Part 2  Language lateralization in schizophrenia

CHAPTER 9

Language lateralization in men with schizophrenia

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ABSTRACT

Anatomical studies have shown that cerebral asymmetry is reduced in schizophrenia. Functional asymmetry appears to be reduced also, as was shown with dichotic listening studies. These studies, however, have not revealed whether reduced lateralization is the result of decreased language activity of the left hemisphere or whether it is the consequence of increased language-related activity in the right hemisphere. To elucidate this, we examined hemispheric dominance for language processing by means of functional MRI. Twelve schizophrenic patients and twelve healthy controls were scanned while they were engaged in a verb-generation and a semantic decision task. Activation was measured bilaterally in the frontal, temporal and temporo-parietal language areas, and a laterality index was derived from activity in these regions of interest in the left and the right hemisphere. Clinical symptoms were rated at time of scanning. The results indicate that language processing is less lateralized in patients than in controls (a mean laterality index of 0.35 versus 0.63 respectively. Analysis of variance of the extent of activity, i.e. numbers of active voxels, revealed a significant hemisphere by group interaction, which was probably due to increased activation in the right hemisphere of the patients. We found no evidence of reduced activity in the left hemisphere. Further analysis of clinical symptoms rated prior to scanning revealed that decreased language lateralization was associated with more severe hallucinations. We postulate that decreased language lateralization in schizophrenia may result from failure to inhibit the right hemisphere.
INTRODUCTION

In healthy individuals the brain exhibits asymmetric organization of anatomy and function. One of the most robust findings is hemispheric dominance for processing of language, in that the brain regions that are critical for language comprehension and production are typically located in the left hemisphere (Galaburda and Geschwind 1981). With the recent advent of in vivo functional neuroimaging techniques it has become clear that lateralization is a graded variable in healthy subjects, ranging from strong leftward lateralization (in most subjects) to bilateral processing, and in rare cases to rightward lateralization (Springer et al. 1999).

Based on studies investigating handedness and cerebral anatomical features, the degree of language lateralization is reportedly decreased in schizophrenia. Handedness is associated with language lateralization, in that left-handed subjects more frequently deviate from strong left cerebral dominance (Annett 1970). Schizophrenic patients are more often left- or mixed-handed as compared to healthy subjects and also as compared to non-schizophrenic psychiatric patients (Sommer et al. 2001). Furthermore, a causal relation between schizophrenia and decreased cerebral lateralization is suggested by the prospective study of Crow et al. (1996) who found that children of mixed hand preference more often developed schizophrenia in later life.

Cerebral dominance for language can be estimated by measurement of structural asymmetry of certain anatomical areas. Structural asymmetry can be found in the frontal lobe, which is generally larger on the right, and the occipital lobe, which is greater on the left in most subjects. These two asymmetrical features give the brain a twisted appearance called “brain torque”. Several studies reported that the direction of brain torque is more often inverted in schizophrenia (Falkai et al. 1995a; Lee et al. 1985; Luchins et al. 1981; Luchins et al. 1986), but other studies could not replicate this (Andreasen et al. 1982; Guerguerian et al. 1998; Jernigan et al. 1982; Luchins et al. 1983). More specific anatomical asymmetry is found in the temporoparietal region, particularly in the planum temporale, which is part of Wernicke’s area (Shapleske et al. 1999). At the surface of the brain, asymmetry of the planum is reflected in a longer and less steep Sylvian fissure at the side of the largest planum (Galaburda and Geschwind 1981). Asymmetry of the planum temporale is associated with handedness (according to Steinmetz et al. 1989), 67% of right-handed subjects have the typical asymmetry described above versus 22% of non-right-handers).
and with language dominance as assessed with the Wada test (Gerschlager et al. 1998). These reports indicate that asymmetry of the planum temporale and Sylvian fissure is an indirect measure of language dominance. Studies on this measure in schizophrenia have produced equivocal results in that some (Barta et al. 1997; DeLisi et al. 1994; Falkai et al. 1992; Falkai et al. 1995b; Hoff et al. 1992; Kwon et al. 1999; Petty et al. 1995; Rossi et al. 1992), but not others (Bartley et al. 1993; Frangou et al. 1997; Jacobsen et al. 1998; Kleinschmidt et al. 1994; Kulynych et al. 1995; Rossi et al. 1994) have found reduced or even inverted asymmetry. Asymmetry of the superior temporal gyrus has also been argued to be a measure of language dominance (Highley et al. 1999; Holinger et al. 1999), but meta-analysis of the healthy control groups in studies on schizophrenia did not support this (Sommer et al. 2001).

Language lateralization can be measured more directly with dichotic listening tests, visual half-field paradigms, event-related potentials and functional imaging. Dichotic listening tests are the most commonly used technique to investigate language lateralization. In a typical dichotic listening test, two different stimuli are presented simultaneously, but separately, to the right and left ear. Verbal stimuli are normally perceived better with the right ear, a phenomenon called the right ear advantage (REA) (Hughdahl 1988). For this effect various verbal tasks can be used. The so-called fused-word and the consonant-vowel task are considered to reflect cerebral dominance most accurately (Wexler and Halwes 1983). When these two tasks are used, 82% of right-handed subjects and 64% of non-right-handed subjects display REA, which corresponds to neurological data on language dominance distribution (Hughdahl 1988). The so-called triad task and the word-monitoring task are less effective, presumably due to ceiling effects in healthy subjects with good performance resulting in relatively low values of REA. Several studies measured the REA in schizophrenia, using the consonant-vowel task (Bruder et al. 1995; Bruder et al. 1999; Loberg et al. 1999; Oie et al. 1998), the fused-word task (Grosh et al. 1995; Ragland et al. 1992; Wexler et al. 1991), the triad task (Gruzeller and Hamond 1980; Sakuma et al. 1996; Seidman et al. 1993) and the word-monitoring task (Carr et al. 1992; Hatta et al. 1984). Overall, the results of these studies are equivocal, but when only those studies are considered that used the consonant-vowel or the fused-word task, the REA is generally significantly reduced in schizophrenic patients (Sommer et al. 2001). On the basis of these dichotic listening studies, it was concluded that in schizophrenic patients the left hemisphere
is dysfunctional, rendering it incapable of assuming a dominant role in language (Bruder et al. 1999; Loberg et al. 1999; Ragland et al. 1992). However, as dichotic listening measures do not reflect brain activity directly, they cannot provide evidence for left hemispherical dysfunction. Reduced REA may also be the consequence of enhanced contribution of brain structures in the right hemisphere. Such a unilaterally increased activity may underlie certain schizophrenic symptoms (Nasrallah 1985).

The purpose of the present study is to compare the degree of language lateralization between schizophrenic and healthy subjects. The advantage of functional neuroimaging is that it allows for measurement of levels of language-related brain activity, and as such can differentiate between decreased activity of the left and increased activity of the right hemisphere as a source of abnormal lateralization. Schizophrenic patients and control subjects participated in a functional Magnetic Resonance Imaging (fMRI) experiment with two language tasks. Language-related brain activity was measured in the frontal, temporal and temporo-parietal areas of both hemispheres. For each individual, a lateralization index was calculated based on activity levels in left and right hemisphere, and this index was compared across groups. Finally we tested the hypothesis that decreased language lateralization is associated with increased severity of hallucinations.

METHODS AND MATERIALS

Subjects(103,409),(872,871)
Twelve male schizophrenic patients aged 27 (S.D. 6) were included in the study. All were diagnosed on the basis of DSM-IV as determined by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) and History Schedule for Affective Disorder and Schizophrenia Lifetime version (SADSL)(Andreasen et al. 1992). Patients with diagnosis of drug dependence or drug use in the three months prior to entry were excluded.

Since we were interested in a possible correlation between hallucinations and lateralization, patients were selected who were actively psychotic, in spite of optimal pharmacotherapy. Auditory hallucinations were a prominent symptom in the clinical picture of all patients. To increase group homogeneity, only patients on clozapine were selected, with the mean dose being 355 mg (S.D. 69 mg)/day. They had received clozapine for a mean
duration of 1.6 years (S.D. 1 year). Mean age at onset of illness was 21 years (S.D. 3). The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) was used for symptom assessment immediately prior to the scan session. Ratings were carried out by a medical doctor and a second rater who had been trained for the interview and scores were determined by means of consensus. Presence and severity of positive and negative symptoms over the last two weeks were scored. The score on item three was used to express severity of hallucinations. In this item, presence and degree of hallucinations are rated on a scale ranging from 1 ("absent") to 7 ("extremely severe").

The control group consisted of 12 healthy men aged 28 (S.D. 5). Subjects with medical or neurological illness were excluded. Subjects met Research Diagnostic Criteria for “never mentally ill” according to the CASH and SADS-L interview. The section “substance abuse” from the CASH was used to determine whether subjects met the DSM-IV criteria for substance dependence, in which case they were excluded.

Parental educational levels were measured by the total number of years of education. No significant differences in parental educational level were found between patients and controls [11 years (S.D. 4) for the fathers of the patients and 9 years (S.D. 3) for their mothers; 11 years (S.D. 3) for the fathers of the controls and 8 years (S.D. 2) for their mothers].

All subjects were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). The primary language of all subjects was Dutch. After complete description of the study to the subjects, written informed consent was obtained.

Task

Two word tasks were used: the verb-generation task (Warburton et al. 1996) and a new word processing task, the reverse-read task (Ramsey et al. 2003). For the verb-generation task a noun appeared on the screen every 3.6 seconds. The subject was instructed to vocalize the presented word silently and then generate and silently vocalize a verb that was appropriate for that word. To avoid head motion, silent vocalization was used.

For the reverse-read task, the subject had to read words that were spelled from right to left (not in mirror-image print). These words also appeared once every 3.6 seconds. The reversed spelling of the words is thought to avoid direct orthographical word recognition and to put more emphasis on phonological decoding. The subject was instructed to vocalize the word
silently and push a button if the word was an animal. Performance was recorded by computer for the reverse-read task. Both tasks were performed during 10 periods of 29 seconds, alternated with 29 seconds rest. During the rest condition, subjects were instructed to keep their eyes open while fixating on a small dot in the center of the screen. Patients were asked to report hallucinations if they occurred during the scan by depressing the scanner alarm button.

**Scans**

Functional scans were acquired with a Philips ACS-NT 1.5 Tesla clinical scanner, using the blood oxygen level dependent (BOLD) sensitive, navigated 3D PRESTO pulse sequence (Ramsey et al. 1998; van Gelder et al. 1995), with the following parameter settings: TE/TR 35/24 ms, flip angle 9°, FOV 225 x180x77 mm, matrix 64x52x26, voxelsize 3.51 mm isotropic, scan time per fMRI volume 2.4s. Following the fMRI procedure an anatomical scan was acquired (3d-FFE, TE/TR 4.6/30 ms, flip angle 30°, FOV 256x256x180 mm, matrix 128x128x150, slice thickness 1.2mm).

**FMRI Analyses**

For each subject the fMRI data were processed off-line on an HPTM workstation using PV-waveTM processing software. The outer two slices (most dorsal and most ventral) of the transaxial fMRI volumes were not analyzed, since registration causes signal fluctuations at the edges of the volume. Functional scans started and ended seven seconds later than the task to compensate for the delay of the vascular response. All scans, including the subjects’ anatomical volume, were registered to the last volume of the last block to correct for head movements (Ramsey et al. 1998).

Brain activity maps were obtained by analyzing the fMRI scans acquired during both tasks conjointly. We have previously shown that such an analysis improves reliability of the subsequently computed laterality index, as compared to that obtained with individual task analyses (Ramsey et al. 2000; Rutten et al. 2000; Ramsey et al. 2001). The rationale for conjoint analysis, which is essentially the same as “conjunction analysis” as described by Price and Friston (1997), is that it improves sensitivity for brain activity that is present in both tasks, while reducing contribution of activity that is specific for individual language tasks. Brain activity maps obtained with different individual tasks have been shown to vary considerably (Curtis et al.1999), resulting in different values of laterality within subjects (Lehericy et al. 183).
The shared components of the verb-generation and the reverse-read task are reading of the stimulus word, interpreting its semantic content and retrieving a verbal answer, while nonspecific components such as planning of motor output are unshared. An additional advantage of conjoint analysis is the increase in statistical power, compared to separate analyses. It also provides greater latitude for the baseline tasks because it is not necessary to control for all unshared components (Price and Friston 1997).

Functional images were analyzed on a voxel by voxel basis using multiple regression analysis (Worsley and Friston 1995) with one factor coding for activity (task versus rest), and three for signal drift (due to scanner hardware). The regression coefficient for activity was converted to a t-value for each voxel, yielding a t-map. Significant activity was then determined in each voxel by applying a threshold. The threshold corresponded to a p-value of 0.05, Bonferroni-corrected for the total number of voxels in the fMRI scan volume, and amounted to a t-value of approximately 4.5 (depending on the number of voxels for each individual). Six volumes of interest (VOI) were manually delineated bilaterally, on the structural MRI of each brain, blind to statistical results. Manual delineation was performed in sagittal orientation using the following landmarks: lateral fissure, its ramus anterior and ramus ascendens and the sulcus temporalis superior. The VOI's comprised Brodmann area (BA) 44 and 45 (Broca's area and its contralateral homologue), dorsolateral prefrontal cortex (BA 9 and 46), middle temporal gyrus (BA 21), superior temporal gyrus (BA 22, 38, 41, 42 and 52), supramarginal gyrus (BA 40) and angular gyrus (BA 39). Together, these VOI's encompassed the main areas where language processing is thought to be mediated. In each VOI the number of active voxels was determined. For subsequent analyses the VOI's were combined, yielding one measure of language-related activity for each hemisphere.

Laterality was compared by means of analysis of variance (patients versus controls) with repeated measures (left versus right hemisphere) on the number of active voxels, investigating main effects for hemisphere, for diagnosis and a hemisphere-by-diagnosis interaction. A logarithmic transformation was applied to the numbers of voxels for this analysis.

A lateralization index was calculated also, to facilitate comparison with other studies (conform Binder et al. 1996). Lateralization index was defined as the difference in number of active voxels in the left versus the right hemisphere (within the VOI's) divided by the total sum of activated voxels.
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in both hemispheres. For the patient group, a correlation between the lateralization index and the score on the hallucination-item of the PANSS was calculated and tested for significance.

RESULTS

The mean total PANSS score at the time of scanning was 60 (S.D. 12.5). The mean total score on the items on positive symptoms was 15 (S.D. 4), and the mean total score on the items on negative symptoms was 13 (S.D. 3.7). The scale of the PANSS ranges from 0 to 112, with a maximum score of 49 for the items on positive and on negative symptoms. Only one patient experienced two brief episodes of hallucinations during the scan. Since this occurred in two of the 20 rest periods and the duration was short as compared to the test protocol, it is unlikely that these hallucinations influenced the activation pattern.

Table 1. Mean activation (number of active voxels) and standard deviations in each volume of interest (VOI) for patients and controls.

<table>
<thead>
<tr>
<th>Volume of Interest (Brodmann areas)</th>
<th>mean activation (S.D.) patients</th>
<th>mean activation (S.D.) controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsolateral prefrontal cortex left (46, 9)</td>
<td>11.2 (10.8)</td>
<td>17.1 (11.2)</td>
</tr>
<tr>
<td>Broca's area left (44, 45)</td>
<td>20.4 (21.3)</td>
<td>14.4 (9.2)</td>
</tr>
<tr>
<td>Angular gyrus left (39)</td>
<td>7.1 (8.4)</td>
<td>8.0 (6.7)</td>
</tr>
<tr>
<td>Supramarginal gyrus left (40)</td>
<td>3.6 (4.9)</td>
<td>4.3 (5.4)</td>
</tr>
<tr>
<td>Superior temporal gyrus left (22, 38, 41, 42, 52)</td>
<td>12.0 (13.9)</td>
<td>6.9 (11.6)</td>
</tr>
<tr>
<td>Middle temporal gyrus left (21)</td>
<td>3.3 (4.4)</td>
<td>3.3 (3.5)</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex right (46, 9)</td>
<td>5.7 (6.8)</td>
<td>2.8 (4.2)</td>
</tr>
<tr>
<td>Right homologue of Broca's area (44, 45)</td>
<td>12.3 (12.4)</td>
<td>5.1 (5.1)</td>
</tr>
<tr>
<td>Angular gyrus right (39)</td>
<td>2.7 (3.3)</td>
<td>0.8 (0.9)</td>
</tr>
<tr>
<td>Supramarginal gyrus right (40)</td>
<td>3.3 (2.7)</td>
<td>1.2 (1.3)</td>
</tr>
<tr>
<td>Superior temporal gyrus right (22, 38, 41, 42, 52)</td>
<td>3.2 (4.4)</td>
<td>1.3 (2.3)</td>
</tr>
<tr>
<td>Middle temporal gyrus right (21)</td>
<td>0.8 (1.5)</td>
<td>0.4 (0.8)</td>
</tr>
</tbody>
</table>
Performance on the reverse-read task was reduced in the patient group: mean of 21 errors (S.D. 10) on 128 trials, versus 8 (S.D. 4) for the controls (t(22)=4.44, p<0.001).

Mean activation in the VOI's of each hemisphere is provided for both groups (table 1). Analysis of variance (with factors hemisphere and diagnosis) revealed a significant main effect for hemisphere (F(1,22)=86.9, p<0.001), no main effect for group (F(1,22)=0.57, n.s.) and a significant hemisphere by group interaction (F(1,22)=11.2, p<0.01). This was due to increased activation in the right hemisphere of the patients relative to the controls (post-hoc t-test: p<0.05), while activation in the left hemisphere was not different between the two groups.

The mean lateralization index was 0.35 (S.D. 0.27) for the patients and 0.63 (S.D. 0.21) for the controls (difference t(22)=-2.91, p<0.01) (figure 1). Within the patient group, there was one subject with right cerebral dominance (lateralization index -0.4), which is an unusual finding for a right-handed subject (Springer et al. 1999). This subject differed more than three times the standard deviation from the group mean and can therefore be regarded

![Figure 1](image-url)  
**Figure 1.** Distribution and mean values of the lateralization index of controls (black) and patients (gray).
an outlier. When this patient was excluded, the difference in mean lateralization index between the groups remained significant (t(21)=-2.41, p<0.01).

There was no significant difference in the size of the VOI's (i.e. the total volume of separate VOI's within each hemisphere) between the groups (right hemisphere VOI's: t(22)=0.09, n.s., left hemisphere VOI's: t(22)=0.31, n.s.), nor was there a difference in VOI size between the right and left hemisphere (paired t-test: t(23)=0.13, n.s.).

Examples of junctional scans of a patient and a control subject are shown in figure 3.

There was no significant correlation between task performance and language lateralization or right hemisphere activation (Pearson correlation: rho=-0.12, n.s.; rho=0.036, n.s. respectively). After exclusion of the outlier, these correlations remained insignificant.

Finally, a significant negative correlation was found between the lateralization index and the severity of auditory hallucinations (Pearson correlation: rho=-0.54, p<0.05), after exclusion of the outlier (figure 2).

Figure 2. Correlation between language lateralization and severity of hallucinations.
DISCUSSION

Language lateralization was assessed with functional MRI in 12 schizophrenic patients and compared to that of 12 healthy subjects. Language lateralization was strongly reduced in the patient group, to almost half the value of that of the control group. This finding suggests that language processing is more bilateral in schizophrenic patients and supports the findings of several dichotic listening studies (Bruder et al. 1995; Kugler et al. 1982; Loberg et al. 1999). As fMRI allows for assessment of activity levels in the brain, we were able to determine that the reduced laterality was due to an increase in language-related activity in the right hemisphere in patients, and not to decreased activity in the left hemisphere. This finding suggests that the decreased degree of language lateralization in schizophrenic patients is due to increased contribution of right-hemisphere structures, which may reflect a failure to inhibit the non-dominant hemisphere, rather than a hypofunctional left hemisphere.

Language activation in schizophrenia has also been studied with functional imaging on similar tasks by other groups (Curtis et al. 1998; Frith et al. 1995; Yurgelun-Todd et al. 1996), but these reports gave no or insufficient data on activation in the right cerebral homologues, which makes it impossible to compare them to our findings. Several Positron Emission Tomography (PET) studies did include measurements in right cerebral homologues and showed

Figure 3. Examples of functional scans of a control subject and a patient.
decreased language lateralization in schizophrenia as well. A PET study by Lewis et al. (1992) reported a decrease in left frontal activity during verbal fluency, resulting in a reversed frontal dominance in schizophrenia. Another PET study by Spence et al. (2000) contrasted activity on a paced verbal fluency task against word repetition, but interpreted the results in terms of connectivity only. After re-analysis of those data, a reduction in lateralization was found in schizophrenic patients (Crow, 2000), but no conclusions were drawn regarding left cerebral hypoactivity or right cerebral hyperactivity. In a recent PET study with an un-paced verbal fluency protocol (Artiges et al. 2000) reduced lateralization in schizophrenia was also observed, which was attributed to both decreased left frontal activity and increased activity of the right-sided frontal areas. In contrast with these earlier studies, we did not find evidence of reduced activity in the left hemisphere. One important factor in functional imaging studies is the type of language task that is used. An un-paced verbal fluency task, for instance, may be problematic if patients cannot generate enough words, as language activity will then not be maintained throughout the task period, potentially resulting in reduced language-related brain activity. The current tasks prompted subjects for each individual word, and as such is less sensitive to failure to self-generate multiple words. This may explain why some groups find hypoactivity in the left hemisphere (eg. Lewis et al. 1992; Artiges et al. 2000). Indeed, decreased frontal activity was not detected when schizophrenic patients were compared to controls matched for performance (Frith et al. 1995). Another potential source of discrepant findings is the selection of patients. When comparing our study to that of Artiges et al. (2000), the mean total score on the PANSS items for negative symptoms was considerably lower (13, S.D. 3.7) than that of the sample of Artiges and colleagues (33.6, S.D.8.0). Increased right-sided language activity was a major finding in both studies, and this may be related to the fact that severity of positive symptoms was quite similar (15, S.D. 4 and 14.5, S.D. 5.6 respectively). This suggests some relationship between symptoms and language-related brain activity patterns, i.e. negative symptoms may be associated with decreased activity in the left hemisphere, whereas positive symptoms may be associated with increased activity in the right hemisphere.

The enhanced contribution to language processing of the right hemisphere may be caused by a genetic factor. Annett (1992), for instance, postulated that normal lateralization, right handedness and normal cerebral asymmetry are coupled to a dominant allele, i.e. the “right shift factor”. According to
this theory, in the absence of this right shift factor handedness, asymmetry and lateralization develop in a random fashion. The right shift factor is thought to accomplish cerebral lateralization by disrupting the growth of right-sided language-related cortex, rather than through enhancement of these areas in the left hemisphere (Annett 1999). Indeed, the asymmetry of the planum temporale normally observed in healthy right-handed subjects, is not the result of a larger left planum, but of a selective decrease in size of the right planum (Galaburda and Geschwind 1981). It has been suggested that schizophrenia is associated with an anomaly of the genetic mechanism that controls lateralization (Crow et al. 1989). An abnormality of the right shift factor has been hypothesized to play a role in mechanisms that promote proneness for psychosis (Crow 1999; Annett 1999). Structural MRI studies appeared to support this notion, in reporting reduced planum temporale asymmetry in schizophrenic patients. Interestingly, this reduction of asymmetry is due to a relatively large right planum in patients, in the presence of a normal-sized left planum (Shapleske et al. 1999).

The third finding of this study was a negative correlation between degree of lateralization and severity of hallucinations. This is in agreement with the reported association between hallucinations and reduced REA in dichotic listening studies (Wexler 1986; Wexler et al. 1991). It has been postulated that relatively high language activity of the right hemisphere may predispose for the emergence of hallucinations (Nasrallah 1985). This is in agreement with studies that found a more associative and less prototypical way of language processing in the right hemisphere in normal subjects (Chiarello et al. 1990; Egorov and Nikolaenko, 1996; Nagakawa 1991; Rodel et al. 1992), and with dichotic listening studies which reported an association between decreased REA and a loosening of associations in both healthy (Leonhard and Brugger 1998) and schizotypal subjects (Poreh et al. 1993).

The results of this study need to be interpreted with some caution, mainly because the sample size is limited, and because the group of patients is not representative in several ways. Firstly, only men were studied. Since men and women may have different lateralization patterns (Shaywitz et al. 1995), the present findings cannot be extrapolated to female patients. Secondly, only actively psychotic patients on clozapine were selected. The choice of psychotic patients, in whom auditory hallucinations were a prominent feature, was deliberate, as it enabled us to investigate a potential association between (positive) symptom severity and degree of lateralization. As a result, it is not clear whether reduced laterality is also present in schizo-
phrenic patients with other symptom profiles. Thirdly, as all patients were on medication, it is possible that medication affected the results and that other types of medication may produce different results. A possible medication effect on language lateralization has not been studied with functional imaging techniques, but a dichotic listening study reported that withdrawal and reinstatement of medication did not affect the REA (Gruzelier and Hamond 1980). An additional limitation of the study is that performance was measured for only one of the two language tasks. One could argue that patients did not perform the verb generation task adequately, but this is unlikely, as one would then expect to find reduced brain activity levels, which was not the case in the present study.

In summary, this study provides evidence that cerebral dominance for language processing is reduced in schizophrenic patients with positive symptoms. This reduction is associated with enhanced activity in the right hemisphere, suggesting that language-related regions in that hemisphere are not adequately suppressed. No evidence was found for hypoactivity in the left language regions, suggesting that those are not impaired. The correlation between degree of language lateralization and severity of hallucinations suggests that decreased lateralization may be a factor in the predisposition for psychosis.
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