Part 2 Language lateralization in schizophrenia

CHAPTER 12

Lateralization of hallucinations

ABSTRACT

Several studies reported decreased language lateralization in schizophrenia, which has been linked to psychotic symptoms. Possibly, language activation of the right hemisphere may become misperceived and lead to auditory verbal hallucinations. To test this hypothesis, functional imaging studies of auditory verbal hallucinations were reviewed in a meta-analysis. The results showed that the language areas of the left hemisphere showed more activity during hallucinations than the right-sided homologues. This finding does not support a right hemisphere origin of auditory verbal hallucinations.
INTRODUCTION

The finding of decreased cerebral asymmetry in schizophrenia, first observed by Crow et al. (1989), has been replicated with several techniques (for reviews see Shapleske et al. 1999; Sommer et al. 2001a). In addition, functional imaging studies reported decreased lateralization of language-related activation in schizophrenic patients as compared to healthy controls (Artiges et al. 2000, Sommer et al. 2001b). Several structural and functional studies correlated decreased asymmetry to psychotic symptoms (e.g., Sommer et al. 20016, Sommer et al. 2003). It could be hypothesized that inner speech, originating from right cerebral homologues of the language areas is perceived as auditory hallucinations. Self-produced language activity normally leads to inhibition of language perception areas (McGuire et al. 1996). When this inhibitory mechanism is failing, verbal thoughts may not be recognised as originating from the self and erroneously be attributed to an external source (Frith 1992). Indeed, inhibition of language perception might be more prone to failure when language activity is derived from an unusual site, i.e. from contralateral homologues areas in the right hemisphere. This hypothesis can be tested by reviewing studies meta-analytically that report functional activation in schizophrenia patients while experiencing hallucinations.

METHOD

The following inclusion criteria were used: valid functional imaging technique, bilateral measurement of activity, right-handed patients with diagnosis of schizophrenia, hallucination-related activity measured either in a block design or with event-related fMRI protocols. Because we are interested in laterality of the verbal component of auditory hallucinations, analysis was restricted to activity in areas that are known to be involved in language: Brodmann areas 21, 22, 38, 39, 40, 41, 42, 44, 45, and 52 (Ramsey et al. 2001). Significant hallucination-related activity was statistically integrated and compared between areas in the left and the right hemisphere using the logaritmic Risk Ratio method (Shadish & Haddock, 1994).

In order to be less dependent on statistical thresholds of the individual studies, data were also analysed with a vote counting method, which compares the number of language-related areas that is significantly activated between the right and left hemisphere.
RESULTS

Five studies met our inclusion criteria: Woodruff et al. 1995 (1 subject), Silbersweig et al. 1995 (5 subjects), Dierks et al. 1999 (3 subjects, from which 2 right-handed), Lennox et al. 2000 (4 subjects), and Shergill et al. 2000 (5 subjects).

Only three studies could be included in the Risk Ratio analysis: Dierks et al. (1999), Lennox et al. (2000) and Shergill et al. (2000), since the Woodruff et al. (1995) study provided insufficient data and the study by Silbersweig et al. (1995) did not report activity in language-related areas at all. The resulting mean, weighted Risk Ratio (left/right) was 3.42 (k=3, total N=11), implying stronger activity of left hemisphere language areas, with a 95% Confidence Interval ranging from 2.89 to 4.81.

All five studies could be included in the vote counting analysis. This analysis also demonstrated that more left hemisphere (n=14) than right hemisphere (n=7) language-related brain areas were significantly activated during auditory verbal hallucinations.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Left hemisphere</th>
<th>Right hemisphere</th>
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<tbody>
<tr>
<td>Woodruff et al. (1995)</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Lennox et al. (2000)</td>
<td>4</td>
<td>3</td>
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<td>Silbersweig et al. (1995)</td>
<td>5</td>
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<td>Dierks et al. (1999)</td>
<td>2</td>
<td>7</td>
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<td>Shergill et al. (2000)</td>
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CONCLUSION

Using two different methods, our results showed that language-related areas in the left hemisphere were significantly more activated than the right sided homotope regions.

Thus, the hypothesis that auditory verbal hallucinations arise from a right hemisphere source of language production (inner speech) and are subsequently perceived as originating from an external source is not supported by the available evidence.
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Summary and discussion
In this thesis, the role of language lateralization in the pathogenesis of schizophrenia is investigated. As with many brain mechanisms studied in schizophrenia, there were gaps in our knowledge on language lateralization in the healthy brain. Therefore, the first part of this thesis is dedicated to aspects of language lateralization in healthy subjects. These studies are essential to interpret subsequent findings in schizophrenia patients.

Since both clinicians and brain researchers may not always be familiar with the details of language lateralization, the aspects of language lateralization relevant to this thesis are discussed in chapter 1.

Chapter 2 presents a hypothetical model on the evolution of language lateralization. In this model, the unilateral development of Broca's and Wernicke's area in most human brains is thought to have resulted from transcription factors that have an expression pattern restricted to the left hemisphere.

In chapter 3, language activation patterns of healthy subjects performing several language tasks are compared. It was concluded that the combined language task protocol is most apt to study cerebral lateralization in schizophrenia. This method was used for all further functional MRI studies in this thesis.

After the method was established, three other aspects of language lateralization in healthy subjects were assessed and described in the following three chapters.

In chapter 4, the issue of sex differences in language lateralization was studied in a meta-analysis. Although women are generally believed to have a more bilateral pattern of language representation than men, our meta-analysis on language activation patterns of 377 men and 442 women yielded no significant difference between healthy men and women. This implies that the sex difference in language lateralization in healthy adults is very small or non-existent.

Chapter 5 is focused on another topic of dispute: language lateralization in monozygotic twin pairs. Approximately 20% of monozygotic twin pairs are discordant for handedness, which is virtually the same percentage as dizygotic twin pairs. Since handedness is genetically determined (Hicks and Kinsbourne 1976), this is an unexpected finding. Handedness is related to language lateralization and thus, language lateralization may also show discordance in an unexpectedly high percentage of monozygotic twin pairs.

To test this prediction, language lateralization was studied in 12 monozygotic twin pairs that were concordant for right-handedness and in 13
monzygotic twin pairs of discordant handedness. All concordant right-handed pairs were left cerebral dominant for language and showed high resemblance for the degree of lateralization. From the twin pairs that were discordant for handedness, the majority also showed high correspondence for language lateralization, similar to the handedness concordant group. However, five handedness discordant twin pairs showed large differences in the degree of language lateralization and even opposite cerebral dominance. It is hypothesized that left-handedness and right or bilateral language dominance in these “mirror-imaged” twin pairs is a result of early embryological determination of asymmetry that was disrupted by the splitting process of monozygotic twinning. The finding that monzygotic twin pairs of discordant handedness can show opposite patterns of cerebral lateralization may have implications for studies that use twins to investigate the relative contribution of genes and environment in cerebral diseases, such as schizophrenia. Decreased language lateralization may be a predisposing factor to develop schizophrenia (Green et al. 2003). The twin with disrupted (i.e. right or bilateral) dominance may thus have a higher risk to develop the disorder than his co-twin with “standard” (i.e. left) cerebral dominance. Such an unequal risk for monzygotic twins of these mirror-imaged pairs may also exist for other cerebral diseases, such as depression, autism and dyslexia (Bruder et al. 2003). Mirror imaging is estimated to occur in 35% of monzygotic twin pairs that are discordant for handedness (Springer and Searleman 1978). Therefore, mirror-imaging in twin studies could lead to an underestimation of the genetic contribution to diseases in which hemispheric lateralization may play a role in the aetiology. For future twin studies on diseases that could be dependent on cerebral lateralization we recommend to include only concordant right-handed twin pairs.

In chapter 6, a challenge study in healthy subjects is described that tests the association between language lateralization and cerebral dopamine concentrations. In rats, the striatum of the dominant hemisphere was found to have higher dopamine levels than the non-dominant striatum (Glick and Shapiro 1984). The concentrations of dopamine in the two rat striata normally differ by about 15%, but this asymmetry could be increased to approximately 25% following administration of amphetamine, which resulted in enhanced directional preference in level pressing and turning behavior (Glick and Shapiro 1984). If cerebral dominance in humans would also be related to differences in striatal dopamine concentrations, this would be an important issue for studies on schizophrenia. For example,
antipsychotic medication would be expected to have major impact on lateralization, and groups could only be compared if they had equal doses of similar antipsychotic medication. To assess the influence of differences in cerebral dopamine concentrations on human lateralization, ten volunteers participated in a double blind cross-over study that compared functional scans under placebo condition to scans of the same subjects two hours after administration of 0.25 mg/kg dextro-amphetamine. The scans during the amphetamine condition showed increased activation in several language-related areas of both hemispheres, which may reflect increased vigilance. However, amphetamine challenge had no significant effect on lateralization, which implies that dopamine does not play a key role in language lateralization.

In part II of this thesis, the studies on schizophrenia are described. Chapter 7 provides an introduction for those readers who are not familiar with the clinical and epidemiological aspects of schizophrenia. In chapter 8, the literature on possible associations between schizophrenia and cerebral lateralization are summarized in a meta-analysis. The results showed that schizophrenia patients are more frequently non-right-handed (i.e. left-handed or ambidexter) than healthy subjects. Also, non-right-handed children have a somewhat higher chance to develop schizophrenia in adulthood than their right-handed peers. Furthermore, the planum temporale (the upper surface of the temporal lobe that largely overlaps with Wernicke’s area) was more symmetrical in patients with schizophrenia than in healthy subjects. In addition, dichotic listening tests generally reported a decreased Right Ear Advantage (REA) in schizophrenia. All three findings suggest that language lateralization is more bilateral in schizophrenia patients, compared to healthy controls. Decreased language lateralization in schizophrenia has generally been considered to reflect a dysfunction of the left hemisphere in schizophrenia. However, this is not in agreement with the findings of the meta-analysis on asymmetry of the planum temporale. Decreased asymmetry of the planum temporale in schizophrenia was not caused by a smaller left planum, but due to a larger right planum. This may reflect a failure to inhibit development of language-related areas in the non-dominant hemisphere rather than a compensation for an underdeveloped left hemisphere.

In chapter 9, the first patient study is described. The lateralization pattern of language functions was assessed in 12 male schizophrenia patients and 12
matched controls. The results were evident: language lateralization is decreased in schizophrenia and this is caused by increased activity of the right cerebral homologues of Broca’s and Wernicke’s area. Language activation of the left sided language areas was equal in patients and controls. Furthermore, decreased lateralization correlated to increased severity of auditory hallucinations in this patient group. This may suggest that language lateralization is a state phenomenon that temporarily decreases during psychosis and may normalize after remission of psychosis. However, other studies found that structural asymmetry was also decreased in schizophrenia (chapter 8), which suggests a more stable decrease in lateralization. Since the first patient study consisted solely of men, the study needed replication in a female sample.

In chapter 10, the results are described of functional language activation scans in 12 female schizophrenia patients and 12 female control subjects. Similar to the findings in men, schizophrenia was associated with decreased lateralization, which resulted from increased language activity of the right hemisphere as compared to healthy volunteers. When these results are compared to the findings in the male patients study, no sex differences in lateralization emerged. In the female patient study, a correlation was observed between decreased lateralization and increased severity of delusions. The correlation with the severity of hallucinations failed to reach significance, possibly because only few female patients were suffering from hallucinations in the days prior to the fMRI scan.

At this point, there was consistent evidence that language lateralization is decreased in patients with schizophrenia. But it was not clear what the significance of decreased language lateralization in schizophrenia may be. All participating patients were using antipsychotic medication. This medication is known to affect several language functions (Docherty and Gottesman 2000), and may also have altered language lateralization. The correlation with the severity of positive symptoms suggests that decreased lateralization may be a state phenomenon accompanying psychosis. Possibly, cerebral ordering systems, such as the thalamic gating mechanism, may become malfunctioning during psychosis (Andreasen 1997). This could result in dysfunction of cortical systems, which may cause both decreased language lateralization and psychosis. Thus, decreased lateralization could be a feature that is associated with psychosis, without having a role in its etiology. On the other hand, decreased lateralization could antedate psychosis.
Decreased lateralization could thus be a risk factor that predisposes the brain for the development of psychosis and may even have a role in the pathogenesis of psychosis. To differentiate between these two possibilities, one would have to assess lateralization in subjects that later develop psychosis. Given the incidence of 1% for schizophrenia, it would take a great effort to study the association between language lateralization and schizophrenia in a prospective design. An alternative strategy is to study monozygotic twin pairs that are discordant for schizophrenia. The non-schizophrenic twin is genetically identical to the schizophrenic twin, but has never suffered from psychosis. This twin will have all the genetic predisposing factors, but not the phenomena that are secondary to the disease or to its treatment.

In chapter 11, language lateralization was measured in 12 monozygotic twin pairs discordant for schizophrenia and 12 healthy monozygotic twin pairs, who were matched for sex, age and education. All participating twin pairs were right-handed. Language lateralization was decreased in the discordant twin pairs as compared to the healthy twin pairs. Language lateralization in the unaffected co-twins of the patients was significantly lower than in control twins. Within the discordant twin pairs, there was a trend towards decreased language lateralization in the non-schizophrenic co-twins as compared to the patients. This may be a medication effect. All schizophrenic twins used antipsychotic medication and this could have corrected their decreased degree of lateralization to a subnormal level. A study is currently undertaken in which language lateralization is measured in medication naive schizophrenia patients, and then again when the patients are taking antipsychotic medication for eight weeks. This study may reveal the effect of antipsychotic medication on language lateralization, and may also shed light on the stability of individual degrees of lateralization when psychotic symptoms have subsided.

The finding of decreased language lateralization in the non-schizophrenic co-twins suggests that decreased language lateralization constitutes a genetic predisposition for schizophrenia. The discordant pairs did not differ from control pairs in the activation of the language-related areas of the left hemisphere, but language-related activation in the right hemisphere was significantly higher in the discordant twin pairs than in the healthy pairs. Possibly, the language activation pattern in schizophrenia patients reflects the use of additional cortical areas in the right hemisphere, to compensate for the left sided language areas that are less efficient in handling language functions. The slightly lower degree of language lateralization in the non-
schizophrenic co-twins as compared to the affected twins may then reflect an even more successful compensation mechanism than in their schizophrenic twins. Alternatively, the language activation pattern in the discordant twin pairs may reflect a failure to inhibit homologue cortical areas in the right hemisphere while the language areas of the left hemisphere are functioning normally. The additional right hemisphere activation may be disadvantageous for language functioning, and may even give rise to language-related psychotic symptoms.

Normal language dominance may be accomplished by a gating mechanism of the thalamus, which selectively facilitates the cortical areas that are specialized for a language function, while inhibiting the contralateral homologue areas (chapter 1). Lesions of the left thalamus, especially of the ventrolateral and pulvinar nuclei are known to cause language deficits consisting of paucity of spontaneous speech, perseverations, dysnomia and neologisms with intact comprehension and repetition (Reynolds et al. 1978). Electro-stimulation of the dominant ventrolateral thalamus during brain surgery leads to activation of the dominant language areas while the contralateral homologues are inhibited (Ojemann 1975). Left-handed subjects have a more bilateral thalamo-cortical facilitation (Ojemann 1975), which may underlie their more bilateral representation of language functions. In Parkinson patients treated with stereotactic thalamotomy, language lateralization increased during direct electrical stimulation of the left ventrolateral thalamus and subsequently decreased after thermocoagulative destruction of this nucleus. These effects are absent when stimulation and coagulation is applied to the right ventrolateral thalamus (Hugdahl and Wester 2000). Thus, the language activation pattern observed in the discordant twin pairs of the present study may result from a failure of the thalamus to perform its normal inhibitory activity on the non-dominant cortical areas. Because the thalamic inhibitory mechanism is failing, inappropriate language activity, originating from the right hemisphere, may emerge. When this “release” language activity is not integrated correctly, subjects may wrongly attribute this self-generated language activity to an external source. Language-related psychotic symptoms such as auditory verbal hallucinations and formal thought disorder may result from incorrect integration of language activity of the right hemisphere (Nasrallah 1985). Therefore, the excess language-related activation in the right hemisphere found in the discordant twin pairs may be a functional substrate of their increased risk to develop psychosis.
In order to test whether language activity in the right hemisphere of schizophrenia patients is a necessary compensation mechanism or a disturbing failure of inhibition, transcranial magnetic stimulation (TMS) is currently used to assess dysphasia after stimulation of right sided language areas in schizophrenia patients. If the right-sided language activation is necessary to maintain normal language functions, patients may become dysphasic when the right sided homologue of Broca’s area is stimulated. Alternatively, if right-sided language activation is causing language-related psychotic symptoms, TMS may give relieve of these symptoms. In this case, TMS could further be tested as a therapeutic instrument for persisting auditory verbal hallucinations. However, results of this study are not yet available.

In chapter 12, meta-analysis was performed on functional imaging studies that have measured cerebral activity during auditory verbal hallucinations in schizophrenic patients. The aim was to test whether cerebral activation during auditory verbal hallucinations is indeed derived from frontal and temporal areas in the right hemisphere. Of the included studies, some reported more extensive activation of the right hemisphere and others reported predominantly left sided activity. Most of the included studies had very small sample sizes and the applied scanning protocols were heterogeneous. The meta-analysis showed that the language areas of the left hemisphere are more frequently activated during hallucinations than the homologue areas of the right hemisphere. This finding does not support the hypothesis that verbal hallucinations arise from inappropriate language activity of the non-dominant hemisphere. Still, the included studies were too small and their results too heterogeneous to fully reject the hypothesis.

In conclusion, this thesis showed that language lateralization is decreased in schizophrenia and that it constitutes a genetic predisposition for the disease. Several issues need further investigation. These include the influence of medication on lateralization and the stability of individual lateralization patterns over periods of variable clinical states. However, the most pressing question is whether the increased language activity of the right hemisphere found on fMRI scans of schizophrenia patients reflects a useful compensation mechanism or a disturbing failure of inhibition.
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