among hemisphere, condition, and time in the thalamus, would be found with a larger study. Nevertheless, these
results demonstrate the type of results achievable with fMRI and are consistent with other imaging data studying language function.

In summary, reliable activations during overt speech without excessive noise can be elicited using functional MRI. Comparison with the same task in the silent condition reveals both differences and similarities in activation across conditions in cerebral cortex and in subcortical structures. Consistent with lesion studies, regions in the thalamus and putamen are activated by this word retrieval task. Though the levels of activation in both thalamic regions correlate somewhat with those in motor cortex across the silent and overt conditions, there is also an asymmetry in activation which may reflect connections with dorsolateral frontal cortex. Whereas the thalamus showed a symmetric decrease in activation in the silent compared with the overt condition, putamen was also more active in the overt condition, but showed a larger decrease in activity on the right than on the left in the silent compared with the overt condition. This suggests that the left putamen may play a unique role relative to the right in the processing of this word retrieval task. The subcortical activations on the silent condition are consistent with multiple interpretations, including higher order processing aspects of word retrieval or subtle motor movements being processed in these subcortical regions. Further studies more specifically addressing this issue need to be performed. The ability to achieve robust activation of cortical and subcortical structures in silent and overt language processing demonstrates that fMRI can be a very useful tool for elucidating the role of these structures in language processing.

REFERENCES


