Altered Hemispheric Functional Dominance During Word Generation in Negative Schizophrenia

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Abstract

Functional brain imaging studies have reported decreased frontal activations in schizophrenia, but hemispheric dominance for language has rarely been assessed. To investigate regional activation and lateralization during word production, we determined normalized regional cerebral blood flow (rCBF) variations with positron emission tomography (PET) and \( H_2^{15}O \) (water labeled with the isotope oxygen 15) in 14 negative schizophrenia patients and 14 volunteers. Subjects were scanned during two trials of three conditions: rest, vocalized verbal fluency, and spontaneous word production. Images were analyzed using an anatomical volumes of interest method, and the two groups' changes were compared, using rest as a baseline. Differences in the lateralization of changes were detected in homologous frontal and inferior parietal regions. The lateralization effects in patients arose from lower activations in the left frontal regions, abnormal right inferior frontal activations, and weaker right inferior parietal deactivation, during the word production tasks. The right hemisphere changes correlated negatively with the performance in verbal fluency. Thus in negative schizophrenia patients, while the activations were less focused on the left hemisphere regions usually engaged in word generation, rCBF changes in the right hemisphere might reflect a compensatory functional pattern.

Keywords: Schizophrenia, brain imaging, positron emission tomography, verbal fluency, language.


Functional neuroimaging studies of schizophrenia patients have focused on regional cerebral activation during cognitive tasks. Several groups have reported altered activation patterns or decreased frontal activation capacity during cognitive tasks thought to engage the frontal regions (reviews in Bachneff 1991; Andreasen et al. 1992; Liddle 1995; Swanson et al. 1997). However, few studies have examined alterations in the lateralization of cerebral functional activations in schizophrenia, even though abnormal functional lateralization has been hypothesized in this disorder (Gruzelier 1973). Indirect experimental approaches of brain activity have been used to investigate this hypothesis (e.g., Newlin et al. 1981; Cutting 1994, for reviews), but no consistent pattern of findings has emerged from these studies. The reduced or even reversed structural asymmetries recently observed in some magnetic resonance imaging (MRI) studies (see DeLisi et al. 1997 for review) has actualized the hypotheses of schizophrenia by taking into account the formation of anatomical asymmetries in the cerebral areas involved in language processing (Crow 1997). However, anatomical cerebral asymmetries provide only an indirect indication of the hemispheric dominance for language, whereas functional neuroimaging techniques are best suited to assess directly the lateralization of regions engaged in this ability.

Among various linguistic tasks, verbal fluency (VF) has been used extensively to examine the cerebral dominance in normal subjects. Functional imaging studies using single photon emission tomography (SPECT) and PET have reported left hemisphere regional activations mainly in the left prefrontal cortex, the Broca area, and the anterior cingulate during verbal tasks such as category fluency, semantic fluency, or verb generation (Parks et al. 1988; Petersen et al. 1988; Frith et al. 1991a, 1991b; Warkentin et al. 1991; Wise et al. 1991; Friston et al. 1993; Raichle et al. 1994; Warburton et al. 1996). Engagement of other regions, such as the left precentral gyrus, the supplementary motor areas, the left temporal, and the parietal cortex, has also been reported, depending on the experimental designs, including vocalized or silent VF compared with various baseline conditions.
The original VF task requires subjects to retrieve (i.e., generate and select) and verbalize (i.e., trigger, execute, and control motor aspects of vocalization) categories of words. These categories are restricted by semantic or orthographic instructions, thus diminishing spontaneous “free-wheeling” word associations. The performance during this type of VF task is generally impaired in schizophrenia patients, who produce fewer words and smaller clusters of words. The deficit is regarded as an alteration of the effortful, volitional retrieval from the inner lexicon (Goldberg et al. 1993), or as an inefficient access to the semantic store (Joyce et al. 1996), inasmuch as the patients’ inner lexicon size appears normal (Allen et al. 1993). In studies of VF tasks in negative schizophrenia subjects, patients with poverty of speech and flat affect have been reported to prematurely terminate their search (Allen et al. 1993), and the pauses between vocalized words were found to correlate with the intensity of these symptoms (Alpert et al. 1997).

Abnormalities, or decreases in functional asymmetries during cognitive activation studies with brain imaging techniques, have been reported in schizophrenia patients by some authors (e.g., Gur et al. 1983; Andreasen et al. 1992; Mattay et al. 1997). However, few studies have been performed to investigate specifically the lateralization of the cerebral activations during verbal production. One PET study of rCBF in schizophrenia patients versus controls reported a decrease in left frontal activation and a reversed frontal dominance (i.e., right is greater than left) during a written word fluency task (Lewis et al. 1992). Frith et al. (1995) studied three groups of six schizophrenia patients, stratified on the basis of prescan VF performance, using a paced form of orthographic VF compared to word categorization and word repetition. They found no left frontal deficit in patients compared with control subjects and no relationship with prior performance in VF; however, they reported an absence of left superior temporal cortex deactivation. In a preliminary functional MRI study in one cerebral slice using an unpaced VF task contrasted to simple counting, Yurgelun-Todd et al. (1996) reported reduced left frontal activation in schizophrenia patients compared with control subjects.

Thus, because VF tasks induce robust frontal activations that are clearly left lateralized in right-handed normal subjects, we used a VF task to examine the functional dominance in schizophrenia patients. We not only analyzed rCBF variations but specifically examined if the engaged regions were similarly lateralized in patients and controls. Also, because impairment in VF is intrinsically linked to core negative symptoms (alogia and flat affect; Allen et al. 1993; Alpert et al. 1993), we investigated how the rCBF variations relate to the performance in VF in schizophrenia patients with prominent negative symptoms, in comparison with control subjects. A spontaneous word production task was also used because it induces fewer constraints in the search and retrieval of words; it allows more spontaneous changes of the course of word associations, and we hypothesized that the number of responses would be greater in this condition.

**Subjects**

The patients were recruited by investigators among inpatients of several psychiatric departments of the Assistance Publique–Hôpitaux de Paris. The patients chosen were those who had both prominent negative symptomatology and relatively moderate doses of antipsychotics, and who also were willing and able to perform the tasks in a clinical setting.

The inpatients recruited were 14 males who were ages 20 to 42 (mean ± standard deviation [SD] = 30.7 ± 5.5 years) and met DSM–III–R (American Psychiatric Association 1987) criteria for schizophrenia. All of the patients were native French speakers and right-handed according to the Annett Handedness questionnaire (Annett 1970). Eleven had a disorganized type and three an undifferentiated type. All but one had a chronic course. Only male patients were recruited because literature suggests that the brain regions engaged in language tasks vary depending on sex.

Three of the patients were neuroleptic-naive, one had been neuroleptic-free for 8 weeks. Individual neuroleptic doses and compounds in ten patients were the following: amisulpride (50, 100, and 200 mg/d), loxapine (90 and 200 mg/d), chlorpromazine (250 mg/d), haloperidol (5 mg/d), levopromazine (25 mg/d), and pipotiazine (15 mg/d), and one patient received cariprizine (150 mg/d) and levopromazine (25 mg/d). All of these patients were treated for several weeks. No patient received antidepressants, lithium, or electroconvulsive therapy before the inclusion. Patients with a history of alcohol or other drug abuse, or neurological disease, were not included in the study.

All patients were rated the day before the PET study with the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen and Olsen 1982), and the Positive and Negative Syndrome Scale (PANSS; Kay and Opler 1988). They had a prominent negative symptomatology. Their mean ± SD score on the SANS was 69.1 ± 20.1 (alogia: 9.5 ± 3.8; avolition, apathy: 9 ± 3; anhedonia-asociality: 15.5 ± 2.6; attention: 1.3 ± 2.3). Their score on the SAPS was 24.8 ± 20.3. On the PANSS, their score was 33.6 ± 8.0 for negative symptoms and 14.5 ± 5.6 for positive symptoms.

Fourteen volunteers were recruited to match the patients’ group verbal level and age. The volunteers were
male, native French speakers, ages 19 to 39 (mean 29 ± 7 years). None had a history of neurological disorder, alcohol or drug abuse, or psychiatric disorder on screening. For each subject, the verbal level was assessed with the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and anxiety was evaluated with the State-Trait Anxiety Inventory (Spielberger et al. 1970).

The protocol of the study was approved by the Bicêtre Hospital ethics committee, and each subject gave a written informed consent.

Task Design

Normalized rCBF was measured six times in each subject by replicating twice a series of three conditions: rest (R), VF, and spontaneous word production (SWP), in the following order: R1, VF1, R2, VF2, SWP1, SWP2. During the rest condition, no instruction was given except to keep the eyes closed and to relax. In the VF condition, subjects were required to produce as many words as possible beginning with a specified letter (c, f). In the spontaneous word production condition, subjects were instructed to produce as many different words as possible, without forming sentences.

Scanning Procedure. A contiguous axial series of 3-mm-thick, T1-weighted, high-resolution MRIs was acquired through the entire brain with a 0.5 Tesla MRI imager (MRMAX, General Electric). Skin marks applied during the MRI exam were used to position the subjects in the PET scanner. rCBF was measured with an ECAT 953B/31 positron tomograph (31 axial slices, 3.4-mm thickness) and the $^{15}$O-labeled water method. The PET gantry was rotated and tilted so that the lowest plane was parallel to the orbitomeatal line defined on the subject’s head during the MRI. A 10-minute 68Ge/68Ga transmission scan, performed for calculating the attenuation factors, preceded the blood flow studies. The subjects were instructed to start the task 30 seconds before the 80-second image acquisition following each intravenous bolus injection of 60 mCi of $^{15}$O-labeled water and to perform the task during this acquisition period. The interval between the injections was 15 minutes. The words verbalized during the image acquisitions were tape-recorded and digitalized in a computer.

Image Analysis

Individual MRI and normalized PET images were realigned in the same coordinates using the AIR package (Woods et al. 1993). Volumes of interest were defined as detailed in Tzourio et al. (1997b). Briefly, the main sulci were traced on the MRI images in each subject, using a dedicated software to reconstruct three-dimensional brain volume (Voxtool; General Electric). Anatomical cerebral regions were drawn on each MRI slice using VIDA software according to the gyri limits and then pooled into anatomical volumes of interest (AVOIs).

A set of 19 pairs of AVOIs was drawn on axial MRI images, based on a parcellation previously described (Tzourio 1997b). There were six frontal regions ( supplementary motor area (SMA), Brodmann’s area 6, precentral gyrus, dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus, orbitofrontal cortex); four parietal regions (postcentral gyrus, inferior parietal cortex, superior parietal gyrus, precuneus); four temporal regions (superior, middle, inferior temporal gyri, and temporal pole); the anterior and the posterior cingulate; the paracentral lobule; the occipital lobe; and the striata. The DLPFC was delimited ventrally by the orbitofrontal cortex, and posteriorly by the inferior frontal gyrus, the Brodmann’s area 6, and the anterior cingulate. Thus, the DLPFC included the superior and middle frontal gyri anterior to the Brodmann’s area 6. The inferior parietal cortex included the supramarginal gyrus and the angular gyrus.

The AVOIs were then copied onto the coregistered PET images. Within each AVOI, normalized rCBF during each condition was estimated as the ratio of the radioactivity concentration in the AVOI to that of the whole brain.

This AVOI method allows the precise delimitation of cerebral regions according to the individual anatomy and thus takes into account possible anatomical variations that may occur in schizophrenia (see De Lisi et al. 1997 for review), such as differences in hemispheric cortical asymmetries. Stereotaxic averaging methods are likely to be insensitive to such lateralized anatomic differences. Furthermore, the AVOI method is better suited to investigate the existence of activation asymmetries between homologous hemispheric regions.

Statistical Analysis. A repeated measures analysis of variance ([M]ANOVA; Systat® 1992) was performed on the rCBF values in each defined pair of homologous AVOIs (left and right). The model included Group (patients, controls) as a between-subjects factor, and three within-subjects factors: a Side factor (lateralization: right, left), a Task factor (R, VF, SWP), and a Repetition factor (1,2).

To investigate differences between patients and controls (regional activations and lateralization differences in patients depending on the conditions), post hoc F tests ($p ≤ 0.05$) were performed in the regions where a significant
Side × Task × Group interaction effect \( (p \leq 0.01) \) was found. In these regions we tested the following: (1) the effect of Group on the laterality balance (Left - Right) in the VF versus R contrast \( ([VF \text{ left} - R \text{ left}] - [VF \text{ right} - R \text{ right}]) \), and in the SWP versus R contrast \( ([SWP \text{ left} - R \text{ left}] - [SWP \text{ right} - R \text{ right}]) \); and (2) the effect of Group in the right and left side regions separately, in the VF versus R contrast \( ([VF \text{ left} - R \text{ left}] \text{ and } [VF \text{ right} - R \text{ right}]) \), and in the SWP versus R contrast \( ([SWP \text{ left} - R \text{ left}] \text{ and } [SWP \text{ right} - R \text{ right}]) \).

The relationships between the average number of words produced in VF and the rCBF changes \( ([VF1 + VF2]/2 - [R1 + R2]/2) \) were analyzed by Pearson’s correlation statistic for the same regions.

To control the type 1 error, the comparisons should be restricted to a small set of regions. This strategy is possible when an a priori hypothesis can select a very limited set of regions putatively linked to the pathophysiology. In schizophrenia, the literature on brain imaging highlights distributed functional abnormalities, rendering this approach less relevant. Also, with a regions of interest (ROI) method, controlling the type 1 error by increasing the significance threshold would have the drawback of increasing the type 2 error. Thus, we limited the type 1 error by pooling the ROIs defined in each plane in larger AVOIs, which led to testing only 19 AVOI pairs. However, given the small number of subjects here, as in other PET scan studies, the results are not readily generalizable to the whole population of schizophrenia patients. The ANOVA therefore has an exploratory value.

**Results**

**Subjects’ Characteristics and Performances.** The groups were compared using unpaired \( t \) tests. All of the subjects were right-handed men (Annett questionnaire: controls: 87 ± 18; patients: 92.5 ± 8.5; \( \bar{t} = 1, p = 0.33 \)), and the groups were matched for age \( (t = 0.91, p = 0.37) \) and for verbal level on the WAIS-R (controls: 43 ± 15.4; patients: 34.8 ± 10.8; \( \bar{t} = 1.61, p = 0.12 \)). The number of words produced in the VF condition was lower in the patients (15 ± 5) than in the controls (25 ± 7; \( \bar{t} = 4.29, p = 0.0002 \)). The patients also produced fewer words \( (24 ± 10) \) than the controls \( (51 ± 13; \bar{t} = 6.17, p < 0.0001) \) in the SWP condition. The number of vocalized words did not differ significantly between treated and untreated patients in the VF (untreated, \( n = 4; 14.7 ± 5.5 \); treated, \( n = 10; 14.4 ± 5.6; \bar{t} = 0.10, p = 0.92) \) and in the SWP condition (untreated: 18.4 ± 11; treated: 26.2 ± 8.9; \( \bar{t} = 1.41, p = 0.18 \)).

The state-anxiety scores did not significantly differ (controls: 33.3 ± 10.5; patients: 37.7 ± 8.4; \( \bar{t} = 1.17, p = 0.25 \)), whereas the trait-anxiety score was higher in patients \( (50.3 ± 7.5) \) than in controls \( (34.9 ± 7.9; \bar{t} = 5.31, p < 0.0001) \).

The verbal level (WAIS-R) correlated with the number of words produced in the VF task \( (r = 0.64, p = 0.01) \) in controls but not in patients. There was no correlation between the verbal level and the number of words produced in SWP in either subject group.

**PET Results**

**ANOVA main effects (table 1).** A Task effect \( (p < 0.01) \) was observed in most regions, and we identified activated (Tasks > Rest) and deactivated (Tasks < Rest) regions by inspecting the rCBF mean values in each condition. Frontal regions \( (i.e., \text{DLPFC, inferior frontal gyrus, SMA, Brodmann's area 6, precenentral gyrus, and anterior cingulate}) \text{ and striatum} \) were activated, while inferior and superior parietal gyri, paracentral lobule, inferior temporal gyrus, precuneus, and occipital lobe were deactivated. There was a significant Group effect in the striatum only: The rCBF were higher in patients than in controls. This is consistent with previous findings of a relatively increased striatal metabolism in neuroleptic-treated patients (Buchsbaum et al. 1992; Wolkin et al. 1996). Here, the average striatal rCBF of the neuroleptic-treated patients \( (m ± SD = 1.292 ± 0.06; n = 10) \) differed from that of the untreated patients \( (m ± SD = 1.218 ± 0.038; n = 4) \); Mann-Whitney \( U: p = 0.024 \), making it likely that neuroleptic treatment underlies the increased striatal rCBF. The Side effect was significant in the superior parietal gyrus and temporal pole only \( (Left > Right) \).

**ANOVA interaction effects (table 1).** A Side × Task interaction effect revealed significant asymmetrical regional activations. The left DLPFC, inferior frontal gyrus, SMA, Brodmann’s area 6, precenentral gyrus, postcentral gyrus, and superior temporal were significantly more activated than the right, whereas the right orbitofrontal gyrus, inferior and superior parietal gyri, and medium temporal gyrus were more deactivated than the left, when all subjects were considered together. There was no significant Side × Group interaction effect. A Task × Group interaction effect was observed in SMA, precenral gyr, inferior parietal, and precunei.

The ANOVA revealed four pairs of AVOIs with a significant Side × Task × Group interaction effect: three frontal regions \( (\text{inferior frontal gyr, DLPFC, and precen-tral gyr}) \) and the inferior parietal cortex. These interaction effects were further analyzed post hoc.

**Post hoc tests: side effects (table 2).** In these pairs of homologous regions, the laterality balance \( (Left-Right) \) of the changes in rCBF was significantly higher in controls than in patients. In both tasks, the activations were more lateralyzed in the dominant hemisphere in the controls than in the patients in the inferior frontal gyrus, the DLPFC, the precenral gyrus, and the inferior parietal cortex.
Table 1. rCBF analysis of variance

<table>
<thead>
<tr>
<th>AVOIs</th>
<th>Task</th>
<th>Group</th>
<th>Side</th>
<th>Side × Task</th>
<th>Task × Group</th>
<th>Side × Task × Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPFC</td>
<td>0.00003</td>
<td>ns</td>
<td>ns</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>0.003</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>0.0036</td>
</tr>
<tr>
<td>SMA</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
<td>0.0004</td>
<td>0.007</td>
<td>ns</td>
</tr>
<tr>
<td>Brodmann's area 6</td>
<td>0.0006</td>
<td>ns</td>
<td>ns</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Precentral</td>
<td>0.0001</td>
<td>ns</td>
<td>ns</td>
<td>0.00001</td>
<td>0.0063</td>
<td>0.0013</td>
</tr>
<tr>
<td>Orbitofrontal</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.00002</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Paracentral lobule</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Inferior parietal</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
<td>0.0015</td>
<td>0.0007</td>
<td>0.01</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>0.008</td>
<td>0.0007</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Postcentral</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.001</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Precentral</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.009</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>&lt; 0.00001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.0003</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Medium temporal</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.00002</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>0.0002</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Striatum</td>
<td>0.0001</td>
<td>0.0001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Note.—F tests (p) for main and interaction effects. AVOIs = anatomical volumes of interest; DLPFC = dorsolateral prefrontal cortex; ns = nonsignificant (p > 0.01); rCBF = regional cerebral blood flow; SMA = supplementary motor area.

Table 2. Post hoc F tests

<table>
<thead>
<tr>
<th>AVOIs</th>
<th>VF-Rest</th>
<th>% C-P</th>
<th>SWP-Rest</th>
<th>% C-P</th>
<th>Laterality</th>
<th>VF-Rest</th>
<th>% C-P</th>
<th>SWP-Rest</th>
<th>% C-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior frontal (F3)</td>
<td>0.01</td>
<td>4.50</td>
<td>0.007</td>
<td>4.70</td>
<td>Left</td>
<td>0.03</td>
<td>2.50</td>
<td>0.07</td>
<td>2.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>0.04</td>
<td>-2.00</td>
<td>0.01</td>
<td>-2.70</td>
</tr>
<tr>
<td>DLPFC</td>
<td>0.02</td>
<td>2.10</td>
<td>0.001</td>
<td>2.30</td>
<td>Left</td>
<td>0.05</td>
<td>1.00</td>
<td>0.04</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>0.19</td>
<td>-1.10</td>
<td>0.06</td>
<td>-1.20</td>
</tr>
<tr>
<td>Precentral</td>
<td>0.0005</td>
<td>3.80</td>
<td>0.009</td>
<td>3.90</td>
<td>Left</td>
<td>0.00009</td>
<td>3.60</td>
<td>0.0008</td>
<td>3.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>0.73</td>
<td>-0.20</td>
<td>0.56</td>
<td>-0.60</td>
</tr>
<tr>
<td>Inferior parietal</td>
<td>0.03</td>
<td>2.10</td>
<td>0.02</td>
<td>3.00</td>
<td>Left</td>
<td>0.99</td>
<td>0.00</td>
<td>0.55</td>
<td>-0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right</td>
<td>0.007</td>
<td>-2.10</td>
<td>0.0009</td>
<td>-3.40</td>
</tr>
</tbody>
</table>

Note.—AVOIs = anatomical volumes of interest; DLPFC = dorsolateral prefrontal cortex; % C-P = regional cerebral blood flow change differences between controls and patients (in percent) for each contrast; SWP-Rest L-R (p) = Spontaneous Word Production-Rest Left-Right; SWP-Rest (p) = Spontaneous Word Production-Rest; VF-Rest L-R (p) = post hoc F tests for between-group verbal fluency minus rest and left minus right regional cerebral blood flow changes; VF-Rest (p) = post hoc F tests for between-group verbal fluency minus rest rCBF changes.
Post hoc tests: within hemisphere effects. Table 2 and figure 1 show significant rCBF differences between patients and controls in each task and each lateralized region. The direction of the changes in these differences within each group of subjects (increases [i.e., activations] or decreases [i.e., deactivations] of rCBF during the word production tasks with respect to the rest condition) was determined by inspection of the rCBF profile in each region (figure 2).

The magnitude of rCBF changes (between VF or SWP condition and rest in each group) is expressed below in percentages. In both tasks compared with rest, two left frontal regions were significantly more activated in controls than in patients: the left precentral gyrus (controls: \( \text{VF} = 4.1\% \pm 2.1, \text{SWP} = 4\% \pm 1.9 \); patients: \( \text{VF} = 0.5\% \pm 2, \text{SWP} = 0.6\% \pm 2.7 \)) and the left DLPFC (controls: \( \text{VF} = 2.1\% \pm 1.3, \text{SWP} = 3.0\% \pm 1.5 \); patients: \( \text{VF} = 1.1\% \pm 1.3, \text{SWP} = 1.9\% \pm 1.2 \)). The left inferior frontal gyrus was significantly more activated in controls (\( \text{VF} = 6.3\% \pm 3 \)) than in patients (\( \text{VF} = 3.8\% \pm 2.9 \)) during the VF condition.

In both tasks, the right inferior frontal gyrus was significantly more activated in patients (\( \text{VF} = 1.6\% \pm 1.3, \text{SWP} = 1.6\% \pm 2.3 \)) than in controls (\( \text{VF} = -0.5\% \pm 3.3, \text{SWP} = -1.1\% \pm 2.9 \)).

The right inferior parietal cortex was significantly less deactivated in patients than in controls in both tasks (patients: \( \text{VF} = -1.1\% \pm 1.6, \text{SWP} = -1.0\% \pm 2.7 \); controls: \( \text{VF} = -3.2\% \pm 2.2, \text{SWP} = -4.4\% \pm 2 \)).

Correlations with performance (table 3 and figure 1). In both groups, the number of words produced during the VF task correlated positively with the magnitude of the activations (\( (\text{VF1} + \text{VF2})/2 - (\text{R1} + \text{R2})/2 \)) in the left precentral gyrus (figure 1). In patients, a positive correlation between the number of words produced in VF and the magnitude of activations was also found in the left inferior frontal gyrus. However, the number of words vocalized by the patients in VF correlated negatively with the magnitude of activations in the right DLPFC, inferior frontal gyrus, and inferior parietal cortex (figure 1).

In patients, the number of words vocalized during VF correlated positively with the laterality balance (L-R) in precentral and inferior parietal gyri. We also noted a positive correlation in controls with the DLPFC laterality balance.

Discussion

Differences in the functional lateralization of the rCBF changes in pairs of homologous frontal or parietal regions were detected in this H215O PET word production study comparing schizophrenia patients with healthy subjects matched for age, sex, handedness, and verbal level. The schizophrenia patients had prominent negative symptoms with marked alogia. Despite a comparable WAIS-R verbal score, they had lower performances in the word production tasks than the controls. In addition, the WAIS-R verbal score of the patients did not correlate with their performance, in contrast with the significant correlation observed for the controls. Thus, the lower verbal performance of the patients is likely to be an important aspect of the negative features, consistent with previous studies demonstrating a marked alteration in speech fluency in patients with such a symptom profile (Allen et al. 1993; Alpert et al. 1997). Because previous studies have shown that neuroleptic treatment can improve VF performance in patients (Verdoux et al. 1995), and here the treated and untreated patients vocalized a comparable number of words during both word production tasks, it is unlikely that the lower performance of the patients was a result of treatment.

A crucial issue in functional imaging investigations using cognitive paradigms is the choice of the baseline condition. We used rest as a baseline because our main purpose was to compare schizophrenia patients with controls for regional activations and their hemispheric lateralization, rather than to isolate regions involved in a specific step of the information processing during word production. Also, our results can be compared more directly with a number of previous neuroimaging studies of schizophrenia patients during activation tasks that have used rest as a baseline condition (e.g., Weinberger et al. 1986; Andreasen et al. 1992; Kawasaki et al. 1993; Steinberg et al. 1996), as well as with studies investigating hemispheric dominance during word generation versus rest (Parks et al. 1988; Warkentin et al. 1991; Weiler et al. 1994).

Choosing a verbal task on which the two groups perform at similar levels is a different research strategy. This approach looks for abnormalities attributable to diagnoses, or it may select out important aspects of the disease by focusing on unaffected neural functions. However, the lower performance of patients in VF tasks reveals a defect intrinsic to core negative symptoms such as alogia and flatness of affect (Allen 1993; Alpert 1997). Consequently, trying to disentangle the effect of behavioral differences associated with symptoms from "disease" effects, by experimentally matching the performances between patients and controls, has the drawback of ignoring the links between symptoms, cognitive performance, and brain function. Rather, our aim was to study the regional correlates of a cognitive defect reflecting a (negative) symptomatology. Therefore, we chose not to equalize the responses but to take into account the individual performances. This approach looks for physiological mechanisms associated with degraded performance.
Figure 1. Group comparison: rCBF changes during verbal fluency vs. rest

Patients with schizophrenia showed more activation than controls. $p = 0.04$

Patients with schizophrenia showed less deactivation than controls. $p = 0.007$

Negative correlation between NrCBF changes and number of words produced during verbal fluency in patients

Right hemisphere

Patients with schizophrenia showed less activation than controls: $p \leq 0.05$

Patients with schizophrenia showed less activation than controls: $p = 0.0001$

Positive correlation between NrCBF changes and number of words produced during verbal fluency in both groups

Left hemisphere
Figure 2. Regional rCBF variations for verbal fluency and single word production minus rest in both groups

**Note.**—SWP-R = single word production minus rest; VF-R = verbal fluency minus rest.

1 Magnitudes of rCBF variations expressed in percent are displayed with SE (standard interval to the mean) bars. In the schizophrenia group the activations were lower in the left inferior frontal gyrus and dorsolateral prefrontal cortex and higher in the right homologous regions, as compared to controls. In the right inferior parietal cortex and in the left precentral gyrus, the rCBF changes were lower in patients.

Table 3. Correlations between words vocalized and activations in each group

<table>
<thead>
<tr>
<th>AVOIs</th>
<th>Group</th>
<th>Right Pearson r</th>
<th>p</th>
<th>Left Pearson r</th>
<th>p</th>
<th>L-R Pearson r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior frontal (F3)</td>
<td>Controls</td>
<td>-0.21</td>
<td>0.46</td>
<td>0.18</td>
<td>0.54</td>
<td>0.32</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>-0.55</td>
<td>0.04</td>
<td>0.24</td>
<td>0.40</td>
<td>0.69</td>
<td>0.007</td>
</tr>
<tr>
<td>DLPFC</td>
<td>Controls</td>
<td>-0.14</td>
<td>0.63</td>
<td>0.03</td>
<td>0.92</td>
<td>0.66</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>-0.82</td>
<td>0.0003</td>
<td>-0.38</td>
<td>0.17</td>
<td>0.04</td>
<td>0.90</td>
</tr>
<tr>
<td>Precentral</td>
<td>Controls</td>
<td>0.32</td>
<td>0.26</td>
<td>0.52</td>
<td>0.05</td>
<td>0.17</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>0.28</td>
<td>0.34</td>
<td>0.83</td>
<td>0.0002</td>
<td>0.57</td>
<td>0.032</td>
</tr>
<tr>
<td>Inferior parietal</td>
<td>Controls</td>
<td>-0.13</td>
<td>0.64</td>
<td>-0.22</td>
<td>0.45</td>
<td>0.06</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>-0.65</td>
<td>0.01</td>
<td>0.06</td>
<td>0.83</td>
<td>0.58</td>
<td>0.028</td>
</tr>
</tbody>
</table>

**Note.**—AVOIS = anatomical volumes of interest; DLPFC = dorsolateral prefrontal cortex.
In the present study, differences between patients and controls were found for the laterality balance (i.e., the difference of rCBF variations between left and right homologous regions during the task vs. rest) in four pairs of homologous frontal or parietal regions. Indeed, the laterality balance during the VF task was larger in controls than in patients in the inferior frontal gyrus, the DLPFC, the precentral gyrus, and the inferior parietal gyrus. This reflects a left dominance for VF processing in our control group, consistent with previous neuroimaging studies in normal subjects during VF tasks (Petersen et al. 1988; Frith et al. 1991a, 1991b; Wise et al. 1991; Friston et al. 1993; Raichle et al. 1994; Warburton et al. 1996).

The diminished laterality balance in schizophrenia patients can be accounted for by a lower activation in left frontal regions, and an abnormal activation in the right inferior frontal region coupled with a smaller right inferior parietal deactivation. The activations in patients (i.e., rCBF increase between rest and task conditions) were fewer than in controls in the left hemisphere regions classically engaged in word production tasks such as the inferior frontal gyrus, the DLPFC, and the precentral gyrus. These results are consistent with those in previous studies of unpaced VF performed in schizophrenia patients, which reported a left frontal hypoactivation with SPECT (Lewis et al. 1992) or functional MRI (Yurgelun-Todd et al. 1996). Our results, however, do not replicate the findings of Frith et al. (1995), who reported no difference in left frontal regions between patients and controls during a paced VF. This is probably attributable to differences in task designs: The VF task in our study required the subjects to maintain a continuous retrieval effort for 2 minutes; in paced VF, the retrieval effort was less intense and more fragmented than in the classic form of VF that we used. Also, Frith et al. used word categorization or repetition as a baseline.

Among the phenomena involved in these left hypoactivations, the lower performances of patients during lexical tests may play a role in the frontal subregions involved in motor function: A positive correlation between the number of words produced during the tasks and the rCBF change was found in both groups in the left precentral gyrus. Thus, the lower performance of the patients was linked to the hypoactivation of this motor region, although correlation analysis cannot lead to causal inference. Furthermore, examination of the activation percentages of the left precentral gyrus shows that the magnitude of its activation was lower in patients than in controls, whatever the task (figure 2), although they articulated as many words in SWP (24 ± 10) as the controls did in VF (25 ± 7). This finding confirms that motor performance is not the sole factor accounting for the hypoactivation observed in the left precentral gyrus of the patients (Mattay et al. 1997). In the other left frontal regions (DLPFC, inferior frontal gyrus), the number of words produced did not correlate to the rCBF changes in both groups, indicating that the performance and the rCBF changes are not straightforwardly related.

Activation in the right inferior frontal gyrus, and a weaker deactivation in the right inferior parietal cortex, also contributed during both tasks to the decreased left-right balance in frontal and inferior parietal regions in patients. The magnitude of the rCBF changes in the right inferior frontal gyrus, in the right DLPFC, and in the right inferior parietal cortex negatively correlated to the individual performance in patients but not in controls. Thus, the fewer words vocalized, the more these regions were activated in patients. A tempting interpretation, in line with Frith et al. (1995), would be that patients fail to shut off non-task-related processing in these regions, which interferes with successful performance of the task. The alternative explanation rests on several lines of evidence suggesting that these right hemisphere regions are part of a cerebral network involved in sustained attention and in intentional retrieval efforts. First, functional imaging studies have consistently demonstrated prominent right DLPFC activation when subjects actively retrieve information in paradigms of episodic memory, auditory sentence recognition, or auditory verbal memory (Kapur et al. 1994; Shallice et al. 1994; Tulving et al. 1994; Fletcher et al. 1995). Second, activation of the right inferior frontal gyrus is not modality-specific because it has been reported during a variety of tasks (Pardo et al. 1991; Kosslyn et al. 1993; Mazoyer et al. 1993). Third, the right inferior frontal gyrus is also engaged in the attentional resources allocation (Tzourio et al. 1997a; Petit et al. 1999). Taken together, these studies suggest that the right DLPFC and inferior frontal gyrus are activated both in memory retrieval and in sustained attention, independent of the modality of the task. Fourth, the right prefrontal cortex and medial/lateral parietal regions were reported to activate when the recall of verbal material is intentional (Rugg et al. 1997).

In the schizophrenia patients' results, the negative relationship between rCBF changes and individual performance suggests that these right hemisphere regions are inversely related to efficient retrieval of words matching the task instruction. This is consistent with studies in normal subjects that found no right prefrontal activation related to retrieval success (Kapur et al. 1995; Nyberg et al. 1995). Rather, rCBF variations in right frontoparietal regions have been ascribed in normal subjects to the intentional retrieval attempts—that is, to the control of retrieval effort (Nyberg et al. 1995; Schacter et al. 1996; Rugg et al. 1997). In the patients studied here, the abnormal activity of the right frontoparietal regions might be related to an increased effort to retrieve words.
This interpretation can also be drawn from analogies with two other pathological conditions, aphasia and dyslexia, in which abnormal right hemisphere regional activations have been reported in neuroimaging studies during linguistic tasks. These two conditions are associated with the disruption of the dominant hemisphere regions involved in language generation, and the right hemisphere regional activations were ascribed to compensatory mechanisms (Rumsey et al. 1994; Weiler et al. 1994). Although the subjects of the present study had no readily identified structural lesions in the dominant hemisphere, the focalization of their activations on the left hemisphere regions engaged in word production was decreased, and they had an impoverished ability to generate speech (alogia). This raised the possibility that the activity in the right frontoparietal regions might be related to alogia. To investigate this, we examined a relationship between individual alogia scores and the abnormal rCBF changes in these right hemisphere regions. The alogia scores correlated with the magnitude of the rCBF changes in the right inferior frontal regions during both word generation tasks (VF: Pearson’s \( r = 0.53 \), \( p = 0.05 \); SWP: \( r = 0.59 \), \( p = 0.02 \)). In light of the studies of aphasic and dyslexic patients and of the literature in normal subjects, this post hoc observation suggests that the activation in the right inferior frontal region may form part of a (compensatory) mechanism when schizophrenia patients are faced with a heavy cognitive load, as in the present verbal generation tasks.

In conclusion, our results show, in patients, a decreased focalization of the activations in the left hemisphere regions involved in the word generation tasks. However, this study further relativizes the notion of hypofrontality in schizophrenia. Compared with controls, higher rCBF levels in right inferior frontal and lower deactivation in right inferior parietal regions can be observed, even in prominently negative schizophrenia patients, during a cognitive task. These right hemisphere changes may reflect a compensatory functional pattern.

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