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fMRI study of language activation in schizophrenia, schizoaffective disorder and in individuals genetically at high risk

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Abstract

Background: Structural and functional abnormalities have been found in language-related brain regions in patients with schizophrenia. We previously reported findings pointing to differences in word processing between people with schizophrenia and individuals who are at high-risk for schizophrenia using a voxel-based (whole brain) fMRI approach. We now extend this finding to specifically examine functional activity in three language related cortical regions using a larger cohort of individuals.
Method: A visual lexical discrimination task was performed by 36 controls, 21 subjects at high genetic-risk for schizophrenia, and 20 patients with schizophrenia during blood oxygenation level dependent (BOLD) fMRI scanning. Activation in bilateral inferior frontal gyri (Brodmann's area 44–45), bilateral inferior parietal lobe (Brodmann's area 39–40), and bilateral superior temporal gyri (Brodmann's area 22) was investigated. For all subjects, two-tailed Pearson correlations were calculated between the computed laterality index and a series of cognitive test scores determining language functioning.
Results: Regional activation in Brodmann's area 44–45 was left lateralized in normal controls, while high-risk subjects and patients with schizophrenia or schizoaffective disorder showed more bilateral activation. No significant differences among the three diagnostic groups in the other two regions of interest (Brodmann's area 22 or areas 39–40) were found. Furthermore, the apparent reasons for loss of leftward language lateralization differed between groups. In high-risk subjects, the loss of lateralization was based on reduced left hemisphere activation, while in the patient group, it was due to increased right side activation. Language ability related cognitive scores were positively correlations with the laterality indices obtained from Brodmann's areas 44–45 in the high-risk group, and with the laterality indices from Brodmann's areas 22 and 44–45 in the patient group.
Conclusions: This study reinforces previous language related imaging studies in high-risk subjects and patients with schizophrenia suggesting that reduced functional lateralization in language related frontal cortex may be a vulnerability marker for schizophrenia. Future studies will determine whether it is predictive of who develops illness.

Keywords: fMRI; Schizophrenia; High risk; Genetic; Language lateralization; ROI based study

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1. Introduction

Although first-degree relatives of individuals with schizophrenia have an almost 10-fold increased risk of developing schizophrenia (Gottesman and Shields, 1972; Gottesman, 1991), the underlying genetic mechanism for the pathogenesis of the disorder is not well understood. By studying individuals who are at high-risk for developing schizophrenia, one can determine biological factors that may be important for distinguishing people who are likely to later develop the illness. Subjects at high genetic risk for schizophrenia can be defined as individuals between the ages of 13 and 30, who have never been diagnosed with schizophrenia, but have a first-degree relative with the illness (Johnstone et al., 2000; Li et al., 2007). These individuals share on average 50% of genes with their diagnosed relatives and thus have a heightened risk of developing the disorder.

Several studies indicate that patients with schizophrenia may have anomalies of language functioning (reviewed in DeLisi, 2001). Structural and functional magnetic resonance imaging (MRI/fMRI) made it

Table 1
Functional MRI findings in language related brain areas in schizophrenia

Reference	Sample size (*n*)	Mean age (years)	Sex (m/f)	Task design	Major findings
Kircher et al. (2001)	SZ 6, NC 6	SZ 34.3, NC 34.0	All m	Speech generation task. Seven Rorschach cards were presented on the screen during scanning and subjects were asked to describe them. Event-related design.	Severity of thought disorder was correlated positively with activity in the cerebellar vermis, right body of caudate, right precentral gyrus; and correlated negatively with left superior temporal gyrus, and the posterior part of middle temporal gyrus.
Kiehl and Liddle (2001)	SZ 11, NC 11	SZ 26.6, NC 27.0	6m/5F in SZ, 6m/5f in NC	Auditory oddball task. Event-related design.	Patients showed reduce activation in the bilateral anterior superior temporal gyri, left supramarginal gyrus, right superior and inferior parietal lobule, anterior and posterior cingulated, thalamus, and right lateral frontal cortex
Menon et al. (2001)	SZ 11, NC 13	SZ 44.6 NC 42.5	All m	2-back auditory working memory (WM) task. Block design.	Patients showed decreased lateralization of activation and significant WM related activation deficits in bilateral dorsolateral prefrontal cortices, frontal operculum, inferior parietal , and superior parietal cortex.
Ngan et al. (2003)	SZ 14, NC 29	SZ 35.1, NC 29.3	12m/2f in S2 21m/8f in NC	Auditory oddball task. Event-related design.	Patients showed greater differential activation between speech and nonspeech in right temporal cortex, left superior frontal cortex, and the left temporal–parietal junction. The magnitude of the difference in the left temporal parietal junction was significantly correlated with severity of disorganized thinking.
Woodruff et al. (1997)	SZ trait-positive 8, trait-negative 7, NC 8	SZ trait-positive 36, trait-negative 34.6, NC 35.3	All m	Auditory perception of speech task. Block design.	Reduced in the left superior temporal gyrus but increased in the right middle temporal gyrus in the combined schizophrenic groups relative to the healthy comparison group. Comparison of the trait-positive and trait-negative patients revealed no clear difference in the power of temporal cortical activation.
Curtis et al. (1998)	SZ 5, NC 5	SZ 29.6, NC 31.6	All m	Verbal fluency task. Block design.	Schizophrenic subjects showed significantly reduced power of response in the left dorsal prefrontal cortex, the inferior frontal gyrus, and the insula but significantly increased power of response in the medial parietal cortex.
Sommer et al. (2001)	SZ 12, NC 12	SZ 27.0, NC 28.0	All m	Verb generation and semantic decision reverse read task. Block design.	Reduced leftward language-laterality in SZ group was related to increased action in the right hemisphere.
Sommer et al. (2003)	SZ 12, NC 12	SZ 33.6 NC 32.0	All f	The same task as in Sommer et al. (2001)	Reduced leftward language-laterality in SZ group was related to increased action in the right hemisphere. No gender difference was found compared with the findings in Sommer et al. (2001).

SZ = Schizophrenia, NC = normal controls, m = males, f = females.