Reduced language lateralization in first-episode schizophrenia: An fMRI index of functional asymmetry

Maya Bleich-Cohen, Talma Hendler, Moshe Kotler, Rael D. Strous

Abstract

Patients with schizophrenia exhibit a decrease or loss of normal anatomical brain asymmetry that also extends to functional levels. We applied functional magnetic resonance imaging (fMRI) to investigate language lateralization in patients with schizophrenia during their first episode of illness, thus excluding effects of chronic illness and treatment.Brain regions activated during language tasks of verb generation and passive music listening were explored in 12 first-episode patients with schizophrenia and 17 healthy controls. Regions of interest corresponded to Broca’s area in the inferior frontal gyrus (IFG) and Wernicke’s area in the superior temporal sulcus (STS). Patients with schizophrenia had significantly smaller lateralization indices in language-related regions than controls. A similar effect was observed in their IFG and STS regions. There was no difference between the groups in the auditory cortex for the music task. Patients with schizophrenia demonstrated greater activation than the controls in temporal regions: the difference was larger in patients with more severe positive symptom subscores. In conclusion, patients with schizophrenia demonstrated loss of normal functional brain asymmetry, as reflected in diminished lateralization of language-related activation in frontal and temporal regions. This phenomenon was already present during their first episode of psychosis, possibly reflecting developmental brain abnormalities of the illness.

Keywords: Schizophrenia; Verb generation; Inferior frontal gyrus; Superior temporal sulcus; Broca’s area; Wernicke’s area

1. Introduction

Brain asymmetry refers to the normal differences in regional hemispheric structure and/or function. This asymmetry is apparent in brain regions related to language processing, which are usually located in the left hemisphere and associated with right-hand dominance in 90% of cases. In contrast, patients with schizophrenia are more frequently left- or mixed-handed (Yan et al., 1985; Sommer et al., 2001a), and children of mixed-hand preference more often develop schizophrenia in later life (Crow et al., 1996). There is an indication for reduced motor asymmetry that reflects abnormal brain lateralization. The establishment of anatomical and functional asymmetry in the human brain has been indicated as a
component of the normal neurodevelopmental process (Hutsler and Galuske, 2003). Structurally, normally developed right-handed adult individuals show wider right frontal and left occipital lobes, phenomena known as the “developmental torque”, on computerized tomography (CT) and magnetic resonance imaging (MRI). This opposing regional asymmetry was noted to be inverted in schizophrenia (i.e., wider left frontal and right occipital lobes) by some studies (Luchins et al., 1981; Falkai et al., 1995), but not by others (Andreasen et al., 1982; Jernigan et al., 1982). Asymmetry favoring the left in the planum temporale and sylvian fissure has also been shown in healthy right-handed subjects (Barta et al., 1997). This structural asymmetry has been related to language lateralization and is often missing in schizophrenia (Sommer et al., 2001a).

In addition to decreased anatomical asymmetry, there is also evidence for decreased functional brain asymmetry in schizophrenia. For example, several studies have indicated a decrease in language asymmetry, particularly with reference to the fused word and consonant-vowel tasks, as evidenced by dichotic listening tests (Sommer et al., 2001a). Brain-imaging techniques used to investigate functional asymmetry in schizophrenia brains have also recently shown decreased left lateralization in various language tasks. For example, in one functional magnetic resonance imaging (fMRI) study, patients with schizophrenia demonstrated less overall left hemispheric lateralization than healthy controls in performing language tasks. This difference was accounted for by increased activation in their right hemisphere relative to controls (Sommer et al., 2001b, 2003). In addition, Weiss et al. (2004, 2006) demonstrated reduction in language lateralization of the frontal cortex in clinically stable schizophrenia patients (2004) as well as in unmedicated schizophrenia men (2006) compared with controls due to bilateral activation in patients in comparison to primarily left activation in controls.

The current fMRI study was designed to further investigate at an early stage of schizophrenia this reduced language-related brain lateralization in terms of its regional distribution within the hemisphere. We reasoned that the effects of chronic illness, such as long-term treatment, institutionalization and aging, may be largely excluded by studying relatively young first-episode patients with schizophrenia. For language-related activation, we alternated the auditory verb generation task with music and silent periods. The paradigm of auditory verb generation has been used extensively in fMRI studies of healthy and neurosurgical populations. It has been shown to be a reliable test for language lateralization comparable to the gold-standard Wada test (Desmond et al., 1995, Kloppel and Buchel, 2005). We used a region of interest (ROI) approach to point to the localization of the abnormality within the hemispheres, and chose the classical language-related regions, including the inferior frontal gyrus (IFG, representing Broca’s area) and the superior temporal sulcus (STS, representing Wernicke’s area). Since the language test was auditory, the primary auditory cortex was examined for non-language-related activation.

2. Materials and methods

2.1. Study population

Twelve right-handed patients with schizophrenia (study group) (6M, 6F) and seventeen right-handed apparently healthy volunteers (control group) (10M, 7F) participated in this study. Right-handedness was verified using a dominance questionnaire (consisting of 10 questions relating to dominance functioning such as writing, drawing, and eating). All participants were native Hebrew speakers. The patients were all hospitalized at a large state psychiatric referral institution for their first-episode of schizophrenia psychosis. Eligibility for study participation was limited to right-handed patients between the ages of 18 and 45 years. Two board-certified psychiatrists verified the patients’ diagnoses, which were determined according to the guidelines of the Structured Clinical Interview for DSM-IV Axis I, Patient Edition (First et al., 1994). Patients with any significant medical or neurological illness or who were pregnant or engaged in any substance abuse were excluded from the study. Medical and neurological illnesses were ruled out by physical and neurological examinations, routine laboratory investigation, reports of the patients’ treating physicians and medical records. Prior to the imaging, the patients with schizophrenia were rated by the clinical assessment scales of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Clinical Global Impression-Severity Scale (CGI-S) (Guy 1976) (Table 1).

All study entrants provided written informed consent after receiving a full explanation of the nature of the study and potential risks and benefits of study participation. The study was approved by the Beer Yaakov Mental Health Center and the Tel Aviv Sourasky Medical Center Institutional Review Boards.

2.2. fMRI paradigm

While being scanned, the subjects participated in an auditory language task or listened to periods of music,
interspersed with periods of no stimuli. All subjects prior to entering the fMRI phase of the investigation underwent a preparatory session in which adequate compliance was documented and assured. Patients for whatever reason demonstrating lack of complete understanding and compliance were not included in the study. The language task was composed of 18 spoken Hebrew words presented through headphones during three 18-s periods. Each block consisted of six different words, at a rate of 1/3 Hz. There were 24 s of no stimuli at the beginning and at the end of the paradigm: although MRI scanning is inherently accompanied by noise, the noise is constant and monotonous, whereupon “no stimuli” can be considered as “rest” (Fig. 1A). Each verbal period was alternated with three 18-s periods of classical music and five 9-s periods of rest. Two more rest periods of 30 s appeared in the beginning and ending of the experiment. Only one version of the experiment was used (the order of the music and verb generation tasks was not randomized between the participants).

The verbal and musical periods were recorded separately and organized in a block paradigm to be presented by the GoldWave program (5.1.2600.2180; Microsoft Windows). The words were three- to five-letter nouns that described commonly used objects, such as a brush and a table. The subjects were instructed to think of but not utter a verb that best described what they could do with the object that was named. For example, when “cup” was heard, they could think of “drinking”. Each verbal period was terminated with an audible ring. The music condition consisted of an instrumental piece of classical music composed by Mozart. During the periods of music, the participants were instructed to listen passively to the music. They were told to do nothing during the rest condition. To avoid contamination by patient movement, the subject was requested to remain still during scanning. (All the subjects had performed with a >90% accuracy score in a prior practice session in which they were presented with auditory nouns and were instructed to say a verb that best described what they could do with the object.)

2.3. Behavioral testing

Seven first-episode patients with schizophrenia (4 males) and 10 healthy subjects (7 males) (who did not perform the fMRI experiment) were part of the behavioral experiment outside the scanner. Eighteen spoken Hebrew nouns were presented through headphones. The subjects were instructed to articulate a verb that best described what they could do with the object that was named. Responses were recorded by Presentation software (Neurobehavioral Systems, Inc., 2003). Reaction time and accuracy were analyzed. Two-tailed, unpaired Student’s t-tests were used in the statistical analysis.

2.4. Brain scanning

Imaging was performed on a GE 1.5 T Signa Horizon LX 8.25 echo speed scanner (Milwaukee, WI, USA) with a resonant gradient echoplanar imaging system. All images were acquired using a standard quadrature head coil. The scanning session included anatomical and functional imaging. The anatomical imaging consisted of 17 contiguous axial T1-weighted slices of 4-mm thickness, with 1-mm gaps that were prescribed based on a sagittal localizer and covered the whole brain. In addition, a three-dimensional (3D) spoiled gradient echo (SPGR) sequence with high resolution (a slice thickness of 2 mm) was acquired for each subject, in order to

### Table 1

Clinical data of first-episode schizophrenia patient subpopulation

<table>
<thead>
<tr>
<th>No.</th>
<th>Age, years</th>
<th>Gender</th>
<th>Handedness</th>
<th>PANSS positive</th>
<th>PANSS negative</th>
<th>PANSS general</th>
<th>PANSS total</th>
<th>CGI-S</th>
<th>Length of hospitalization</th>
<th>Medications</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>Male</td>
<td>Right</td>
<td>17</td>
<td>12</td>
<td>23</td>
<td>52</td>
<td>4</td>
<td>2 weeks</td>
<td>Risperidone</td>
</tr>
<tr>
<td>2</td>
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<td>Right</td>
<td>30</td>
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<td>32</td>
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<td>1 week</td>
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</tr>
<tr>
<td>3</td>
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<td>Right</td>
<td>25</td>
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<td>36</td>
<td>76</td>
<td>5</td>
<td>3 weeks</td>
<td>Tisperidone</td>
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<tr>
<td>4</td>
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<td>60</td>
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<td>3 weeks</td>
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<tr>
<td>5</td>
<td>28</td>
<td>Male</td>
<td>Right</td>
<td>32</td>
<td>18</td>
<td>36</td>
<td>84</td>
<td>5</td>
<td>4 weeks</td>
<td>Quetiapine</td>
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<td>2 weeks</td>
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<td>7</td>
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<td>Female</td>
<td>Right</td>
<td>22</td>
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<td>65</td>
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<td>1 week</td>
<td>Peiphenazine</td>
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<tr>
<td>8</td>
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<td>Male</td>
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<td>28</td>
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<td>2 weeks</td>
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</tr>
<tr>
<td>9</td>
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<td>3 weeks</td>
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<tr>
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<td>2 weeks</td>
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<td>Right</td>
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<td>15</td>
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<td>2 weeks</td>
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<tr>
<td>12</td>
<td>26</td>
<td>Female</td>
<td>Right</td>
<td>17</td>
<td>17</td>
<td>36</td>
<td>70</td>
<td>3</td>
<td>2 weeks</td>
<td>Olanzapine</td>
</tr>
</tbody>
</table>

CGI-S, Clinical Global Impression Severity Scale; PANSS, Positive and Negative Syndrome Scale.
allow volumetric statistical analyses of the functional signal change. The functional imaging included T2*-weighted images that were acquired at the same locations as the spin-echo T1-weighted anatomical images, at runs of 1190 images each (70 images per slice). BOLD contrast was acquired with a gradient echo echoplanar imaging (EPI) sequence (TR/TE/Flip angle = 3000/55/90°; with FOV 24×24 cm²; matrix size 80×80).

2.5. Imaging data analysis

The fMRI data were processed using BrainVoyager 4.4 software package (http://www.brainvoyager.com). Preprocessing of functional scans included head movement assessment (scans with head movement > 1.5 mm were rejected), high-frequency temporal filtering, and removal of low-frequency linear trends. To allow for T2* equilibration effects, the first six images of each functional scan were rejected. Pre-processed functional images were incorporated into the 3D datasets through trilinear interpolation. The complete dataset was transformed into Talairach space. Three-dimensional statistical parametric maps were calculated separately for each subject using a general linear model (GLM) in which all stimuli conditions were positive predictors, with a lag of 3–6 s (individual account for the hemodynamic response delay). Note that this GLM model does not make a priori assumptions regarding the behavior of the fMRI signal in the various conditions (i.e., language versus music).

2.6. Regions of interest (ROIs)

Specific effects were studied in pre-determined regions that are part of the language network and auditory cortex. The regions were defined for each
individual based on commonly used anatomical landmarks that corresponded with activated clusters in functional imaging of verb generation (VG) versus music (Fig. 1B). We focused on two language-related areas: one was confined to the inferior frontal gyrus and Brodmann’s areas 44 and 45 (IFG). This region represented the frontal system of language (i.e., Broca’s area). The second area was confined to the superior temporal sulcus and gyrus and Brodmann’s area 41 (STS). This region represented the posterior language area (i.e., Wernicke’s area) (for average Talairach coordinates, see Table 2).

Language-related activated clusters were obtained individually within the described anatomical landmarks ($P_b < 0.05$, uncorrected) using the GLM with the language condition as a positive predictor and the period of rest as a negative predictor. Music-related activated clusters were collected using GLM contrasts of the music condition as a positive predictor and the rest condition as a negative predictor. The number of activated voxels in each of the defined ROIs on the left and right hemispheres was counted separately for each subject. These counts were used to compute a language-related lateralization index (LI) for each region (i.e., $LI = L - R / L + R$, with $L =$ number of voxels on the left and $R =$ number of voxels on the right). The more positive the number, the more left lateralized would be the activation, while a negative number negative yielded lateralization to the right.

2.7. Statistics

Analysis of variance (ANOVA) was performed to explore the group differences in lateralization using both the averaged LIs and number of active voxels in the language-related brain regions using Statistica (version 5.0). In addition, time courses were extracted for each condition (see details below) from bilateral activated clusters of at least 100 voxels and applied for further analysis in Excel. The individual’s averaged signal was calculated from all epochs of the same condition and transformed into percent signal changes relative to the averaged baseline signal (i.e., the periods of rest) for each ROI. Lastly, this averaged signal change was correlated with the subject’s PANSS scores by Pearson correlation in Statistica (version 5.0).

2.8. Voxel-based whole brain analysis

Using random effect models, we compared brain responses of healthy controls and schizophrenia patients to test for any significant differences that were outside our a priori ROIs. We compared responses to the language condition (+) with responses to the music condition (−) and responses to the music condition (+) with responses to the language condition (−) in the controls and patients at a threshold of $P < 0.01$.

3. Results

3.1. Study sample

Table 1 presents the demographic and clinical data of the 12 schizophrenia patients (aged 19–36 years; 6M, 6F). The control group consisted of 17 apparently healthy age- and gender-matched (aged 22–46 years; 10M, 7F) individuals. Clinical ratings of the patients indicated the following mean scores: total PANSS=71.9, positive PANSS subscale=23.3, negative PANSS subscale=17.5, general PANSS subscale=30.9, mean hallucinations PANSS=2.66, mean delusions PANSS=4.25 and mean CGI-S score=4.45. All patients were receiving medication at the time of imaging for a mean period of 15.75 days (S.D. =12.8). While the time on medication ranged from 7 to 60 days, 11 of the patients were in the range of 7–27 days and one patient had received medication for 60 days. Medications received by the subjects include risperidone ($N=9$, dose range 2–5 mg, mean = 3.2 mg, S.D. =0.9), quetiapine ($N=1$, dose=700 mg), perphenazine ($N=1$, dose=16 mg) and haloperidol ($N=1$, dose=2 mg).

3.2. Behavioral results

Subjects from both groups performed the task with no mistakes (100% accuracy). No difference was found in reaction time between the two groups ($P=0.36$).

3.3. Whole brain analyses

We next applied a whole brain analysis in order to explore task-specific activation using a group random effect approach. Tables 3A and 4A show the regions obtained when contrasting the language condition (+)
with the music condition (−) in the controls and patients, respectively. These contrasts evoked activation in our a priori language-related ROIs in the IFG and STS in both groups. This contrast also evoked activation in the insula, premotor, DLPFC and putamen of the controls (Table 3A), and in the MTS, premotor, DLPFC and putamen of the patients (Table 4A). Tables 3B and 4B present the extent of activation that was preferentially evoked by contrasting the music condition (+) with the language condition (−) for the two groups: this contrast evoked activation mainly in the auditory cortex for both. It also evoked activation in the medial frontal gyrus of the controls (Table 3B) and in the posterior cingulate and medial frontal gyrus of the patients (Table 3B).

3.4. Hemispheric activation

Fig. 2A demonstrates the lateralization of group activation obtained for the language task versus rest for the healthy controls (Fig. 2A1) and for the patients with schizophrenia (Fig. 2A2). The lateralization of the healthy controls is clearly greater than that of the patients with schizophrenia for the language task. Fig. 3A and B shows the difference in lateralization between the groups across language ROIs (i.e., Broca’s and Wernicke’s areas). This difference is demonstrated by larger and more positive LIs in the controls than in the patients ($F(1,54)=22.54; P<0.00001$, Fig. 3A). In order to further quantify this group difference, the number of activated voxels for language versus rest that was obtained for each hemisphere was used as a dependent variable in a two-way ANOVA (group and hemisphere as factors), and a significant interaction was found showing greater asymmetry (i.e., left hemisphere dominance) for the controls than for the patients ($F(1,54)=21.41; P<0.00005$). Post-hoc analyses revealed that this main group difference was due to less right hemisphere activation for the controls than for the patients (Tukey HSD post-hoc, $P<0.001$) (Fig. 3B). This group difference of lateralization was significant for the verbal

<table>
<thead>
<tr>
<th>ROI</th>
<th>Left Peak</th>
<th>Right Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Language &gt; music</td>
<td>IFG (BA 44, 45)</td>
<td>−46,13,3</td>
</tr>
<tr>
<td></td>
<td>STS (BA 41)</td>
<td>−52, −46,10</td>
</tr>
<tr>
<td></td>
<td>Insula (BA 13)</td>
<td>−32,20,7</td>
</tr>
<tr>
<td></td>
<td>Premotor</td>
<td>−40, −2,36</td>
</tr>
<tr>
<td></td>
<td>DLPFC</td>
<td>−41,23,28</td>
</tr>
<tr>
<td></td>
<td>Putamen</td>
<td>−16,4,8</td>
</tr>
<tr>
<td>B. Music &gt; language</td>
<td>Auditory cortex</td>
<td>−42, −17,9</td>
</tr>
<tr>
<td></td>
<td>Medial frontal gyrus</td>
<td>3,51,17</td>
</tr>
</tbody>
</table>

IFG = inferior frontal gyrus; STS = superior temporal sulcus; MTS = middle temporal gyrus; DLPFC = dorsolateral prefrontal cortex.
task but not for the music task in the auditory cortex (Fig. 3C). There was, however, an overall greater activation for music in the auditory cortex of the patients than in the controls \((P<0.005)\) (Fig. 5B), although no significant lateralization effects were found in either group.

A similar analysis for verbal tasks was applied for each language-related ROI (Fig. 4) and a similar pattern was obtained for activation per group and hemisphere both in Broca’s area (i.e., IFG) and Wernicke’s area (i.e., STS). There was a significant interaction in Broca’s area \((F(1,26)=20.77; P<0.0001)\) in which controls, but not patients, demonstrated a significant left dominance for the STS (Tukey HSD post-hoc, \(P<0.0001)\) (Fig. 4A). There was a significant interaction in Wernicke’s area \((F (1,26)=5.83; P<0.05)\) in which controls, but not the patients, demonstrated a significant left dominance for the STS (Tukey HSD post-hoc, \(P<0.001)\) (Fig. 4B).

Lastly, the group effect was tested per brain region across hemispheres for each task (Fig. 5). For the periods of verb generation versus rest, the IFG was similarly activated in both groups, but a larger activation was obtained among the patients with schizophrenia than among the controls for the STS (Tukey HSD post-hoc, \(P<0.0005)\) (Fig. 5A). Similarly, a larger activation in the auditory cortex in response to passive listening of music was seen for the schizophrenia group than for the controls \((F(1,52)=8.084; P<0.005)\) (Fig. 5B).

3.5. Correlations between brain activation and symptom severity

Analysis of the PANSS subtotal and total symptom scales revealed a positive correlation between the positive symptom subscale of the PANSS and the averaged percent signal change during verb generation in the left \((r=0.79; P<0.05)\) and right \((r=0.85; P<0.05)\) STS (Fig. 6A and B, respectively).

Analysis of the PANSS hallucination and delusion scales revealed no correlation with the language lateralization during verb generation. The correlation between the hallucination subscale of the PANSS and the left STS

Fig. 2. Language- and music-related activation maps. Axial views of parametric activation maps obtained during language tasks for the healthy (A1) and the schizophrenia (A2) groups and during music task for the healthy (B1) and the schizophrenia (B2) groups. Colored regions indicate greater activation during VG than during periods of rest \((P<0.005,\) uncorrected with random effect).
is $-0.45$, and the corresponding correlation for the right STS is $-0.18$. Correlations between the delusion subscale of the PANSS and the left STS and the right STS are 0.16 and 0.36, respectively.

4. Discussion

The results of the current fMRI study indicated an overall reduced functional brain asymmetry in the language-related network that includes Broca’s and Wernicke’s areas (i.e., IFG and STS, respectively) in first-episode patients with schizophrenia compared with healthy matched controls. Interestingly, this decrease in brain asymmetry was due to increased activity in the right hemisphere compared with the findings in healthy subjects rather than to relatively decreased activity in the patients’ own left hemispheres (Fig. 3A and B). In addition, the patients demonstrated significantly more activation in the temporal lobe regions (i.e., STS and auditory cortex) for both linguistic and musical stimuli than the controls (Fig. 5).

4.1. Language-related brain lateralization

Our finding of reduced language-related brain lateralization in first-episode patients with schizophrenia is in agreement with behavioral studies using auditory dichotic tests (Wexler et al., 1991; Bruder et al., 1995) as well as with functional imaging findings in young patients with schizophrenia (Luchins et al., 1981; Falkai et al., 1995; Sommer et al., 2001b, 2003). The specificity of our findings to language function is evidenced by the absence of a similar abnormality for music (Figs. 2B and 3C). Since the establishment of

Fig. 3. Task-related activation per group and hemisphere. (A) Lateralization index (LI) for language task across language-related regions. (B) Averaged number of activated voxels for VG versus rest across language-related regions. (C) Averaged number of activated voxels for music versus rest in the auditory cortex. Error bars represent standard error of the mean (SEM). Stars indicate significant differences in activation between groups.
brain asymmetry for language is considered to be part of normal development, the finding of early stage abnormalities suggests disordered brain development in schizophrenia (Weinberger 1987; Crow et al., 1989; Falkai and Bogerts, 1992). In support of this view are findings of reduced right ear advantage for words in a dichotic listening test in first-degree relatives of patients with schizophrenia (Grosh et al., 1995). Whether asymmetry measurements may be applied for early detection of risk for schizophrenia is still undetermined.

Our finding that reduced lateralization in first-episode patients with schizophrenia is due to a relative increase of activity in the right hemisphere is also consistent with the findings of others in young patients with schizophrenia (Sommer et al., 2001b, 2003). We demonstrate for what we believe to be the first time that this “right hemisphere advantage” can be found during language testing in the right homologues of both Broca’s and Wernicke’s areas (Fig. 4). It has been suggested that the “right shift factor”, a dominant allele, is responsible for normal cerebral
asymmetry in healthy subjects by disrupting the growth of language-related regions in the right hemisphere (Annett 1992). Accordingly, it has been proposed that patients with schizophrenia might suffer from an abnormality in this “right shift factor” that is associated with the appearance of psychosis (Crow et al., 1996). Increased homologue right-sided activation in the patient group during the language task might also reflect known abnormalities in prosodic processing in schizophrenia (Leitman et al., 2007). Our study demonstrates that a relatively simple language fMRI test can probe an abnormal “right hemisphere advantage” already evident in young patients with schizophrenia at the time of their first-ever episode, thus excluding long-term effects of medication and aging. Future studies should combine imaging and genetic markers to further explore whether such a “hemispheric advantage” can be considered as an early biological marker of functional resource depletion in schizophrenia.

4.2. Temporal lobe activation

Our study demonstrates that the patients had more overall activation in the temporal lobe (STS and auditory cortex) for both language (Fig. 5A) and music (Figs. 2B and 5B) tasks compared with healthy controls. Other studies have provided evidence of left planum temporale gray matter volume reduction and bilateral Heschl’s gyrus gray matter volume reduction in first-episode patients with schizophrenia compared with healthy controls (Hirayasu et al., 2000). Similarly, Sumich et al. (2002) noted that right-handed male patients experiencing their first episode of psychotic illness had smaller left planum temporale volumes than healthy subjects. Kasai et al. (2003) reported

Fig. 6. Correlation of language activation with symptom severity in the schizophrenia group. Significant correlation between scores on the positive scale of the PANSS and the averaged % signal change in the left (A) and right (B) superior temporal sulcus (STS).
that patients with first-episode schizophrenia showed significant decreases in gray matter volume over time in the left superior temporal gyrus compared with patients with first-episode affective psychosis or healthy subjects. Others have shown volume reduction only in the right superior temporal gyrus in patients with early-onset schizophrenia in relation to matched controls (Matsumoto et al., 2001). The results from the current study suggest that these anatomical abnormalities observed on MRI may be reflected at the functional level as bilateral excessive activation extending beyond the STS in the temporal lobe (i.e., the auditory cortex) (Fig. 5). In support of the role of the temporal lobe in schizophrenia phenomenology is our finding of a significant correlation between signal changes during language tasks in the STS and the severity of positive psychotic symptoms on the PANSS (Fig. 6A and B). This effect, already detectable at the first episode of schizophrenia, also corresponds with the findings of others who have suggested that the temporal lobes are primarily involved in the appearance of positive symptoms (Shenton et al., 1992; McGuire et al., 1998; Crespo-Facorro et al., 2004). A possible explanation for the finding of extended activation in the temporal lobes could reflect increased anxiety in the patients. This may also explain the correlations with symptom severity. It may also be suggested that a further explanation for the increased temporal activation could be non-selective recruitment of temporal brain structures due to impaired specialization (Dolfus et al., 2005).

Previous imaging reports have found that reduced regional hemispheric volume asymmetry is associated with more severe negative symptoms in chronic schizophrenia (Bilder et al., 1994). We cannot yet conclude whether our findings of functional asymmetry of language may also be associated with negative symptoms, but it is possible that they may be predictive of a more chronic form of the disorder (i.e., to emerge in the future). A study of larger patient samples with more variable clinical presentations will also allow further exploration of this possibility. It should be noted that within the rubric of verb generation there are several linguistic functions (including lexical search processes, subvocal representations and processes of working memory). While each of these is important and would be interesting to examine individually, the scope of this study did not allow for the breakdown of “verb generation” into its component parts, and further research should explore these components. A further limitation of the study was that despite patients being in their first episode of psychosis, many had already received some antipsychotic medication, albeit for a very short period of time. While results may have been influenced by an immediate effect of antipsychotic medication, the short-term use of antipsychotic medication was permitted in this study in these first-episode psychosis patients for ethical reasons (no delays in clinical management). Furthermore, precedent exists in many studies of first-episode psychosis patients to include patients in investigation despite recent short-term use of antipsychotic medication in order to maintain patient ease and protocol compliance.

In summary, our fMRI study demonstrates reduced language-related brain asymmetry in Broca’s (i.e., IFG) and Wernicke’s (i.e., STS) areas already present at the time of the first episode of schizophrenia psychosis. These observations appeared to be as a result of regional of increased activity in the right hemisphere rather than decreased activity in the left hemisphere. In addition, overall activation of the temporal lobe was greater for both language and music stimuli in patients with schizophrenia than in healthy controls, but only the language-related activation in the temporal lobe regions directly correlated with the severity of positive symptoms in the patient group. Confirmation of these findings with a larger sample size and with broader, more comprehensive neurocognitive reflections of language-related functional asymmetry would be recommended.

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