CHAPTER 10

Language lateralization in women with schizophrenia
ABSTRACT

Gender differences in schizophrenia are among the most consistently reported findings in schizophrenia research. However, the biological substrate underlying these gender differences is still largely unknown. Differences in language lateralization between men and women may underlie some gender differences in schizophrenia. In previous functional imaging studies, language lateralization was found to be decreased in male schizophrenia patients as compared to healthy males, which was due to enhanced language activation of the right hemisphere as compared to the healthy males. It could be hypothesized that decreased language lateralization in schizophrenia is gender specific; i.e. decreased lateralization in male patients and normal lateralization in female patients.

To test this hypothesis, language activation was measured in 12 right-handed female patients with schizophrenia and 12 healthy females and compared to findings in 12 male patients and 12 male controls of an earlier study.

Language lateralization was significantly lower in the female patients (0.44) as compared to the female controls (0.75), which was due to increased activation of the right sided language areas (patients: 19 voxels, controls: 8 voxels), while left hemisphere activation was similar in patients and controls. When these data are compared to the male patients and controls, both patient groups had lower lateralization than their healthy counterparts, but there was no difference between male and female patients. In both sexes, decreased lateralization resulted from increased right hemispheric language activation, which suggests a failure to inhibit non-dominant language areas in schizophrenia. These findings indicate that lower language lateralization in women is not likely to underlie gender differences in schizophrenia.
INTRODUCTION

As is well known, gender is an important factor in schizophrenia, since differences in age at onset and course of schizophrenia between male and female patients are among the most consistent findings in schizophrenia research (Leung and Chue 2000). The most striking gender difference is the age of onset (first appearance of psychotic symptoms), which is typically around five years later in females (Jablensky et al. 1992). Secondly, symptom profile is different between the sexes, with men having more negative symptoms and women having more paranoid psychosis and more affective symptoms (World Health Organization 1973, 1975). Thirdly, male patients are reported to have poorer premorbid social competence (Lewine 1981). Finally, female patients generally respond better to treatment and outcome is also better in female than in male patients (Sikich and Todd 1988; Leung and Chue 2000). The biological substrate(s) underlying these gender differences in onset and course of schizophrenia are still largely unknown, though estrogens are hypothesized to play an important role (DeLisi et al. 1989). Gender difference in language lateralization is another factor that could be speculated to underlie some of the gender differences in schizophrenia (Ragland et al. 1999; Gur et al. 2000).

Several functional imaging studies found higher language lateralization in healthy men as compared to women (Shaywitz et al. 1995; Pugh et al. 1996; Gur et al. 2000; Kansaku et al. 2001). However, other studies, including the large study by Frost et al. (1999), found no gender difference in language lateralization (Price et al. 1996; van der Kallen et al. 1998). Though results are inconsistent, there is some evidence that women may have a more bilateral pattern of cortical language representation, which could provide more “brain reserve” to counter a possible left hemisphere dysfunction in schizophrenia (Sikich and Todd 1988).

In schizophrenia, left cerebral dominance may be decreased. This is suggested by the higher incidence of left-handedness, decreased structural asymmetry of language-related areas and decreased perceptual asymmetry on the dichotic listening paradigm in schizophrenia (for a quantitative review see Sommer et al. 2001a). Several functional brain imaging studies provide information on language lateralization in schizophrenic patients. Lewis et al. (1992) reported decreased left frontal activity during verbal fluency, resulting in reversed frontal dominance in schizophrenia. Crow (2000) re-analyzed the data of a study by Spence et al. (2000) and reported
reduced lateralization in schizophrenic patients. Artigues et al. (2000) also observed reduced lateralization in schizophrenia using a verbal fluency protocol. In an earlier study of our group, language lateralization was decreased in male schizophrenic patients (Sommer et al. 2001b). In that study, decreased lateralization in the patient group resulted from increased language-related activation of the right hemisphere, while language activation of the left hemisphere was similar in patients and controls. Furthermore, decreased language lateralization correlated with increased severity of hallucinations. The latter finding suggests that decreased language lateralization may play a role in the etiology of psychosis, at least of hallucinations.

It is not clear whether the results obtained in male schizophrenia patients can be extrapolated to female patients with schizophrenia, since neurobehavioral laterality indices, i.e. performance on motor, sensory, and spatial and verbal cognitive tests, were reportedly different in male and female schizophrenia patients (Ragland et al. 1999). Furthermore, a possible gender difference in language lateralization may be a factor underlying some of the gender differences in onset and course of schizophrenia. It could be hypothesized that decreased language lateralization in schizophrenia is gender specific (i.e. decreased lateralization in male schizophrenia patients and normal lateralization in women with schizophrenia). To test this hypothesis, we studied language lateralization in female schizophrenia patients and compared the results to the data from the earlier study in male patients.

METHODS

Subjects
Twelve women were included that fulfilled DSM-IV criteria for schizophrenia, paranoid subtype, 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 (SADS-L) (Andreasen et al. 1992). Patients with comorbid depression were excluded. The mean age of the patients was 33.6 (s.d. 8) and the mean age at onset (first appearance of psychotic symptoms) was 28 (s.d. 5). Patients with diagnosis of drug dependence or substance abuse in the three months prior to entry were excluded. All patients were on atypical antipsychotic medication: six patients used clozapine (mean dose 339 mg, s.d. 67), five patients used
olanzapine (all 15 mg) and one patient used risperidone (3 mg). No additional medication was used, except oral contraceptives in five patients. The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) was used for symptom assessment immediately prior to the scan session. Presence and severity of several positive and negative symptoms were scored over the last two weeks. Ratings were carried out by a physician and a second rater who had been trained for the interview. Scores were determined by means of consensus.

Twelve healthy women aged 32 (s.d. 12), who were free of medical or neurological illness, were also included. Subjects met Research Diagnostic Criteria for “never mentally ill” according to the CASH and SADS-L interview and had no first or second degree relatives with schizophrenia. 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. Seven females from the control group used contraceptive pills.

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.

All subjects were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). Mean score on the Edinburgh Handedness Inventory was 0.92 (s.d. 0.1) for the patients and 0.92 (s.d. 0.2) for the controls. Four patients and four controls had left-handed first-degree relatives. The primary language of all subjects was Dutch.

After complete description of the study to the subjects, written informed consent was obtained.

Tasks

Tasks and scan technique are described in detail by Ramsey et al. (2001). Briefly, two word tasks were used: the verb-generation task and the reverse-read semantic decision task. For the verb-generation task a noun appeared on the screen every 3.6 seconds. The subject was instructed to generate 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 (but 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 orthographic word recognition and put more
emphasis on phonologic decoding. The subject was instructed to vocalize
the word silently and push a button if the word was an animal. For the
reverse-read task performance was recorded by a computer. 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 an asterisk in the center of the screen. A simple button-
press task (i.e. respond to an asterisk, which appeared at the same rate as
the targets) was used as a baseline condition for the reverse-read task.

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 Gelderen et al. 1995),
with the following parameter settings:
TE/TR 35/24 ms, flip angle 9°, FOV 225 x180x91 mm, matrix 52x64x26,
voxel size 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
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 and translated and
rotated to the standard brain from the Montreal Neurological Institute
(Collins et al. 1994) without scaling. Brain activation maps were obtained
by analyzing the fMRI scans acquired during both tasks together. Advantages
of this combined task analysis are discussed by Ramsey et al. (2001). Functional images were analyzed on a voxel by voxel basis using
multiple regression analysis (Worsley and Friston 1995) with one factor
coding for activation (task versus rest), and three for signal drift (due to
scanner hardware). The regression coefficient for activation was converted
to a t-value for each voxel, yielding a t-map. Significant activation was then
determined in each voxel by applying a threshold. The threshold corre-
sponded to a p-value of 0.05, Bonferroni-corrected for the total number of
voxels in the brain, and amounted to a t-value of approximately 4.5 (depending on the number of voxels for each individual). Five 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 DISPLAY tool from the Montreal Neurological Institute. The VOI’s comprised Brodmann area (BA) 44 and 45 (Broca’s area and its contralateral homologue), 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 of visually presented words is thought to be mediated (Springer et al. 1999; Perry et al. 1999).

In each VOI the number of active voxels was determined. For subsequent analyses the VOI’s were combined, yielding one measure of language-related activation for each hemisphere.

A lateralization index was calculated, 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 in both hemispheres.

For the patient group, correlations between the lateralization index and the score on the main psychotic symptoms, i.e. delusions (item one of the PANSS) and hallucinations (item three of the PANSS), were calculated and tested for significance (bivariate correlations, tested one-sided).

Comparison to the male patients and controls
The data of the male patients and controls were obtained two years ago (Sommer et al. 2001b). Since then, our method of measuring language lateralization has been updated in two aspects. Firstly, the dorso-lateral prefrontal cortex (DLPC) is no longer considered to be a language area and is therefore no longer included as a VOI for language activation. Secondly, there has been a renewal of the statistical software. In order to make the male data exactly comparable to the present data in females, the raw scan data were re-analyzed with the new statistical package and with exclusion of the DLPC as a VOI.

Laterazation indices and summed language activation in the VOI’s of both hemispheres of both sexes were analyzed in an ANOVA, testing a main effect for Gender, a main effect for Diagnosis and a Gender-by-Diagnosis interaction. A direct comparison (independent t-test) between male and female patients was also performed since this test has more discriminative power than the ANOVA.
RESULTS

Symptoms
The mean total PANSS score at the time of scanning was 60 (s.d. 12). The mean subscore on all positive items of the PANSS was 16 (s.d. 5) and the mean subscore on all negative items was 13 (s.d. 4). This indicates that symptom severity in the female patients is in the same range as symptom severity in the study on male patients (total score: 60, positive subscore: 15, negative subscore: 14).

Performance
Performance on the reverse-read task was reduced in the patient group: mean of 20 errors (s.d. 8) on 128 trials, versus 10 (s.d. 6) for the controls (t(22)=2.2, p<0.05). This was similar to performance in the male study (21 and 8 errors respectively)

Manual segmentation
There was no significant difference in the size of the VOI’s (i.e. the total volume of all VOI’s within each hemisphere) between the groups, nor was there a difference in total VOI size between the right and left hemisphere.

Activation pattern in the females
Mean activation in the language areas of the left hemisphere was not significantly different between patients (49 voxels, s.d. 32) and controls (50 voxels, s.d. 35).
The mean activation in the language areas of the right hemisphere was significantly elevated in the patients (19 voxels, s.d. 15), as compared to the controls (8 voxels, s.d. 7), t=2.4, p<0.05. The mean lateralization index of the patients (0.44, s.d. 0.23) was significantly lower than that of the controls (0.75, s.d. 0.2), t=3, p<0.01.

Correlation with symptom severity
Decreased language lateralization was significantly correlated with increased severity of delusions (rho= -0.54, p<0.05), but not with the severity of hallucinations (rho= -0.36, n.s.).
Comparison males and females

When the lateralization indices of these women are compared to the indices of the male patients and controls, a main effect for Diagnosis emerged (F(2,44)=13.1, p<0.001) and a main effect for Gender (F(2,44)=4.6, p<0.05), but no Gender by Diagnosis interaction (F(2,44)= 0.2, n.s.). Lateralization indices of all four groups are plotted in figure 1.

For the language activation in the VOI’s of the left hemisphere, no main effects and no interaction emerged. For the language-related activation in the VOI’s of the right hemisphere a significant main effect for Diagnosis (F(2,44)=10.8, p<0.005), but no main effect for Gender and no interaction emerged.

In the direct comparison between male and female patients no differences were found in lateralization index (t=-1.2, n.s.), neither in left hemisphere language activation (t=-0.1, n.s.) nor in right hemisphere activation (t=0.5, n.s.)

![Figure 1](image)

Language lateralization in healthy men (black), men with schizophrenia (grey), in healthy women (black) and in women with schizophrenia (grey)
DISCUSSION

Language lateralization was studied in 12 female patients with schizophrenia and 12 healthy females. Lateralization was decreased in the patients as compared to healthy women, which resulted from increased activation of right hemispheric language areas in the patient group. Activation of left hemispheric language areas was similar in both groups. When the results of this study are combined with the results of our previous study in male patients (Sommer et al. 2001b), lateralization was decreased in patients of both sexes as compared to their healthy counterparts, but there was no difference in language activation between female and male patients. Women, as a group, had higher degrees of language lateralization than men, which is probably a chance finding. In both patient groups, decreased language lateralization was due to increased language activation of the right hemisphere, while left hemisphere language activation was normal. These results suggest that decreased language lateralization in schizophrenia is not gender specific. It is therefore not likely that gender differences in language lateralization underlie gender differences in age at onset and course of schizophrenia.

Decreased lateralization was correlated to the severity of delusions, which suggests that relatively increased participation of right hemisphere areas for language may lead to delusional thinking. Indeed, an association was reported between decreased language lateralization, as measured with dichotic listening tests and increased loosening of associations in healthy (Leonhard and Brugger, 1998) and in schizotypal subjects (Poreh et al. 1993).

Other functional imaging studies that assessed language activity in patients with schizophrenia either studied only men (Artiges et al. 2000; Curtis et al. 1999; McGuire et al. 1996; Lewis et al. 1992), or did not analyze male and female patients separately (Ragland et al. 2001; Crespo-Facorro et al. 1999; Dye et al. 1999; Frith et al. 1995; Wood et al. 1990; Yurgelun-Todd et al. 1996; Spence et al. 2000). Only the early functional imaging studies by Gur et al. (1983 and 1985) provided separate data on language activity in male and female patients. In these studies language lateralization was lower in female patients as compared to healthy females. In men, language lateralization was not found in the patients, nor in the control group. However, these studies were among the first functional imaging studies in schizophrenia and
the signal to noise ratio may have been relatively low, which can explain the unusual finding of absent language lateralization in healthy males. In the present (female) and the previous (male) study (Sommer et al. 2001b), activation of right sided language areas was significantly increased in schizophrenia patients, while language activation of the left hemisphere areas was normal. This activation pattern could result from a more bilateral cortical representation of language functions, or it could result from a failure to inhibit non-dominant language-related areas. With fMRI it is not possible to differentiate between activation from critical language areas (i.e. areas were lesions would lead to aphasia) and activation from additional areas (i.e. areas that are not essential for language function). The pattern of language activation of the schizophrenia patients, with increased activation of the right hemisphere and normal activation of the left hemisphere, differs from the activation patterns reported for healthy women. Studies that reported decreased lateralization in women (Shaywitz et al. 1995; Pugh et al. 1996; Gur et al. 2000; Kansaku et al. 2001), found that women showed increased language activation in the right hemisphere, which was coupled with decreased language activation in the left hemisphere, although not all functional imaging studies on language found lower lateralization in women as compared to men (Price et al. 1996; van der Kallen et al. 1998; Frost et al. 1999). The difference in activation patterns between healthy women with low lateralization (i.e. a shift in language activation from the left to the right hemisphere) and schizophrenia patients with low lateralization (i.e. additional right hemisphere activation with normal left hemisphere activation) could imply that decreased lateralization in healthy women reflects a more bilateral cortical language representation, while decreased lateralization in schizophrenia patients results from a different mechanism. Increased language activation of the right hemisphere in schizophrenia, in the absence of decreased language activation in the other hemisphere, may reflect a failure to inhibit the non-dominant language areas, while the critical language areas are located at their regular site in the left hemisphere.

However, the results of this study need to be interpreted with caution, mainly because the sample size is limited. Furthermore, all patients were using atypical antipsychotic medication. It is not clear whether antipsychotic medication has an effect on language activation, and whether this effect is different for atypical and typical antipsychotics.

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. However, this is unlikely, as one would then expect to find reduced brain activity levels, which was not the case in the patients of this study.

In summary, language lateralization was decreased in female schizophrenia patients as compared to controls, which was due to increased activation of the right hemisphere. No difference in language lateralization between female and male patients was found. Thus, it appears unlikely that the gender differences in onset and course of schizophrenia are related to a gender difference in language lateralization. The consistent finding of increased right-sided language activation in schizophrenia may be explained by a failure to inhibit non-dominant language areas.
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