Activity in the Paracingulate and Cingulate Sulci during Word Generation: An fMRI Study of Functional Anatomy

The supracallosal medial frontal cortex can be divided into three functional domains: a ventral region with connections to the limbic system, an anterior dorsal region with connections to lateral prefrontal systems, and a posterior dorsal region with connections to lateral motor systems. Lesion and functional imaging studies implicate this medial frontal cortex in speech and language generation. The current functional magnetic resonance imaging (fMRI) study of word generation was designed to determine which of these three functional domains was substantially involved by mapping individual subjects’ functional activity onto structural images of their left medial frontal cortex. Of 28 neurologically normal right-handed participants, 21 demonstrated a prominent paracingulate sulcus (PCS), which lies in the anterior dorsal region with connections to lateral prefrontal systems. Activity increases for word generation centered in the PCS in 18 of these 21 cases. The posterior dorsal region also demonstrated significant activity in a majority of participants (16/28 cases). Activity rarely extended into the cingulate sulcus (CS) (3/21 cases) when there was a prominent PCS. If there was no prominent PCS, however, activity did extend into the CS (6/7 cases). In no case was activity present on the crest of the cingulate gyrus, which is heavily connected to the limbic system. Thus, current findings suggest that medial frontal activity during word generation reflects cognitive and motor rather than limbic system participation. The current study demonstrates that suitably designed fMRI studies can be used to determine the functional significance of anatomic variants in human cortex.

For some time, it has been known that the medial frontal cortex in primates plays a role in the initiation of vocal communication. For monkeys, lesion studies (Sutton et al., 1974; Aitken, 1981) and electrical stimulation studies (Sloan and Kaada, 1953; Robinson, 1967; Jürgens and Ploog, 1970) have implicated anterior cingulate cortex in instrumental and spontaneous vocalization. Although these studies have primarily involved Brodmann’s (1909/1994) area 24 anterior and superior to the genu of the corpus callosum, the upper and lower banks of the cingulate sulcus above the body of the corpus callosum have also been implicated (Sloan and Kaada, 1953; Robinson, 1967).

It has been clear which parts of the human medial frontal cortex are involved in the initiation of speech and language. For example, patients with medial frontal lesions present with akinetic mutism, a syndrome in which little or no spontaneous spoken language is initiated (Nielson and Jacobs, 1951; Barris and Schuman, 1953). The global nature of the initiation deficit suggests the contribution of the medial frontal cortex to initiation is not limited to the language domain. Although lesions in this syndrome frequently impinge upon the anterior cingulate gyrus and/or supplementary motor area (SMA), they are rarely confined to a single region (e.g. Barris and Schuman, 1953; Jonas, 1981; Tijssen et al., 1984), leaving some doubt about which structures are necessary for the initiation of speech and language.

Early and recent positron emission tomography (PET) studies pointed to the anterior cingulate cortex as important in language generation. This cortex (see Fig. 1) includes both the liminal cortex in Brodmann’s area 24 (24a and 24b) and the paralimbic cortex in Brodmann’s area 32 (Petersen et al., 1988; Frith et al., 1991a,b; Paus et al., 1993; Herholz et al., 1996). However, three recent studies by Warburton et al. (1996) indicated activity during word generation was centered in the paracingulate sulcus (PCS), which runs parallel and dorsal to the cingulate sulcus (CS), or even above the PCS in the anterior portion of medial Brodmann’s area 6, recently called pre-SMA (Luppino et al., 1993; Matsuzaka et al., 1992; Picard and Strick, 1996).

Although centered in or above the PCS, the medial frontal activity in Warburton and colleagues’ studies seems to occupy both medial Brodmann’s areas 6 and 32. In a meta-analysis of ‘effortful versus automatic speech’ from previous PET studies, Paus et al. (1996a) found activity clusters in both the PCS and the CS. Thus, one unresolved question regarding the role of the medial frontal cortex in language generation relates to location on the superior to inferior dimension. Unlike lesion (Aitken, 1981; Sutton et al., 1974) and stimulation (Jürgens and Ploog, 1970; Robinson, 1967; Sloan and Kaada, 1953) studies of monkey vocalization, which implicate the cingulate cortex just rostral to the genu of the corpus callosum, these functional imaging studies of human language generation generally have involved the medial frontal cortex superior to the corpus callosum.

Precision in anatomic localization has further suffered from complications of the group averaging techniques used in these PET studies (Nadeau and Crosson, 1995; Steinmetz and Seitz, 1991). Specifically, the studies discussed above performed substantial smoothing of images to compensate for individual differences in structural and functional anatomy, deformed images into a common atlas space (Talairach and Tournoux, 1988) and performed group statistics on a voxel-by-voxel basis. One problem with this technique is that activity peaks across individual subjects do not lie in exactly the same position in atlas space. Thus, activity peaks for the group do not necessarily correspond to activity peaks for individual subjects. A related problem is the use of a brain atlas constructed from a single subject. Individual variations in presence or absence and location of anatomic structures occur. Group analyses are affected by these variations, but information about anatomic variations and their relationship to functional activity is lost during group averaging. Indeed, such anatomi cal variations are quite evident for the medial frontal cortex (Vogt et al., 1995; Paus et al., 1996a).

These data indicate some ambiguity regarding the location of supracallosal medial frontal activity during language generation, and the variation in medial frontal anatomy between individuals suggests that medial frontal activity during language generation should be mapped in individual subjects. In the present study, we have used functional magnetic resonance imaging (fMRI;
we know about the structure and connectivity of the medial frontal cortex studied in this investigation. The vertical lines represent planes perpendicular to the AC–PC line through the rostral-most point of the genu of the corpus callosum (vgcc), the posterior margin of the anterior commissure (vac) and the posterior commissure (vpc). Segments of the PCS (above) and the CS (below) are unfolded to show the cortex buried within each sulcus. Brodmann’s area 24 can be divided into subareas. From ventral to dorsal, areas 24a and 24b are on the crest of the cingulate gyrus, and area 24c is on the ventral bank of the cingulate sulcus. Area 32 occupies the gyrus between the CS and the PCS. Above the PCS, area 6aβ of Vogt and Vogt (1919) corresponds to pre-SMA. A portion of medial area 8 also may lie behind the vgcc and above the PCS. Area 6a6 of Vogt and Vogt corresponds to SMA proper.

Bandettini et al., 1993) and a word generation task which robustly activates the medial frontal cortex across individual subjects to map functional activity onto high resolution anatomic images (MRI) of individual brains. Activity was mapped into medial frontal regions above, below and within the CS and into subregions above, below and within the PCS when the latter was prominent (per Paus et al., 1996a). We have further divided the regions around the CS into anterior and posterior divisions at the anterior commissure, as recommended by Picard and Strick (1996). The findings, when considered in the context of what we know about the structure and connectivity of the medial frontal cortex, are illuminating regarding the role of the medial frontal cortex in language generation.

Materials and Methods

Subjects

Twenty-eight students, faculty or staff at the University of Florida or residents of Gainesville, FL (15 male, 13 female) participated. Ages ranged from 19 to 50 years (mean = 26.4, SD = 7.1); education ranged from 13 to 20 years (mean = 16.9, SD = 2.0). All subjects spoke English as a native language and were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects gave written informed consent in accordance with a protocol approved by the Health Center Institutional Review Board at the University of Florida.

Word Production Task

The task used for mapping medial frontal activity in individual subjects was a free generation task. Subjects heard a single semantic category and silently generated as many exemplars as possible during a 17.5 s task period. After the category was given, subjects were given the cue ‘begin’ to start generation of category exemplars. No further auditory stimuli were given until the end of the 17.5 s period when the cue ‘end’ informed subjects to cease generating words. At this point, a 17.5 s rest period commenced during which no auditory stimuli were given. Periods of free generation were alternated with periods or rest. During 17.5 s rest periods, subjects were discouraged from thinking any words to them- selves. One of three lists of six categories was used for the free generation of each subject. Examples of categories are ‘farm animals’, ‘weather events’ and ‘tools’.

The free generation task was given during scanning sessions in which subjects performed three other language production tasks that were not used for analyses presented herein. Since only free generation consistently produced medial frontal activity increases for individual subjects that met criteria discussed below, free generation was used exclusively to perform the current mapping study. For this reason, other language tasks are not discussed here, but results are presented elsewhere (e.g. Sadek et al., 1999).

Stimulus Presentation

An experimental run consisted of 6.4 cycles of rest-task alternation, taking 224 s for the entire run. The average rate of word production for free generation was 10.0 words per 17.5 s half cycle (60 words per experimental run), as determined by a pilot study with different subjects which was run outside the scanner prior to the current experiment and during which subjects spoke responses aloud. Each scanning run began and ended with a rest period. All word production was accomplished silently to avoid image artifacts created when subjects speak during scanning. Silent language production has been used successfully in previous functional neuroimaging studies (Herholz et al., 1996; Martin et al., 1996; Warburton et al., 1996). The order of presentation between free generation and the other three language production tasks was randomized. The three lists of categories were randomly assigned to free generation and two of the other production tasks for each subject; thus, all three lists were used for different subjects in the free generation task.

Word lists were presented using an IBM 380ED notebook computer using specially written software. Output from the computer was amplified using a Kenwood KR-A4070 amplifier and biased toward the high end of the frequency spectrum using a Realistic 31-2005 Ten Band Stereo Frequency Equalizer to compensate for high frequency loss through the air conduction apparatus. A JBL 244J 16 ohm speaker was attached to an insulated air conduction transducer. Foam insert earphones were positioned in the external auditory meatus as the final link in the air conduction transducer. These foam inserts attenuate scanner noise by −20 dB sound pressure level (Binder et al., 1995). Before beginning experiments, words were played above threshold while the scanner was operating, and sound levels were reduced until target words in a list could no longer be distinguished. Then stimuli were delivered at 30–35 dB above threshold.

Image Acquisition

Functional, structural and angiographic images were acquired on a GE 1.5T Sigma scanner using a dome-shaped quadrature radio frequency head coil. T1-weighted axial scout scans were acquired to determine location of sagittal functional images. To ensure optimal coverage of the medial frontal cortical surface, head alignment in the coil was adjusted, if necessary, such that the interhemispheric fissure was within 1° of vertical. The most medial sagittal slice for functional images was placed such that the most medial edge of the slice corresponded with the medial boundary of the left hemisphere. Care was taken not to include any of the medial surface of the right hemisphere; careful inspection of the position of functional images indicated that little if any cortex on the medial surface of the left hemisphere was excluded. Nine slices (6.4–6.9 mm thick) covered the entire left hemisphere. Before functional images were acquired during task presentation, a time-of-flight MR angiogram (TE = 6.6 ms, TR = 40 ms, FA = 60°, FOV = 18 cm, matrix = 256 × 192) was acquired with exactly the same nine slices used for functional images. In this way functional images could be overlaid onto MR angiogram slices to ascertain the existence of large vessel effects. For functional scans, a series of 64 images was acquired for each of the nine sagittal slices using a gradient echo spiral scan technique (Macowksi, 1985; King et al., 1995; Noll et al., 1995) with TE = 40 ms, TR = 870 ms, FA = 45°, FOV = 18 cm.
matrix size = 128 × 128, four subfields. Subsequent to functional imaging runs, structural images were acquired for 124 × 1.3 mm thick sagittal slices, using a 5-D spoiled GRASS volume acquisition (TE = 7 ms, TR = 27 ms, NEX = 1, FON = 24 cm, matrix size = 256 × 192).

Image Analysis

Images were analyzed on a Silicon Graphics O2 workstation using AFNI software from the Medical College of Wisconsin (Cox, 1996), a program developed to exclude voxels where amplitude of signal change was above a preset criterion, and Location of Functional Activity (LOFA) software developed by the authors to locate activity relative to sulci or other anatomical structures (Gokcay et al., 1998).

To reduce effects of head motion, images from each run were spatially registered in-plane to a base image using an iterative linear least squares approach (Keren et al., 1988). The last image of the last functional imaging run was selected as the base image because its acquisition immediately preceded acquisition of the anatomic images on which the functional images were overlaid. Prior to analysis, time series were examined for artifact caused by residual motion not corrected by this procedure or by other sources. Data from two subjects were not included with the 28 subjects reported here because of artifact.

All voxels in which the SD of acquired time series exceeded 5% of the mean signal (i.e. SD/mean signal intensity ≥ 0.05) were set to zero to minimize large temporal effects downstream from activity changes or other sources of artifact such as slight motion near boundaries. Using AFNI, the time series (64 images) within each voxel of functional scans was correlated with ideal, sinusoidal reference waveforms. These ideal waveforms were time-locked to the alternating periods of rest and task performance. Nine phase-shifted waveforms were used to compensate for the temporal offset between slices during acquisition. Reference waveforms reached a peak between 7.0 and 14.0 s after task onset to allow for hemodynamic response time. The highest correlation between the multiple reference waveforms and the acquired time series was the functional intensity for each voxel. Each functional and anatomic image was converted to 1 mm3 voxels and deformed into atlas space (Talairach and Tournoux, 1988) to minimize large vessel effects downstream from activity changes or other sources of artifact such as slight motion near boundaries. Using AFNI, the time series were examined for artifact caused by residual motion not corrected by this procedure or by other sources. Data from two subjects were not included with the 28 subjects reported here because of artifact.

Prior to analysis, time series were examined for artifact caused by residual motion not corrected by this procedure or by other sources. Data from two subjects were not included with the 28 subjects reported here because of artifact.

And posterior-most points in the brain. No smoothing of images was performed.

The two investigators disagreed on the number of subjects with activity within, above or below gaps was included in our analyses. The ROI above the CS, the corpus callosum and posterior to the AC was the posterior-superior (post. sup.) region. (5) The ROI within the CS and anterior to the AC was the anterior-superior (anti-super.) region. (6) The ROI below the CS, the corpus callosum and anterior to the AC was the posterior-cingulate gyrus (post. cing. gyrus) region. Contiguous clusters of activity with a product moment correlation of 0.50 or greater (P < 0.001) and a total volume of 25 µl or greater (i.e. at least two acquisition voxels) were identified using the cluster option in AFNI. A small volume of 25 µl was chosen because it was recognized that a single volume of significant activity was likely to be divided between two or more ROIs, resulting in two smaller volumes of activity. In such instances, we wished both ROIs to be represented in analyses.

Next, two statistical analyses were performed. First, the number of subjects with activity meeting the above criterion in each region was tallied, and the presence versus absence of activity was compared between pairs of regions using a 2 × 2 chi-square test (Siegel, 1956). Second, for regions where ≥ 50% of the subjects showed some activity, the percentage of activity was compared using a t-test.

The ant. sup. region was divided into subregions based upon the tracing of the PCS. Identification of the PCS was more difficult than identification of the CS. We elaborated upon Paus and colleagues’ (1996a) criteria to identify a prominent PCS as follows: the PCS must be parallel to the CS and at least 20 mm in length. A clearly defined horizontal element dorsal to the CS must be present and at least 15 mm in length, excluding vertically oriented branches. Segments with activity below gaps was included in our analyses. The PCS was not traced across gaps. Occasionally, the most inferior portion of a separate vertical segment was included in tracings if the above criteria were met since such elements were defined as a part of the PCS by Paus et al. (1996a). Since sulci were not traced across gaps (as defined above), no activity within, above or below gaps was included in our analyses. The PCS was traced from medial to lateral as long as it was prominent (a minimum depth of 7 mm and a maximum depth of 10 mm). PCs which were merely present but not prominent (Paus et al., 1996a) could not be traced sufficiently to form the ROIs and were not included in our analyses.

Finally, the PCS was traced from medial to lateral as long as it was prominent (a minimum depth of 7 mm and a maximum depth of 10 mm). PCs which were merely present but not prominent (Paus et al., 1996a) could not be traced sufficiently to form the ROIs and were not included in our analyses. Usually, the PCS ended before reaching the posterior border of the ant. sup. ROI (i.e. the AC plane). In instances where the PCS did not reach the posterior or anterior border of the ant. sup. region, the respective border of the subregion was defined as the termination point of the PCS. Since the resulting subregions were derived from the ant. sup. region, the anterior border of the subregion was always at or caudal to the vertical plane through the rostral-most point of the genu of the corpus callosum. Although this division may assign a variable and undetermined amount of the posterior portion of medial area 8 to the subregion above the PCS, evaluation of various renderings of medial frontal anatomy (Brodmann, 1909/1914; Talairach and Tournoux, 1988; Vogt et al., 1995) suggests the main constituent of this subregion to be the rostral portion of medial area 6, i.e. pre-SMA. In order to ensure reliability in assessing the presence or absence of a prominent PCS, two investigators familiar with the criteria (J. R. S. and J. A. B.) independently rated PCs on this dimension. On those PCs where these two investigators disagreed, the two investigators met with the senior author and jointly resolved the disagreement according to the criteria.

Once the PCS was traced, it was ‘thickened’ to 3 mm on either side of the sulcus to encompass the cortex within the PCS. Since the PCS was confined almost exclusively to the ant. sup. region, this region was subdivided into three subregions. The first subregion above the PCS was called the pre-SMA+ subregion since pre-SMA was its main constituent. The ROI within the PCS was called the PCS subregion.
Figure 2. Activity and regions for a single subject. Within each region, red indicates significant activity (product moment correlation $\geq 0.50$, volume $\geq 25 \mu l$); blue highlights the rest of the region. (a) Sagittal anatomy of the subject 3 mm to the left of midline. (b) All significant medial frontal activity for this subject on the same slice as (a). (c) Coronal slice for this subject through the CS and PCS 12 mm rostral to the AC, with activity shown. (d) Anterior-superior region. (e) Posterior-superior region. (f) Anterior cingulate sulcus region. (g) Posterior cingulate sulcus region. (h) Anterior cingulate gyrus region. (i) Posterior cingulate gyrus region. (j) Pre-SMA+. (k) Paracingulate sulcus (PCS). (l) Paracingulate gyrus (PCG).
The ROI between the PCS and the CS was the paracingulate gyrus (PC gyrus) subregion. Figure 2j–l shows examples of these subregions in a single subject. As with the analysis of activity around the CS, contiguous clusters of activity with a product moment correlation of 0.50 or greater and a total volume of 25 µl or greater were identified within each subregion. As before, two statistical analyses were performed. First, the number of subjects with activity meeting the above criterion in each subregion was tallied, and the presence versus absence of activity was compared between pairs of subregions using a 2 × 2 chi-square test. Second, for subregions where >50% of the subjects showed some activity, the percentage of the subregion showing activity was compared using a t-test.

After the above analyses had demonstrated that many subjects had activity within the PCS, activity on the dorsal versus the ventral bank of the sulcus was determined, using the PCS to split the PCS subregion into an anterior and a superior component. The same statistical analyses as described above were used to compare activity on the dorsal versus the ventral bank of the PCS. Finally, the presence versus absence of significant activity in the CS was compared for subjects with and without a prominent PCS using a 2 × 2 chi-square test.

In order to ensure reliability of tracings, a randomly selected subset of tracings (n = 10) was drawn by a second operator (J.R.S.) trained by the first operator. The volume of significant activity within each region and subregion was correlated for the two operators to yield indices of reliability.

**Results**

In rating the presence or absence of the PCS, the two raters agreed on 24/28 cases (86%). After resolving the four instances of disagreement, the PCS was rated as prominent in 21/28 cases (75%). Table 1 presents the correlations for the volumes of significant activity contained within the various regions and subregions that were derived from the tracings of the two operators on 10 randomly selected cases. It can be seen that these correlations were quite high, indicating adequate reliability of the tracings.

**Analysis of Regions around the CS**

Table 2 displays the number of subjects with significant activity in each region. Among the anterior regions, more subjects showed significant activity in the ant. subregion than either the ant. CS region ($\chi^2 = 19.50$, df = 1, $P < 0.001$) or the ant. cing. gyrus region ($\chi^2 = 44.87$, df = 1, $P < 0.001$). More subjects showed significant activity in the ant. CS region than in the ant. cing. gyrus region ($\chi^2 = 8.47$, df = 1, $P < 0.01$). Among the posterior regions, more subjects showed significant activity in the post. sup. subregion than either the post. CS region ($\chi^2 = 16.56$, df = 1, $P < 0.001$) or the post. cing. gyrus region ($\chi^2 = 19.69$, df = 1, $P < 0.001$). Among anterior–posterior pairs of regions, more subjects showed significant activity in the ant. subregion versus the post. sup. region ($\chi^2 = 7.71$, df = 1, $P < 0.01$); more subjects showed activity in the ant. CS versus the post. CS region ($\chi^2 = 5.97$, df = 1, $P < 0.05$). No other differences were significant.

Another way to compare regional differences in activity is to examine differences in volume of activated voxels. Only the ant. sup. and post. sup. regions demonstrated significant activity for >50% of the subjects. Since the distance between the genu of the corpus callosum and the anterior commissure was invariably greater than the distance between the anterior commissure and the posterior commissure, the ant. sup. region was invariably larger than the post. sup. region in every subject. In order to equate the regions for size, the percentage of the total region occupied by significant activity was used for comparison. A conservative test of the activity difference between these two regions is to compare only those subjects with activity in both. When only those subjects demonstrating significant activity in both regions (n = 16) were considered, a significantly greater percentage of the ant.-sup. region (5.9%) than the post.-sup. region (2.6%) showed significant activity ($t = 2.83$, df = 15, $P < 0.05$).

**Analysis of Subregions around the PCS**

As noted above, a prominent PCS was present in the ant.-sup. region for 21 of the 28 subjects. For these cases, it was desirable to know the location of activity in the ant.-sup. region relative to the PCS since the PCS could provide an important landmark for functional activity in the medial frontal cortex. Table 3 presents the number of subjects with significant activity in pre-SMA+ (dorsal to PCS), PCS and the paracingulate gyrus (PC gyrus) (ventral to PCS). Activity was present within the PCS for a clear majority of cases (18/21). Although a number of cases also had activity above the PCS in pre-SMA+, there was a significant difference in the number of subjects with activity in the PCS versus pre-SMA+ ($\chi^2 = 4.01$, df = 1, $P < 0.05$). Further, significantly more subjects had activity in the PCS than in the PC gyrus ($\chi^2 = 15.84$, df = 1, $P < 0.001$). There was no significant difference in the number of subjects with activity in pre-SMA+ and in the PC gyrus. It should be noted that the PC gyrus was located between two ‘thickened’ sulci and was frequently rather narrow. This narrowness may contribute to the somewhat low number of subjects with significant activity in PC gyrus.

In this analysis of subregions, only pre-SMA+ and the PCS demonstrated significant activity for >50% of the subjects. Eleven subjects had activity in both pre-SMA+ and the PCS during word generation. For these subjects, the PCS (20.2%) showed a

### Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>Anterior (no. of subjects)</th>
<th>Posterior (no. of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior</td>
<td>26/28</td>
<td>16/28</td>
</tr>
<tr>
<td>Cingulate sulcus</td>
<td>9/28</td>
<td>1/28</td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>0/28</td>
<td>0/28</td>
</tr>
</tbody>
</table>

*All values or all but one value for both raters were zero; therefore, correlation was not appropriate.*

### Table 2

<table>
<thead>
<tr>
<th>Region</th>
<th>Significant activity ($\geq 0.50$, volume $\geq 25$ µl) in regions around CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior</td>
<td>Anterior</td>
</tr>
<tr>
<td>PCS</td>
<td>28/28</td>
</tr>
<tr>
<td>Anterior cingulate gyrus</td>
<td>0/28</td>
</tr>
<tr>
<td>Anterior cingulate sulcus</td>
<td>0/28</td>
</tr>
<tr>
<td>Posterior cingulate sulcus</td>
<td>0/28</td>
</tr>
</tbody>
</table>

*Volume $\geq 25$ µl is presented.*
significantly greater percentage of activation than pre-SMA+ (6.5%) ($t = 3.58$, $df = 10$, $P < 0.005$). Table 4 shows the raw volumes of significant activity in pre-SMA+, PCS and PC gyrus, as well as the percent of these regions with voxels showing significant activity for each subject with a prominent PCS. Of three subjects showing no activity in any of these subregions, subject 113 had absolutely no medial frontal activity, while subjects 104 and 112 had activity in the ant.-sup. region which was parsed in such a way that no volume greater than 25 µl occupied any of the three subregions.

**Activity on the Dorsal versus Ventral Bank of the PCS**

The volume of significant activity in dorsal and ventral banks of the PCS was calculated as described above. There was no significant difference in the number of subjects showing activity on the dorsal (16/21) versus the ventral (15/21) bank of the sulcus. However, for subjects with activity on both the upper and the lower bank ($n = 14$), the percent of activity on the dorsal bank (26.2%) was greater than that on the ventral bank (14.3%) ($t = 2.84$, $df = 13$, $P < 0.05$).

**Activity in the CS for Subjects without a PCS**

For subjects without a prominent PCS in the left hemisphere (Fig. 3), 6/7 (86%) had significant activity in the CS, while for subjects with a prominent PCS only 3/21 (14%) had significant activity in the CS. This difference is significant ($\chi^2 = 9.22$, $df = 1$, $P < 0.01$). Six of seven subjects without a prominent PCS also had significant activity in the ant.-sup. region, which was similar to the proportion of subjects with a PCS who had significant activity in the ant.-sup. region.

**Discussion**

The medial frontal cortex above the corpus callosum can be divided on the superior-inferior and anterior-posterior dimensions (Fig. 1). The CS is present in all normal brains. The division between areas 24 and 32 usually occurs within the CS, though the location within the CS may vary (Vogt et al., 1995). The PCS is prominent in the majority of brains, though it is absent or not well defined in a significant number. Above the corpus callosum, the PCS is thought to contain the border between area 32 and medial area 6 (Paus et al., 1996a), and it probably separates area 32 from areas 8 and 9 anterior to area 6. In the medial frontal cortex above the corpus callosum, there is an inferior-to-superior transition from the limbic cortex on the crest of the cingulate gyrus (areas 24a and 24b) (Kunishio and Haber, 1994) to the true neocortex with premotor functions in area 6. The posterior part of medial area 6 has been designated as the supplementary motor area (SMA) proper; the anterior part as the pre-supplementary motor area (pre-SMA) (Matsuzaka et al., 1994; Picard and Strick, 1996). The SMA is connected with the motor cortex and the spinal cord, and the pre-SMA is connected to the lateral prefrontal cortex and lateral premotor areas (Barbas and Pandya, 1987; Bates and Goldman-Rakic, 1993; Lu et al., 1994; Luppino et al., 1993; Picard and Strick, 1996). Cingulate motor areas which have connections similar to the SMA and pre-SMA can be defined within the CS of monkeys (Hutchins et al., 1988; Dum and Strick, 1991; He et al., 1995; Picard and Strick, 1996). The human equivalent of monkey cingulate motor areas appears to lie in supracallosal area 32, but may extend into supracallosal area 24 within the CS (Picard and Strick, 1996; Fink et al., 1997). The medial frontal cortex anterior to the anterior commissure (AC) is involved in initiation of complex motor activities, including word generation, and the cortex posterior to the AC is involved in the initiation of simple motor activities, including repetition of words (Picard and Strick, 1996). The previous literature on the medial frontal cortex and language has left some ambiguities regarding the area(s) of the medial frontal cortex involved in speech and language initiation, and it has not taken individual variations in gross structural anatomy (i.e. the presence of a prominent PCS) into account.

We have used fMRI to map functional activity in the supracallosal medial frontal cortex during the generation of as many words as possible from various semantic categories. Maps

---

**Table 4**

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Pre-SMA+</th>
<th>PCS</th>
<th>PC gyrus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw volume of significant activity (µl)</td>
<td>Percent of region with significant activity</td>
<td>Raw volume of significant activity (µl)</td>
<td>Percent of region with significant activity</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
<td>-----</td>
<td>----------</td>
</tr>
<tr>
<td>104</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>106</td>
<td>75</td>
<td>4</td>
<td>220</td>
</tr>
<tr>
<td>107</td>
<td>67</td>
<td>6</td>
<td>81</td>
</tr>
<tr>
<td>108</td>
<td>0</td>
<td>0</td>
<td>82</td>
</tr>
<tr>
<td>110</td>
<td>93</td>
<td>2</td>
<td>245</td>
</tr>
<tr>
<td>112</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>113</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>114</td>
<td>438</td>
<td>8</td>
<td>491</td>
</tr>
<tr>
<td>115</td>
<td>150</td>
<td>21</td>
<td>96</td>
</tr>
<tr>
<td>116</td>
<td>0</td>
<td>0</td>
<td>251</td>
</tr>
<tr>
<td>117</td>
<td>0</td>
<td>0</td>
<td>148</td>
</tr>
<tr>
<td>202</td>
<td>0</td>
<td>0</td>
<td>123</td>
</tr>
<tr>
<td>203</td>
<td>270</td>
<td>7</td>
<td>816</td>
</tr>
<tr>
<td>204</td>
<td>201</td>
<td>9</td>
<td>181</td>
</tr>
<tr>
<td>205</td>
<td>0</td>
<td>0</td>
<td>150</td>
</tr>
<tr>
<td>213</td>
<td>101</td>
<td>3</td>
<td>736</td>
</tr>
<tr>
<td>216</td>
<td>97</td>
<td>3</td>
<td>200</td>
</tr>
<tr>
<td>217</td>
<td>0</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>219</td>
<td>74</td>
<td>6</td>
<td>103</td>
</tr>
<tr>
<td>220</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>221</td>
<td>47</td>
<td>2</td>
<td>62</td>
</tr>
</tbody>
</table>

All clusters in each region with volumes of activity < 25 µl were set to zero.
Figure 3. Sagittal sections showing the CS region for a subject without a PCS (a–c) and a subject with a PCS (d–f). Sections are at a similar depth in the CS 5 mm to the left of midline for the top subject and 7 mm to the left of midline for the bottom subject. The subject with a PCS is the same subject shown in Figure 2, at a slightly different sagittal plane. Sections show anatomy with no overlay for activity (a and d), with all significant medial frontal activity at that level shown (b and e) and with the CS region shown (c and f). Red indicates significant activity (product moment correlation ≥ 0.50, volume ≥ 25 µl); blue highlights the rest of the region. These two subjects are prototypical of findings in this study in that the subject without a PCS shows activity in the CS and the subject with a PCS shows activity in the PCS but not the CS.
for individual subjects were segmented according to location with respect to the CS and the PCS. The resulting regions around the CS were further divided into anterior and posterior subdivisions using the coronal plane through the AC. The PCS was prominent in 21/28 of our subjects, and when the PCS was prominent, activity changes in the medial frontal cortex during word generation centered on the PCS (18/21 subjects). Although activity was found on both the dorsal and ventral banks of the PCS, the volumes of activity were larger on the dorsal than on the ventral bank. In many cases, activity changes were also present dorsal and/or ventral to the PCS. Occasionally, activity extended into the CS, but activity was never seen below the CS in the cingulate gyrus. Thus, the cortex in and around the PCS was reliably involved in word generation. Activity also was frequently present in the region posterior to the PCS and above the CS (16/28 subjects). When the PCS was not prominent, activity was almost always present within the CS, as well as above the CS in the ant.-sup. region. The implications of these findings for subjects with a prominent PCS are as follows:

(1) Although activity during word generation occasionally extended into the CS, it never extended into the cingulate gyrus. Thus, the supracallosal medial frontal cortex most heavily connected to the limbic system (e.g., Kunishio and Haber, 1994) did not show any activity increases for word generation in the current paradigm. In this regard, it should be noted that the emotional content of the categories we presented was relatively neutral; further, no attempts were made to enhance subjects' motivation to generate words. However, preliminary analyses from another fMRI study we just completed suggest that generation of words with emotional connotations is not accompanied by extension of activity into the cingulate gyrus during word generation.

(2) Anterior to the AC and posterior to a plane through the genu of the corpus callosum, the region dorsal to the CS can be divided into subregions by the PCS. In the vast majority of our cases where a prominent PCS was identified, activity was located within the PCS, and to lesser degrees above and below the PCS. There was some tendency for greater volumes of activity to be located on the dorsal versus the ventral bank of the PCS. Thus, based on what we know about medial frontal anatomy, the activity during word generation appeared to center on the border between supracallosal area 32 on the one hand and pre-SMA (and perhaps posterior area 8 at times) on the other, with some activity present on both sides of the border but biased towards the dorsal side. This finding confirms results of the meta-analysis of Picard and Strick (1996), who located peak activity from group studies of speech in this general region of the Talairach atlas. It is also consistent with a similar meta-analysis by Paus et al. (1996a), who found activity in their probabilistic map of the PCS for studies of 'effortful versus automatic speech' tasks. However, in contrast to the meta-analysis of Paus et al., we did not find much activity in the CS or in the cingulate gyrus as long as the subjects had a prominent PCS. It is possible that findings of activity in or near the CS in previous studies result from inclusion of a significant number of subjects without a prominent PCS. When there is no prominent PCS, our findings indicate that significant activity is almost always found in the CS. It also should be noted that a few studies of complex language have shown activity at or just anterior to the coronal plane through the anterior-most point of the genu of the corpus callosum (Pardo et al., 1990; Paus et al., 1993; Klein et al., 1995).

Although this region was not included in our analyses, a review of our data revealed that activity was not generally located there for individual subjects. Only 10/28 subjects showed activity at or anterior to this plane in the medial frontal cortex, and the most common location of this activity was at the frontal pole. The lack of activity at or just anterior to the plane through the anterior-most point of the genu of the corpus callosum is generally consistent with the majority of language production studies reviewed by Picard and Strick (1996).

In short, our findings indicate that the cortex within the PCS, and to some extent dorsal and ventral to the PCS, contributes to language generation. Based on the analysis of Paus et al. (1996a), this cortex appears to include portions of supracallosal area 32, pre-SMA (i.e. area 6α of Vogt and Vogt [1919]), and at times a portion of caudal medial area 8. Since these areas are connected to the lateral prefrontal cortex, their function most likely relates to the initiation of cognitive processes related to generating the words. This interpretation is consistent with the meta-analysis of Picard and Strick (1996), who noted that simple speech activities like repetition tend to activate SMA while more complex speech/language activities like word generation tend to activate pre-SMA. It is also consistent with recent data from our laboratory (Crosson et al., 1998) which indicate that medial frontal activity during word generation is anterior to the AC when the effects of repetition are removed. With respect to the contrasting roles of cortex in the CS and the PCS, our findings also are consistent with the observations of Paus et al. (1996b) who noted a right→left asymmetry in volume for the CS and a left→right asymmetry for the PCS. Given left-hemisphere lateralization for language, these asymmetries would imply a greater importance for cortex in the PCS than the CS for language.

(3) The PCS usually does not extend posterior to the AC. The region above the CS that lay between the AC and the coronal plane through the posterior commissure also frequently demonstrated increased activity during word generation, though somewhat less frequently than the more anterior region. Based upon the analysis of Vogt et al. (1995), the superior portion of this region contains SMA, and the more inferior segment contains a portion of supracallosal area 32. In their meta-analysis, Paus et al. (1996a) did not demonstrate increased activity in this region for 'effortful versus automatic' speech. Likewise, activity peaks in this region were not found in the Picard and Strick (1996) meta-analysis for complex 'speech' activities such as word generation but were found for simple 'speech' activities such as word repetition. These discrepancies are easily explained. Paus et al. used studies which compared activity during 'effortful versus automatic' speech. To the degree that automatic speech activates the SMA, as Picard and Strick's (1996) analysis indicated, it would have been excluded from analyses where automatic speech was used as a control activity. Petersen et al. (1988) demonstrated activity in SMA during repetition. We have found a similar area of activity during repetition (Crosson et al., 1998). Picard and Strick used a number of different types of analyses and mapped only the peaks of activity from PET studies. Some of the latter studies overlapped with the Paus et al. meta-analyses, and these other studies may have excluded SMA activity when repetition or automatic speech was used as a control task for word generation. In other studies, activity which demonstrated a peak in the pre-SMA region might have extended into the SMA, but since the peak was in the pre-SMA, activity in the SMA would not have been recorded in the meta-analysis. Indeed, when activity is present in both the ant. sup. and post. sup. regions in our study, 14/16 cases demonstrated higher peak correlation values in the ant. sup. than the post. sup. region (P < 0.005). Further, activity in the
post. sup. region in our subjects was generally quite close to the coronal plane through the AC, as predicted by the meta-analysis of Picard and Strick (1996). The average distance of peak activity in the post. sup. region from this plane is 3.8 mm (SD = 3.5) for those subjects who have activity in the region. Finally, when we have combined data across individuals in the free generation task used in this study (Crosson et al., 1998; Sadek et al., 1999), we have seen one large region of medial frontal activity extending from the SMA to the pre-SMA. We conclude that SMA activity is needed both for automatic speech output during tasks like word repetition and for complex language output during tasks like word generation. This SMA participation undoubtedly relates to preparing for the execution of the motor activity necessary for verbal expression.

One caution should be mentioned in generalizing from the current results. Data were acquired with the long dimension of our voxels (6.4–6.9 mm) extending across the width of the acquisition plane, i.e. perpendicular to the sagittal plane. Since the depth of the CS and the PCS also were roughly perpendicular to the sagittal plane, and since the sulci generally were at least 7 mm in depth, acquisition voxels in these sulci were highly likely to be situated entirely within the gray matter on the banks of the sulci for the most medial functional slice. On the other hand, the crest of gyri in the medial frontal cortex ran parallel to the sagittal plane. With a cortical thickness of ~3 mm, the acquisition voxels on gyral crests almost certainly averaged cortex with a significant amount of underlying white matter. Changes in blood oxygenation during cognitive activation take place in gray matter where synapses are located, not in white matter (for a review see Nadeau and Crosson, 1995). Thus, our methodology may have been more sensitive to activity in the sulci than on the crest of gyri because volume averaging with white matter occurred on gyral crests whereas it did not in the sulci. A further factor that might bias images in favor of showing activity in sulci as opposed to gyral crests is that veins tend to track the surface indentations of sulci. We have excluded activity from veins large enough to appear on MR angiograms, and in some instances (e.g. see Fig. 2c) activity clearly occurs in the depths of sulci away from such veins. Nonetheless, smaller veins tracking sulci could have contributed to the greater activity in the sulci. For these reasons, we must be cautious in generalizing about the lesser activity on gyral crests (i.e. in the pre-SMA+ and the PCG) than in sulci (i.e. the PCS). On the other hand, there should be a substantial difference regarding sensitivity within the CS and the PCS. Therefore, differences between the CS and the PCS can be considered the main finding of this study. That is, when there is a prominent PCS, significant activity during word generation almost always occurs in the PCS and rarely occurs in the CS, but when there is no prominent PCS, significant activity almost always extends into the CS.

In conclusion, the present findings demonstrate great promise for the use of fMRI to help resolve questions of functional anatomy with greater precision than is available by other methods. When a paradigm can be found that produces reliable activity changes in the region of interest across individual subjects, then the activity can be plotted on each individual’s unique structural anatomy and precisely located relative to individual anatomic landmarks. In this way, it is possible to compensate for individual differences in structural and functional anatomy, and to avoid the pitfalls of techniques that have lower resolution or that rely on averaging anatomy and activity across groups. When combined with knowledge derived from other techniques or animal models, the specific contributions of various components of functional systems can be determined. In this respect, our findings suggest that the pre-SMA, adjacent supracallosal area 32 and perhaps posterior medial area 8 on occasion are functionally related, and given their presumed connectivity to the lateral prefrontal cortex, we surmise that they play a role in initiating cognitive processes necessary for word generation. During word generation, the SMA is also necessary for preparing to express words orally. Our findings have yielded no evidence of participation of the limbic cortex within area 24 in our word generation paradigm which was relatively neutral with respect to motivation and emotion. Our findings are consistent with a majority of the studies reviewed by Picard and Strick (1996) which show activity peaks in or above the CS, even though a few of these studies have shown activity in the cingulate gyri. Thus, fMRI of activity changes in individual subjects has the potential to remove ambiguity present in the findings of other functional imaging techniques, leading to more precise knowledge regarding the anatomical bases of cognition.

Notes
This research was supported by grant R01-DC03455 from the National Institute on Deafness and Other Communication Disorders (NIDCD). The authors also would like to thank the NIMH Center for the Study of Emotion and Attention (grant P50-MH52384, P.J. Lang, Director) for its support; Douglas C. Noll for developing and making available the spiral scan pulse sequences, Margaret Bradley for her assistance in implementing the acquisition protocol, and Jeffrey R. Fitzsimmons for designing and providing the head coil used in this study. The authors also thank Wayne King for constructing the air conduction transducer.

Address correspondence to Bruce Crosson, PhD, Department of Clinical and Health Psychology, University of Florida Health Science Center, Box 100165, Gainesville, FL 32610-1665, USA. Email: bcrosson@hp.ufl.edu.

References

Cerebral Cortex Jan 1999, V 9 N 4 315


