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Short communication

Language lateralization in monozygotic twins discordant and concordant for schizophrenia. A functional MRI pilot study

Filip Spaniel [a,c,d,*], Jaroslav Tintera [b,d], Tomas Hajek [a,c,d], Jiri Horacek [a,c,d], Monika Dezortova [b,d], Milan Hajek [b,d], Colleen Dockery [a,d], Jiri Kozeny [a,c,d], Cyril Höschl [a,c,d]

[a] *Psychiatric Center, Ústavní 191, 181 03 Prague 8, Czech Republic*
[b] *MR Unit ZRIR, Institute for Clinical and Experimental Medicine, Czech Republic*
[c] *3rd Faculty of Medicine, Charles University, Prague, Czech Republic*
[d] *Center of Neuropsychiatric Studies, Prague, Czech Republic*

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Abstract

Aim. – Previous studies have suggested altered structural and functional asymmetry of the brain in schizophrenia.

Methods. – Functional MRI was used to assess differences in cortical activation during a verbal task in Broca's area and its contralateral homologue in four pairs of right-handed monozygotic (MZ) twins discordant and concordant for schizophrenia with low and high familial loading for the illness and four healthy control MZ twin pairs.

Results. – Pooled data from all subjects with schizophrenia showed increased activation in the right homologue of Broca's area in contrast to healthy individuals. Concordant twins (i.e. high familial loading group) showed prominent between co-twin differences in lateralization index within given region of interest. Intra-pair differences in lateralization index were significantly higher in concordant twins compared to the controls (0.69 ± 0.4 vs. 0.13 ± 0.13, $P < 0.03$), albeit no significant differences in the variable were shown between the discordant and control groups.

Conclusion. – This study provides evidence of reduced cerebral dominance for language processing in patients with schizophrenia. The findings further suggest the need for additional research on relative proportion of genetic and environmental factors underlying deviations of functional asymmetry in schizophrenia.

Keywords: Functional MRI; Schizophrenia; Language lateralization; Monozygotic twins

1. Introduction

The phenomenon of altered cerebral lateralization in schizophrenia has been repeatedly observed using several methodological approaches. [4,9,10,14]. Albeit relative contribution of genetic and environmental factors in development of cerebral dominance remains unclear, it was hypothesized that the reported loss of cerebral asymmetry in schizophrenia could be related to a genetically determined failure to establish cerebral dominance [3].

In the present study we initially sought to explore possible differences in language lateralization within Broca's region and its contralateral homologue between sporadic and familial cases using specific study sample consisting of affected subjects from monozygotic (MZ) twin pairs discordant for schizophrenia with no familial loading of major mental illness and concordant MZ twins with first-degree relatives affected with schizophrenia or schizophrenia-spectrum disorders.

* Corresponding author. Psychiatric Center, Ústavní 191, 181 03 Prague 8, Czech Republic. Tel.: +42 02 6600 3390; fax: +42 02 6600 3366.
E-mail addresses: spaniel@pcp.lf3.cuni.cz (F. Spaniel), jati@medicon.cz (J. Tintera), hajek@pcp.lf3.cuni.cz (T. Hajek), horacek@pcp.lf3.cuni.cz (J. Horacek), mode@medicon.cz (M. Dezortova), miha@medicon.cz (M. Hajek), dockery@pcp.lf3.cuni.cz (C. Dockery), kozeny@pcp.lf3.cuni.cz (J. Kozeny), hoschl@pcp.lf3.cuni.cz (C. Höschl).

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2. Methods

2.1. Subjects

The study subjects consisted of four MZ twin pairs discordant for schizophrenia without any family history of schizophrenia or other major psychiatric disorder. Affected twins formed "sporadic group". Four MZ twin pairs concordant for schizophrenia formed the high familial loading (HFL) group. Three twin pairs from this group had first-degree relatives with schizophrenia or schizophrenia spectrum disorder. One concordant female twin pair did not show any familial history of psychiatric illness. The control group consisted of four healthy MZ twin pairs without family history of any psychopathology. Clinical data are summarized in Table 1.

Diagnosis of schizophrenia was made according to the Structured Clinical Interview for DSM-III-R by two experienced psychiatrists. Genetic analysis (concordance in 16 short tandem repeats markers) confirmed homozygosity of the twin pairs (**PowerPlex® 16 System,** Promega, Madison, WI, USA [12]). Subjects with a history of neurological disorders, substance abuse or MRI contraindication were excluded.

According to the Edinburgh Handedness Inventory [6] all subjects enrolled in the study were right-handed. Patients were assessed using the Positive and Negative Symptom Scale, PANSS [5] before the functional magnetic resonance imaging (fMRI) session.

The study was approved by the local Ethics Committee. The procedure was explained to the participants and written consent was obtained.

2.2. fMRI scanning procedure

Sixty-four T2-weighted volume images were acquired during each measurement on a 1.5-T Siemens Magneto Vision (Siemens, Erlangen, Germany) using a single-shot gradient echo EPI sequence (TR = 4 s, TE = 54 ms, flip angle = 90°) in 27 oblique slices of 4 mm thickness each. The matrix size was 128 × 128, with a voxel size of 1.8 × 1.8 × 4 mm. During the verbal fluency task paradigm the subjects were cued to generate covertly as many words as possible starting with a letter of the alphabet presented on a screen. The answers for the verbal fluency test were not recorded during the fMRI investigation to avoid motion artifacts made by verbal response. The experimental condition alternated with the baseline condition in which subjects were asked to count forward at a rate of approximately one per second [7]. Eight scans were performed in each block, i.e. 8 for rest (counting) and 8 for stimulation (word generation), There were four such periods (four different letters: V, R, S, N). Each block lasted 48 s (TR = 6 s, 8 × 6 s = 48 s). There were two dummy scans at the beginning of the measurement without data acquisition to reach steady-state of the magnetization.

2.3. Data analysis

Brain activation during the verbal fluency condition was compared to that of the rest period using SPM99 (Wellcome Department of Cognitive Neurology, University College, London, UK) following realignment, spatial normalization and smoothing (8 mm Gaussian filter). Analysis was restricted to a region of interest (ROI) encompassing pars opercularis and triangularis in the inferior frontal gyrus bilaterally which constitute the anatomical correlates of Broca's region and its contralateral homologue. MARINA software was used as a tool for creating and manipulating masks in MNI space [13]. Data were converted to a *t*-value for each voxel. After transformation of *t*-values to *Z*-values, statistical parametric maps of *Z*-values were created and the anatomical locations of the activated areas were determined in the normalized space. Voxels at a threshold of $P < 0.001$ uncorrected were displayed as activated. The voxel clusters surviving thresholds smaller than five voxels were excluded. The lateralization index (LI) was calculated by subtracting the total number of active voxels within ROI in the left from right hemisphere, and dividing the difference by the sum of the activated voxels in both hemispheres.

3. Results

There were no differences in gender, age, laterality, years of education between group of healthy subjects and patients with schizophrenia (Mann–Whitney *U*-test, two sided).

Table 1
Clinical description of the groups of schizophrenic patients and controls

	Monozygotic twins			Controls
	Discordant Unaffected ("Sporadic group")	Discordant Affected	Concordant("High familial loading group")	
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Subjects	$n = 4$	$n = 4$	$n = 8$	$n = 8$
Gender male/female	2/2	2/2	4/4	4/4
Age (years)	32.7 (11.8)		30.3 (6.5)	28.5 (3.8)
Education (years)	13.2 (2.2)	12.2 (0.4)	10.0 (1.5)	13.5 (1.5)
Duration of illness (years)		8.1 (5.3)	8.1 (4.3)	
PANSS (P)		11.5 (1.8)	12.2 (3.9)	
PANSS (N)		20.0 (10.6)	25.4 (5.5)	
PANSS (G)		33.5 (11.9)	44.0 (13.2)	
PANSS (total)		65.0 (23.8)	81.6 (21.5)	

PANSS, Positive and Negative Symptom Scale.

3.1. Between-group analysis

Due to low number of subjects, this study lacked the power to show a statistical difference between sporadic and HFL groups using a second-level analysis.

However, direct comparison of all patients with schizophrenia (concordant + affected individuals from the discordant pairs) versus all healthy subjects (controls + unaffected twins from the discordant MZ twins) with two-sample *t*-test ($P < 0.001$, uncorrected) showed patients to have statistically increased activation within the right inferior frontal gyrus in BA 47 (53, 25, −3; *Z* score: 3.7) and right BA 45 (55, 11, 18; *Z* score: 3.24).

3.2. Lateralization index (LI)

Significant differences in language LI were found in comparison of all patients with schizophrenia (concordant + affected from the discordant pairs) relative to all healthy subjects (controls + unaffected twins from the discordant MZ twin pairs; mean LI in patients 0.27 ± 0.53, healthy subjects 0.86 ± 0.18; Wilcoxon–Mann–Whitney test, two-sided, $P < 0.002$).

3.3. Intra-pair differences in LI

Apparent intra-pair, between co-twin differences in the LI were observed in the discordant group, but in contrast to the expectation especially in the concordant group (Fig. 1). To analyze this, the absolute value of intra-pair differences in the LI was obtained for each twin pair. Twins from the concordant group showed significantly higher intra-pair differences compared to the controls (mean 0.69 ± 0.4 vs. 0.13 ± 0.13, $P < 0.03$, Mann–Whitney *U* rank sum test, two-sided). However, differences in the variable did not reach statistical significance between the discordant and control groups. The only concordant twin pair without familial history of psychiatric illness exhibited the most apparent intra-pair differences within concordant group: 0.75.

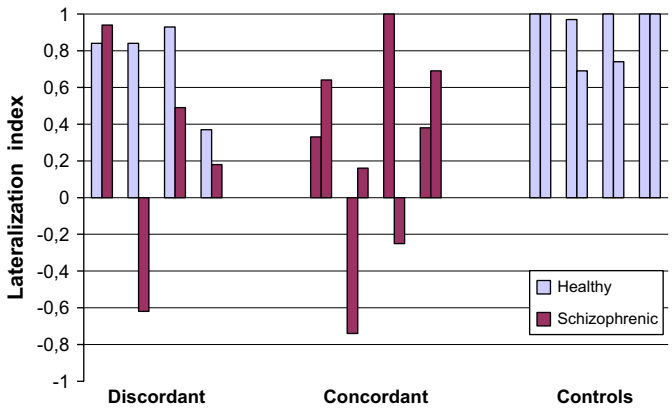

Fig. 1. Language lateralization indexes in 12 pairs of right-handed monozygotic twins - discordant, concordant for schizophrenia and controls. fMRI during verbal fluency task paradigm, activations within pars opercularis and triangularis in the inferior frontal gyrus bilaterally (Broca's area and its proximity together with contralateral homologue).

4. Discussion

Pooled data from all schizophrenic patients revealed a significant decrease in the language LI in pars triangularis and opercularis in inferior frontal gyrus bilaterally compared to healthy individuals. Right-handed subjects with schizophrenia recruited the homologue of Broca's area (Brodmann's area 45) in the right inferior frontal gyrus together with the adjacent right BA 47 in contrast to healthy individuals during the verbal fluency task. This finding corresponds to a previous fMRI study showing an increase with language-related activity in the right hemisphere in patients with schizophrenia resulting from failure to inhibit the right hemisphere during verbal task [10].

To our knowledge, this is the first study assessing functional lateralization by means of fMRI in MZ twins concordant for schizophrenia. An extreme between co-twin differences in activation patterns resulted in significantly higher intra-pair differences in the LI in the concordant, HFL group, compared to controls. No significant differences in the variable were observed between the discordant and control groups.

Under normal conditions, healthy handedness-concordant MZ twins exhibit significant intra-pair correlation for language lateralization [11]. Prominent intra-pair variability in the LI in our concordant group could be explained by a different impact of predisposing factors on the neurobiological substrate resulting in a different recruitment of cortical networks during the given cognitive performance.

An alternative explanation of the finding fits well within the conceptual frame of a genetic model of handedness and brain laterality proposed by Annett [1]. This threshold model suggests that the typical pattern of human cerebral and manual asymmetries depends on a putative "right-shift" (RS+) gene. According to this theory, recessive RS−/RS− MZ twins concordant for handedness could display discordance in cerebral asymmetry, since cerebral dominance is determined by accidental factors in those gene carriers [2].

Whether cases with high genetic risk for schizophrenia are also prevalent carriers of the RS−/RS− homozygosity resulting in deviations in functional asymmetry of the brain remains fully speculative and can not be concluded from this study. Previous findings reporting lack of the normal pattern of cerebral hemispheric volume asymmetries in both schizophrenic patients and those of their relatives who appear to be transmitting the genetic liability for schizophrenia may lend some support to this hypothesis [8].

The results of this study must be interpreted in light of its methodological limitations. Primarily, our power to detect statistical significance was limited by the small sample size. Secondarily, because of uncorrected analyses, between-groups comparison should be interpreted with caution. And finally, our concordant twin group was not homogeneous in terms of the extent of familial loading for schizophrenia and, therefore, may not serve as a population representing exclusively high

genetic risk subjects. Thus, this study requires replication in larger samples of familial and sporadic cases.

In summary, the current study, as well as several other available studies, provides evidence of reduced cerebral dominance for language processing in patients with schizophrenia. The preliminary findings of this pilot study highlight the need for further studies to clarify possible genetic predisposition to deviations in functional asymmetry in schizophrenia.

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