Language activation in monozygotic twins discordant for schizophrenia

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Background In previous functional magnetic resonance imaging (fMRI) studies, participants with schizophrenia showed decreased language lateralisation, resulting from increased activation of the right hemisphere compared with controls.

Aim To determine whether decreased lateralisation and increased right cerebral language activation constitute genetic predispositions for schizophrenia.

Method Language activation was measured using fMRI in 12 right-handed monozygotic twin pairs discordant for schizophrenia and 12 healthy right-handed monozygotic twin pairs who were matched for gender, age and education.

Results Language lateralisation was decreased in discordant twin pairs compared with the healthy twin pairs. The groups did not differ in 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. Within the discordant twin pairs, language lateralisation was not significantly different between patients with schizophrenia and their co-twins.

Conclusions Decreased language lateralisation may constitute a genetic predisposition for schizophrenia.

Declaration of interest None.

In two earlier functional resonance imaging (fMRI) studies we reported that language lateralisation was decreased in male (Sommer *et al*, 2001*a*) and female (Sommer *et al*, 2003) patients with schizophrenia compared with healthy controls. This was caused by increased language-related activation in the right-sided homologues of Broca's and Wernicke's areas in the patient group. Levels of activation in the language-related areas of the left hemisphere were similar in both groups. The increased activation of the right cerebral homologues of the language areas may be a predisposing (genetic) factor for schizophrenia. Alternatively, it could be a result of the disease, or a consequence of the use of antipsychotic medication. In the study reported here we aimed to determine whether decreased language lateralisation is a genetic predisposition for schizophrenia or whether it reflects non-specific functional disturbance caused by schizophrenic cerebral pathology. Therefore, language activation was assessed with fMRI in monozygotic twin pairs discordant for schizophrenia using the same protocol as in the earlier studies. Since monozygotic twin pairs are genetically identical, traits that reflect increased genetic vulnerability for schizophrenia will be present in both twins, while characteristics that are secondary to the disease or medication will be absent in the twins without schizophrenia.

METHOD

Study group

Twelve monozygotic twin pairs discordant for schizophrenia or schizoaffective disorder were included. Diagnosis was established using DSM–IV criteria (American Psychiatric Association, 1994) as determined by an independent psychiatrist using the Comprehensive Assessment of Symptoms and History (CASH) and the Schedule for Affective Disorder and Schizophrenia – Lifetime version (SADS–L) (Andreasen *et al*, 1992).

At the time of scanning, six patients were experiencing psychotic symptoms, as indicated by a score of more than 2 on one or more of the following items from the Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987): hallucinations, delusions, suspiciousness or grandiosity. None of the patients with schizoaffective disorder was in a depressed or manic state at the time of scanning. Hallucinations, if present, were experienced infrequently (once a day or several times a week). In the group of discordant twin pairs, the co-twins of the patients by exclusion had never experienced hallucinations or delusions as assessed in the CASH and SADS–L interview; however, these co-twins were not necessarily free of other psychiatric disorders. Clinical data for the patients and their co-twins are listed in Table 1. Of the co-twins free from schizophrenia, one participant was clinically depressed at the time of scanning. In the discordant twin pairs, the mean time after onset of the first psychotic episode of the twin with schizophrenia was 17 years (s.d.=10). Belmaker *et al* (1974) reported that approximately 70% of monozygotic twin pairs become concordant for schizophrenia within 4 years of the first twin's hospitalisation. Therefore, it is unlikely that these discordant twin pairs would become concordant for schizophrenia in the future.

Twelve healthy monozygotic twin pairs were included who were matched pair-wise for gender, age and education. Individuals with medical or neurological illness were excluded. Participants met research diagnostic criteria for 'never mentally ill' according to the CASH and SADS–L interview. In all twin pairs monozygosity was confirmed by genotyping, using ten highly polymorphic markers (Wijmenga *et al*, 1998). All twins were native Dutch speakers and all were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Familial left-handedness was scored positive if one or more first-degree relatives preferred their left hand for writing. Educational levels were measured by the total number of years of education. Information on birth weight, gestational age at birth and chorionicity was collected from a questionnaire filled out by the mothers of the twins. Demographic characteristics of the patients, the co-twins and the healthy twin pairs are

Table I Clinical characteristics of the discordant twins

	Proband (n=12)	Co-twin (n=12)
DSM–IV diagnosis	2 schizoaffective disorder 10 schizophrenia (1 catatonic, 1 disorganised, 8 paranoid)	1 major depression 2 dysthymia (one of whom also had alcohol dependence) 1 schizotypal personality disorder
Age at onset of first psychotic symptoms (years): mean (s.d.)	25 (4)	
Medication at time of scanning	3 olanzapine (2, 10 mg; 1, 15 mg) 1 risperidone (4 mg) 2 clozapine (1, 350 mg; 1, 100 mg) 3 pimozide (2, 4 mg, 1, 6 mg) 2 zuclopenthixol (1, 15 mg; 1, 20 mg) 1 perphenazine (10 mg)	1 clomipramine 100 mg and lithium 1200 mg 1 fluvoxamine 100 mg
Psychotic symptoms at time of scanning (n)	6	
Total score positive PANSS items: mean (s.d.)	17 (7)	
Total score negative PANSS items: mean (s.d.)	19	

PANSS, Positive and Negative Syndrome Scale.

detailed in Table 2. The participants were given a complete description of the study and their written informed consent was obtained, approved by the human ethics committee of the University Medical Centre, Utrecht.

Symptom assessment

The Positive and Negative Syndrome Scale was used for symptom assessment immediately prior to the scan session. Mean scores on the positive and negative items of the PANSS are listed in Table 1.

Scans

Functional scans were acquired with a Philips ACS-NT 1.5 T clinical scanner (Philips Medical Systems, Best, The Netherlands), using the blood oxygen level dependent (BOLD) sensitive, navigated three-dimensional(3D) PRESTO (principles of echo-shifting with a train of observation) pulse sequence (Ramsey *et al*, 1998) with the following parameter settings: echo time/repetition time (TE/TR) 35/24 ms, flip angle 9°, field of view (FOV) 18 mm × 91 mm, matrix 52 × 64 × 26, voxel size 3.51 mm isotropic, scan time per fMRI volume 2.4 s. Following the fMRI procedure, an anatomical scan was acquired (3D fast field echo TE/TR 4.6/30 ms, flip angle 30°, FOV 25 × 25 × 180 mm, matrix 128 × 128 × 150, slice thickness 1.2 mm).

Activation tasks

Tasks and scan technique have been described in detail by Ramsey *et al* (2001). Briefly, two word tasks were used: a paced verb-generation task and a semantic decision task. For the verb-generation task, a noun appeared on the screen every 3.6 s, and the participant was instructed to generate a verb appropriate for that noun. To avoid head motion, silent vocalisation was used. During the baseline condition of the verb-generation task, participants were instructed to fixate on a number of squares projected on the screen at the same frequency as the words. For the semantic decision task, the participant had to decide if the concrete noun presented on the screen signified an animal. Affirmative responses were given by pushing an air-mediated button with the right hand. The control task included the same number of button press responses, which were cued with a fixed number of asterisks which appeared at random intervals. Performance was recorded with a computer. Both tasks were performed during 10 periods of 29 s, alternated with 29 s of baseline conditions. Tasks were projected in a fixed order: the verb-generation task first and the semantic decision task second.

Combined task analysis

Brain activity maps were obtained by analysing the fMRI scans acquired during both tasks together, i.e. one *t*-map was derived from each participant during the performance of both tasks. The rationale for combined analysis, similar to the 'conjunction analysis' described by Price & Friston (1997), is that it combines methodological advantages of two tasks. Lateralisation varies between individuals, but also between tasks (Curtis *et al*, 1999). In an earlier study in healthy volunteers (Ramsey *et al*, 2001) we found that lateralisation is

Table 2 Demographic data

	Discordant twin pairs (n=12)	Healthy twin pairs (n=12)
Gender	5 male pairs, 7 female pairs	5 male pairs, 7 female pairs
Age (years): mean (s.d.)	42 (10)	37 (12)
Familial left-handedness	In 9 twin pairs	In 4 twin pairs
Gestational age at birth (weeks): mean (s.d.)	36 (4)	37 (3)
Chorionicity	6 monochorionic 1 dichorionic 4 unknown	4 monochorionic 2 dichorionic 6 unknown
Birth weight (g): mean (s.d.)	Patient: 2486 (564) Co-twin: 2403 (492)	Twin 1: 2628 (553) Twin 2: 2819 (447)
First born (n)	Patient: 6 Co-twin: 6	Twin 1: 6 Twin 2: 6
Education (years): mean (s.d.)	Patient: 11.9 (2.8) Co-twin: 12.2 (2.6)	Twin 1: 12.1 (2.7) Twin 2: 12.0 (3.0)

generally low for semantic categorisation tasks. When a task yields only low lateralisation indices, as with semantic categorisation, it is difficult to detect a difference in lateralisation between groups. In contrast, healthy volunteers showed extensive lateralisation of language activity on a verb-generation task. However, the verb-generation task has the disadvantage that performance cannot be recorded (at least not in our laboratory). Combined analyses of these two tasks yields relatively high lateralisation, and also provides a performance measurement. We have previously shown that such an analysis improves reliability of the subsequently computed laterality index, compared with that obtained with individual task analyses (Ramsey *et al*, 2001).

Scan analyses

The outer two slices (most dorsal and most ventral) of the transaxial fMRI volumes were not analysed, since registration causes signal fluctuations at the edges of the volume. Functional scans started and ended 7 s later than the task, to compensate for the delay of the vascular response. All scans, including the anatomical scan, 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. Functional images were analysed on a voxel-by-voxel basis using multiple regression analysis (Worsley & Friston, 1995) with one factor coding for activation (task *v*. 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 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).

Ten volumes of interest (VOIs) were manually delineated on the structural MRI scan of each participant, blind to diagnosis and to the statistical results. Manual delineation was performed in sagittal orientation using the DISPLAY tool from the Montreal Neurological Institute. For manual delineation, the following landmarks were used: lateral fissure, its ramus

anterior and ramus ascendens and the sulcus temporalis superior. The VOI selection was based on the activation pattern of healthy individuals scanned with this protocol (Ramsey *et al*, 2001) and comprised the inferior frontal gyrus pars orbitalis and pars opercularis: Brodmann areas (BA) 44 and 45, 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 VOIs encompassed the main areas where language processing of visually presented words is thought to be mediated.

In each VOI the number of activated voxels was determined. For subsequent analyses the VOIs were combined, yielding one measure of language-related activation for each hemisphere. Finally, a lateralisation index was calculated, defined as the difference in the number of activated voxels in the left *v*. the right hemisphere (within the VOIs) divided by the total sum of activated voxels in the VOIs of both hemispheres. In fMRI scans there generally is a large variability in the total activation shown by an individual when presented with a task. The lateralisation index was used to correct for this large spread. This index divides the difference between left-sided and right-sided activation by the total number of activated voxels. Therefore, the relative measure of the lateralisation index is less susceptible to differences in signal-to-noise ratio than an absolute activation measurement (such as the language activation of the right hemisphere) could be.

Statistical analyses

For the discordant twin pairs, the data for the twins with schizophrenia were placed in the first column (first twins) and the data for their co-twins in the second column (second twins). Control twin pairs were divided in two subgroups based on the birth order of the discordant twin pair that they were matching, i.e. if the affected twin was born first, then the first-born twin of the control pair was also placed in the first column. In this way, control pairs were also matched for birth order. To assess if language lateralisation differed between discordant and healthy pairs, lateralisation indices of the discordant pairs were compared with the control pairs in a repeated-measures analysis of variance (ANOVA). If significant differences emerged, language activation per hemisphere was compared

between discordant and control pairs, to test whether decreased lateralisation resulted from decreased left hemisphere activation or from increased right hemisphere activation. Possible differences between discordant and control pairs in the activation of specific VOIs were evaluated in a repeated-measures multivariate analysis of variance.

To test the possible effects of schizophrenia or of antipsychotic medication use on language lateralisation, the twins of the discordant pairs were compared using a paired *t*-test. If significant differences emerged, language activation per hemisphere was also compared. To test the possible effect of increased genetic risk of schizophrenia on the lateralisation index, the co-twins of the participants with schizophrenia were compared with the control twins, matched for birth order, using an independent *t*-test. If the difference was significant, differences in activation per hemisphere were also tested. Finally, an effect for gender on the lateralisation index was tested for significance in the discordant and control twins separately, by means of a repeated-measures ANOVA. All results reported are based on two-tailed tests of statistical significance.

RESULTS

Performance

Performance on the semantic decision task was not significantly different between the discordant and the healthy twin pairs: mean of 6 errors (s.d.=5) on 128 trials for the discordant pairs and 5 (s.d.=3) for the healthy pairs.

Language activation

Discordant v. control twin pairs

For the lateralisation index a significant main effect for the discordant *v*. control twin pairs ('Group') was found ($F_{(1,22)}=13.3$, $P<0.001$). The main effect for the first and second twins ('Twin') was not significant ($F_{(1,22)}=2.9$, $P=0.1$), nor was the Twin × Group interaction ($F_{(1,22)}=2.0$, $P=0.17$). Differences in the lateralisation index are shown in Fig. 1.

Examples of the activation pattern in healthy and affected twin pairs are shown in Fig. 2. Summed language-related activation in the VOIs of the left hemisphere was similar in both groups (main effect for Group: $F_{(1,22)}=1.2$, NS; main effect for Twin: $F_{(1,22)}=0.05$, NS; Twin × Group
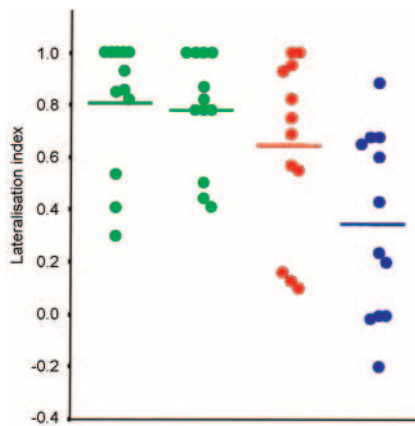
Fig. 1 Language lateralisation indices in 12 control twin pairs (●) and in 12 twin pairs discordant for schizophrenia: (●) probands; (●) unaffected co-twin.

interaction: $F_{(1,22)}=0.03$, NS). For the summed language-related activation in the VOIs of the right hemisphere, a significant main effect for Group was found ($F_{(1,22)}=5.0$, $P=0.02$). No significant main effects for Twin ($F_{(1,22)}=0.17$, NS) or Group × Twin interaction were found for the activation of the right hemisphere ($F_{(1,22)}=0.34$, NS). For the number of activated voxels in the separate VOIs the main effect for Group ($F_{(9,198)}=0.8$, NS), the main

effect for Twin ($F_{(9,198)}=0.04$, NS) and the Group × Twin interaction ($F_{(9,198)}=1.3$, NS) were not significant. The mean activation per VOI for control participants, for probands with schizophrenia and for the probands' co-twins is shown in Fig. 3.

Discordant twin pairs

Language lateralisation was not significantly lower in the twins with schizophrenia compared with their co-twins: $t=-1.9$, d.f.=11, $P=0.09$; in fact, there was a trend towards lower language lateralisation in these co-twins.

Probands' co-twins v. control twins

Language lateralisation was significantly lower in the twins without schizophrenia from the discordant pairs than in the control twins: $t=4.0$, d.f.=22, $P=0.001$. This decreased lateralisation in the probands' co-twins resulted from a trend towards increased language activation in the right hemisphere of these co-twins compared with the control twins ($t=2.7$, d.f.=22, $P=0.1$) whereas language activation in the left hemisphere was similar in both groups ($t=0.6$, d.f.=22, $P=0.54$). To preclude the possibility that the effect on

lateralisation reflected higher levels of psychopathological disorder in the co-twins of the participants with schizophrenia rather than increased genetic risk, the analyses were repeated after excluding the four co-twins with psychiatric disorders. Results were essentially the same: the difference in lateralisation index remained significant ($t=4.4$, d.f.=16, $P=0.003$), there was a trend towards higher language activation of the right hemisphere in the probands' co-twins compared with the control twins ($t=1.7$, d.f.=17, $P=0.1$), and language activation levels of the left hemisphere were equal in both groups ($t=0.5$, d.f.=17, $P=0.65$).

Gender

No significant main effect for gender on the lateralisation index was found in the discordant twin pairs, nor in the healthy twin pairs ($P>0.55$).

DISCUSSION

This study compared the language activation patterns on basic word processing tasks of monozygotic twin pairs discordant for schizophrenia with those of healthy monozygotic twin pairs. We found that language lateralisation was decreased in the discordant twin pairs, owing to increased activation of the right hemisphere homologues of the language areas, whereas activation in the language-related areas of the left hemisphere was similar in healthy and discordant pairs. Furthermore, the probands' co-twins had lower language lateralisation than the control twins. The corollary of these results is that decreased language lateralisation and increased language-related activation of frontal, temporal and parietal areas of the right hemisphere appear to constitute a genetic risk factor for schizophrenia. There also appeared to be a trend towards lower language lateralisation in the participants without schizophrenia in the discordant twin group. This may be a medication effect, since all the participants with schizophrenia used antipsychotic medication, which might have increased their decreased degree of lateralisation to a subnormal level. This hypothesis is now being tested in a medication study, from which the results are not yet available.
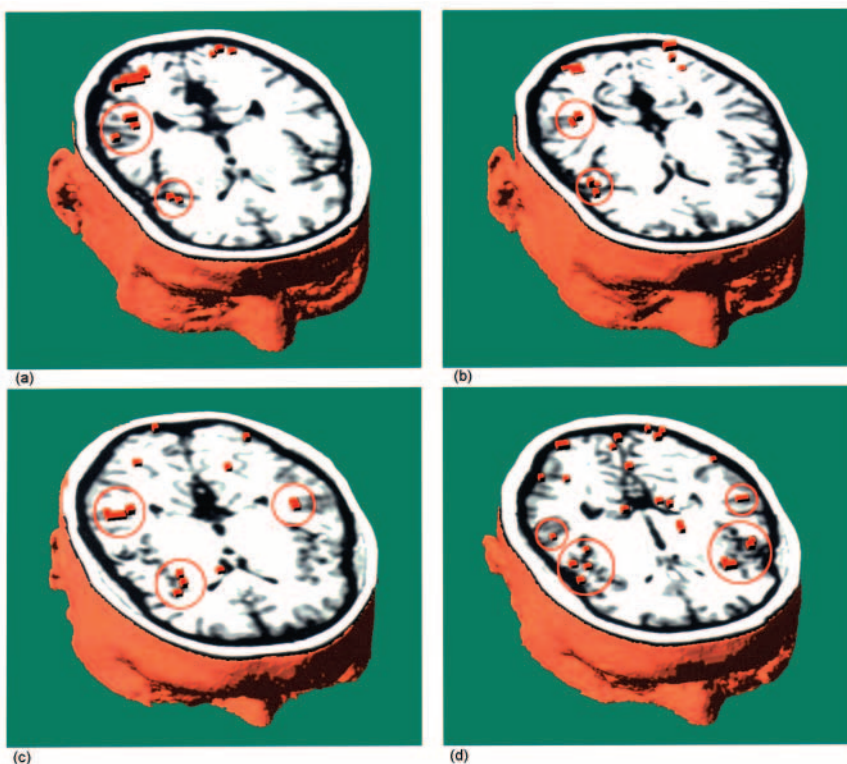

Fig. 2 Examples of language activation patterns in a healthy monozygotic twin pair (a,b), in an unaffected co-twin (c) and in the twin with schizophrenia (d); language-related activation is encircled.
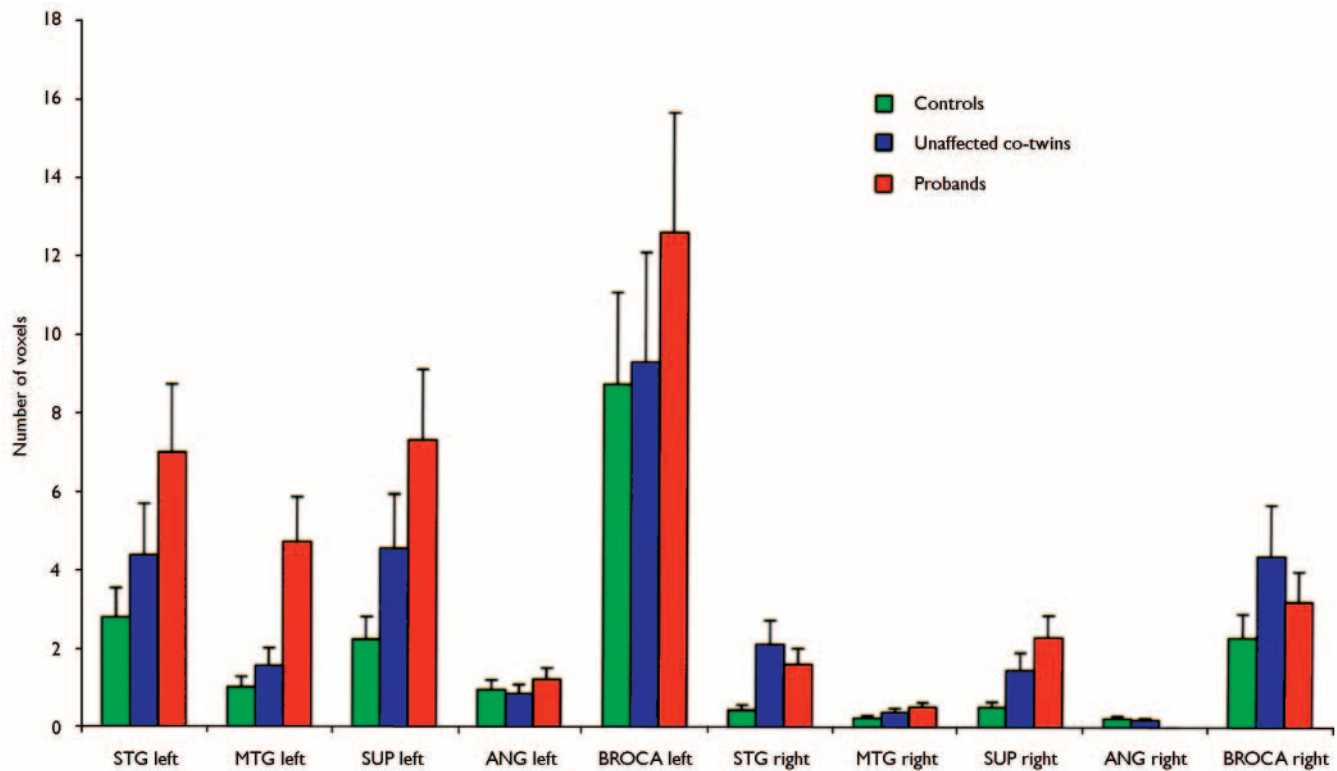
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Fig. 3 Mean number of activated voxels per volume of interest and the standard error of the mean. Volumes of interest are on the *x* axis: STG left, superior temporal gyrus left; MTG left, middle temporal gyrus left; SUP left, supramarginal gyrus left; ANG left, angular gyrus left; BROCA left, Broca's area; STG right, superior temporal gyrus right; MTG right, middle temporal gyrus right; SUP right, supramarginal gyrus right; ANG right, angular gyrus right; BROCA right, contralateral homologue of Broca's area.

Comparison with other studies

Several functional imaging studies measured language activity patterns in patients with schizophrenia (Lewis *et al*, 1992; Frith *et al*, 1995; McGuire *et al*, 1996; Woodruff *et al*, 1997; Curtis *et al*, 1999; Artiges *et al*, 2000; Spence *et al*, 2000; Kircher *et al*, 2001; Sommer *et al*, 2001*a*, 2003). Apart from the previous studies of our group, five functional imaging studies have provided information on language lateralisation. Lewis *et al* (1992) reported decreased left frontal activity in a single photon emission computed tomography (SPECT) study of 25 people with schizophrenia during a verbal fluency task, resulting in reversed frontal dominance. Woodruff *et al* (1997) compared the fMRI activation patterns of 15 people with schizophrenia with those of 8 healthy participants while listening to speech. They found reduced activation of the left superior temporal gyrus and increased activation of the right middle temporal gyrus in the patients compared with the controls. Dye *et al* (1999) found

no difference in positron emission tomography (PET) language activation patterns between 6 patients with schizophrenia and 10 healthy controls on a verbal fluency task. In a PET study by Spence *et al* (2000), 10 patients with schizophrenia showed greater bilateral activation of the frontal areas on a paced verbal fluency task at a qualitative level (Crow, 2000). On formal comparison, increased activation in the right hemisphere in the patients was not statistically significant. Artiges *et al* (2000) also observed reduced lateralisation in 14 patients with schizophrenia using an unpaced verbal fluency PET protocol. Decreased lateralisation was due to both decreased left frontal language activity and increased language activity of the right-sided frontal areas. However, an unpaced verbal fluency task 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 production and hence reduced language-related brain activity. Indeed, decreased left

frontal language activity was not detected when participants with schizophrenia were compared with controls who had performed equally badly (Frith *et al*, 1995; Curtis *et al*, 1999). Although the decreased left-sided language activity described by Artiges *et al* (2000) may reflect low performance, increased language-related activity of the right hemisphere in patients with schizophrenia cannot be explained by poor task performance. Thus, increased language-related activity of the right hemisphere may be a functional characteristic of schizophrenia, or a characteristic of the genetic predisposition for schizophrenia.

Language activation has not been studied previously with functional imaging techniques in monozygotic twin pairs with schizophrenia, but several studies used the dichotic listening paradigm to estimate language lateralisation in relatives of patients with schizophrenia. This method measures perceptual asymmetry of language stimuli, but provides no information on the involvement of each hemisphere in language processing. Ragland *et al* (1992)

studied perceptual asymmetry in 18 monozygotic twin pairs discordant for schizophrenia and seven healthy twin pairs. In contrast to our results, Ragland *et al* found decreased language lateralisation in the affected twins compared with their unaffected co-twins, while lateralisation of the unaffected twins was not significantly different from that of the healthy twins. The difference between Ragland's study and ours may result from a lack of power in the former, since the standard deviation of their lateralisation indices was fairly large. Two groups studied language lateralisation with dichotic listening tests in other first-degree relatives of patients with schizophrenia. Grosh *et al* (1995) studied language lateralisation in 18 parents of people with schizophrenia. Lateralisation in the parents was significantly lower than in healthy controls, to a similar degree to that found in their affected offspring. Hallett *et al* (1986) assessed language lateralisation in 22 children whose parents had schizophrenia; consistent with the findings of Grosh *et al* (1995) and with the present study, significantly lower lateralisation was reported in children of patients compared with 22 children of unaffected parents.

Language activity in the right hemisphere

Our results suggest that increased activation in the contralateral homologues of the language-related areas is not a necessary factor for schizophrenia to develop, given the strong left cerebral dominance for language in some of the people with schizophrenia in our sample. Neither is increased language-related activation in homologue areas of the right hemisphere sufficient to cause schizophrenia, given the absence of psychotic symptoms in the unaffected co-twins of the patients. However, in combination with other factors, more bilateral language activation might facilitate the occurrence of language-related psychotic symptoms such as auditory verbal hallucinations, thought insertion and thought disorder (Nasrallah, 1985). Therefore, it would be useful to gain more insight into the role of the right-sided homologues of the language areas.

Current knowledge on the brain organisation for language functions is based on data from two different types of study (Binder *et al*, 1996). The first type establishes a link between language functions and brain organisation by associating disrupted function of a brain area with a change in linguistic behaviour, usually a deficit. Such studies identify a brain area as 'critical' for a certain aspect of language, which means that aphasia results when a critical area is damaged. This type of study, which includes descriptions of different kinds of aphasia and their corresponding lesions, observations using the carotid amylobarbitone sodium (Wada) procedure and findings with intraoperative electrical stimulation, indicated that Broca's area (BA 44 and 45 of the left hemisphere) and Wernicke's area (the upper part of the superior temporal gyrus of the left hemisphere) are in most people critical language areas (Grodzinsky, 2000). The other type of study records physiological measures of brain activity while individuals are engaged in tasks that address certain language functions, using techniques such as PET and fMRI. Changes in physiological parameters during a language task may also be detected at sites that are not critical for that language function, but may be activated for non-specific supporting functions. Examples of areas that are frequently found to be activated during language tasks with functional imaging, but do not produce aphasia when lesioned, are the anterior cingulate gyrus and the superior frontal gyrus (Binder *et al*, 1997).

When their left hemisphere is anaesthetised during the Wada procedure, people who are right-handed are generally unable to speak or to read (Rasmussen & Milner, 1976). The left hemisphere can thus be defined as being critical for language. Aphasia is generally not present, however, after anaesthetising the right hemisphere of people who are right-handed; in these people, the right hemisphere thus appears not to contain critical language areas. In contrast, in approximately 30% of left-handed people tested, the right hemisphere does have critical language areas, since these people become aphasic after anaesthesis of the right hemisphere (Rasmussen & Milner, 1975). A common approach in aphasia and Wada test research is to classify participants into 'exclusively left dominance', 'bilateral language' and 'exclusively right dominance' categories (Binder *et al*, 1996). However, functional imaging studies show that there is considerable variation, even among healthy right-handed people, in the relative contribution of the right hemisphere to basic language tasks, varying on a continuum from almost exclusively left hemisphere activity to bilateral processing and in rare cases right cerebral dominance (Binder *et al*, 1997; Frost *et al*, 1999). Considering this, the increased language activation in the homologue areas of the right hemisphere in our discordant twin pairs can be interpreted in two ways. First, language functions of the discordant twin pairs may have a fundamentally different cortical organisation with a more bilateral distribution of critical language areas. Indirect support for this explanation is provided by structural MRI studies in schizophrenia, reporting decreased asymmetry of the Sylvian fissure and the planum temporale, though not all studies found significant differences (reviewed by Sommer *et al*, 2001b). Such a more bilateral distribution of critical language areas is frequently encountered in left-handed people (Pujol *et al*, 1999; Knecht *et al*, 2001). Possibly, twin pairs discordant for schizophrenia are similar to healthy left-handers, in that they also have a more bilateral cortical representation of language functions. However, the activation patterns of the discordant twin pairs argue against this explanation. In an earlier study by our group eight healthy left-handed people were scanned with the same protocol as in this study, and compared with eight healthy right-handed people (Ramsey *et al*, 2001). The left-handed participants indeed showed increased language activation of the right hemisphere, which can be assumed to arise from a more bilateral representation of critical language functions; however, language-related activation of the left hemisphere was decreased in these participants, i.e. they displayed a shift in language activation from the left to the right hemisphere. Other functional imaging studies comparing larger samples of left-handed and right-handed volunteers also found increased language activation of the right hemisphere in tandem with decreased language activation of the left hemisphere (Pujol *et al*, 1999; Knecht *et al*, 2000). In contrast to this activation pattern in healthy left-handers, both twins of the the discordant twin pairs in our study showed an additional increase in language activation of the right hemisphere, while left hemisphere language activation remained normal (i.e. high). Therefore, another interpretation of our data is more plausible, namely that language representation in the discordant twin pairs is not similar to that in healthy left-handers. Instead, the language activation pattern in the discordant twin pairs may reflect the use of additional cortical

areas in the right hemisphere while the critical language areas are located at their regular sites in the left hemisphere. The additional activation of homologue areas in the right hemisphere is probably not essential for performing the word tasks, since the language areas of the left hemisphere show normal task-related activation. In fact, increased language activation of the right hemisphere areas may result from insufficient inhibition of these non-dominant areas.

Limitations

Theoretically, we cannot differentiate between genetic effects and the effects of shared environmental influences on decreased language lateralisation in the discordant twin pairs of this study, since the results are not compared with findings in dizygotic discordant twin pairs. However, for this type of research the comparison with dizygotic twin pairs may be less effective, since environmental factors that are generally shared in both monozygotic and dizygotic twin pairs – such as upbringing, nutrition, education and sociocultural circumstances – are unlikely to have any effect on cerebral dominance (Hicks & Kinsbourne, 1976; Bryden & Allard, 1981). 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. Finally, the affected twins were a heterogene group. First, patients with both schizophrenia and schizoaffective disorders were included. Furthermore, symptom severity and type and dose of antipsychotic medication varied. All three factors might have influenced the relative contribution of the right hemisphere to language activity.

In summary, monozygotic twin pairs discordant for schizophrenia display lesser degrees of language lateralisation, caused by higher language-related activation in the homologue areas of the right hemisphere compared with healthy monozygotic twin pairs, whereas activation of the left-sided language-related areas is equal in both groups. Decreased language lateralisation in the discordant twin pairs may be a functional substrate of their genetic predisposition to develop psychotic symptoms of schizophrenia.

CLINICAL IMPLICATIONS

■ Decreased language lateralisation appears to constitute a genetic predisposition for schizophrenia and could thus be used as an endophenotype for research on high-risk groups.

■ Increased language activity of the right hemisphere may have a causative role in precipitating psychosis.

■ Increased activation in the contralateral homologues of the language-related areas is neither a necessary factor for schizophrenia to develop, nor is it sufficient to cause schizophrenia.

LIMITATIONS

■ Dizygotic twin pairs were not included in the study.

■ Performance was recorded for only one of the two language tasks.

■ The sample was small.

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