ORIGINAL ARTICLE

Neural Correlates of Formal Thought Disorder in Schizophrenia

Preliminary Findings From a Functional Magnetic Resonance Imaging Study

Tilo T. J. Kircher, MD, PhD; P. F. Liddle, PhD, MRCPsych; Michael J. Brammer, PhD; Steve C. R. Williams, PhD; Robin M. Murray, MD, MRCPsych; Philip K. McGuire, MD, PhD, MRCPsych

Background: Formal thought disorder (FTD) is a core symptom of schizophrenia, but its pathophysiology is little understood. We examined the neural correlates of FTD using functional magnetic resonance imaging.

Methods: Blood oxygenation level–dependent contrast was measured using functional magnetic resonance imaging while 6 patients with schizophrenia and 6 control subjects spoke about 7 Rorschach inkblots for 3 minutes each. In patients, varying degrees of thought-disordered speech were elicited during each "run." In a within-subject design, the severity of positive FTD was correlated with the level of blood oxygenation level–dependent contrast in the 2 runs that showed the highest variance of FTD in each patient.

Results: The severity of positive FTD in patients was negatively correlated ($P<.001$) with signal changes in the left superior and middle temporal gyri. Positive correlations were evident in the cerebellar vermis, the right caudate body, and the precentral gyrus.

Conclusions: The severity of positive FTD was inversely correlated with the level of activity in the Wernicke area, a region implicated in the production of coherent speech. Reduced activity in this area might contribute to the articulation of incoherent speech. Because of the small sample size, these findings should be considered preliminary.

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From the Section of Neuroimaging (Drs Kircher and McGuire), the Division of Psychological Medicine (Dr Murray), the Department of Biostatistics and Computing (Dr Brammer), and the Neuroimaging Research Unit (Dr Williams), Institute of Psychiatry and GKT School of Medicine, De Crespigny Park, London; the Department of Psychiatry, University of British Columbia, Vancouver (Dr Liddle); and the Department of Psychiatry, University of Tuebingen, Tuebingen, Germany (Dr Kircher).

FORMAL THOUGHT disorder (FTD) is regarded as one of the core features of schizophrenia,[1] yet little is known about its pathophysiology. It can be subdivided into positive and negative FTD, with the former characterized by incoherence, use of peculiar words, and distractibility and the latter by a reduction in the amount and content of speech.[2] These subtypes of FTD seem to have distinct clinical and neuropsychologic correlates,[3,4] and their respective pathophysiologic mechanisms might thus be different.

Functional neuroimaging provides a means of investigating the pathophysiology of FTD in vivo. To date, most studies[5-9] have measured cerebral blood flow in patients with schizophrenia in the resting state and have correlated this with the severity of positive FTD, assessed outside the scanner. These investigations have linked the disorganization syndrome (which predominantly comprises positive FTD) with the level of resting activity in several regions, including the anterior cingulate, inferior frontal and superior temporal gyri, and the caudate nucleus, although there has been some inconsistency across studies.

An alternative approach is to scan patients while they are articulating disorganized speech and examine the relationship between the severity of FTD and brain activity "on-line." In the present study, patients produced varying degrees of FTD as they were verbally describing Rorschach inkblots while regional blood oxygenation level–dependent (BOLD) contrast was being continuously measured using functional magnetic resonance imaging (fMRI). The relationship between the severity of FTD and the BOLD response over time was examined within each individual and in patients as a group. We predicted that the severity of positive FTD in patients would be inversely correlated with activation in the left superior temporal cortex.[5,10-12]

RESULTS

The severity of positive FTD (per 20-second epoch, as rated with the Thought Disorder Index) ranged from 0.5 to 48.5 points (mean [SD], 15.9 [15.9] points) in patients and from 0.0 to 4.0 points (mean [SD], 1.2 [1.3] points) in controls (difference, $U=4.5$; $P=.03$). The amount of speech produced (number of words per

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SUBJECTS AND METHODS

SUBJECTS

Six men with schizophrenia (*DSM-IV*) were recruited from the Maudsley and Bethlem Royal Hospitals, London, England. Patients were selected if they were currently exhibiting prominent symptoms of positive FTD, with relatively low levels of hallucinations and delusions. Forty-six patients were assessed: 4 were not native speakers, 10 did not have high levels of FTD at the time of scanning, 5 were left-handed, 6 were unable to complete the task, 8 refused to participate, and 7 were too agitated or distractible to tolerate scanning. A control group of healthy volunteers was matched for sex, age, and demographic variables with the patient group. All subjects were right-handed.[13] Only subjects able to completed 3 "runs" of the task to be used during scanning and patients who articulated positive FTD speech on these runs were included. Verbal IQ, immediate memory recall, and attention were also assessed on the day of scanning using the National Adult Reading Test,[14] Digit Span,[15] and the Continuous Performance Test,[16] respectively. There were no significant differences between groups on these measures or on sociodemographic variables (**Table 1**). The mean (SD) duration of illness in patients was 13.0 (9.9) years, and all were taking stable doses of typical antipsychotic medications (mean [SD] dose in chlorpromazine equivalents, 1042 [738] mg/d).

Patients were clinically assessed (by T.T.J.K.) using the Schedule for Affective Disorder and Schizophrenia–Lifetime version,[18] the Scale for the Assessment of Positive Symptoms (SAPS),[19] and the Scale for the Assessment of Negative Symptoms (SANS)[20] the day of scanning, before collection of imaging data. Patients had high levels of positive FTD (mean [SD] SAPS score, 3.83 [0.75]) and relatively low levels of hallucinations (mean [SD] SAPS score, 0.33 [0.52]), delusions (mean [SD] SAPS score, 0.83 [0.75]), and negative symptoms (total mean [SD] SANS score, 3.33 [2.34]; total mean [SD] SAPS score, 6.17 [0.75]). Permission for the study was obtained from the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

PROCEDURES

Subjects were given a standard set of verbal instructions about the experiments and performed 3 trials of the task (using different stimuli from those presented during scanning) on each of 2 occasions: 1 to 5 days before and immediately before scanning. During scanning, stimuli (7 Rorschach inkblot plates) were presented on a screen viewed by the subject via a mirror. These inkblots were previously found to evoke positive FTD when patients with schizophrenia were asked to describe them.[21,22] In the present study, subjects were asked to speak about whatever came to mind on viewing the inkblot, starting as soon as the stimulus appeared, and to maintain their gaze on the screen throughout the presentation. Subjects spoke freely, and no prompting was given if they paused or stopped. Each plate was presented for 3 minutes (1 run), with breaks of approximately 1 minute between each presentation (total speech time, 21 minutes per subject). Subjects' speech during scanning was recorded on a computer in digitized form using a nonmetallic microphone positioned close to the mouth. Subjects wore customized headphones that reduced the noise of image acquisition but still allowed them to hear themselves speak.

Acoustic noise generated by image acquisition was filtered from recordings of subjects' speech using commercially available software (Cool Edit 96; Syntrillium Software Corp, Phoenix, Ariz). Subjects' speech was transcribed verbatim[23] from these recordings and subsequently analyzed from these transcripts. The severity of FTD was evaluated using the Thought and Language Index[24] by one of us (P.F.L.), who was masked to subject identity. This scale includes 5 items that assess positive FTD (looseness, peculiar word usage, peculiar sentence construction, peculiar logic, and distractibility). Instances of disorder are scored 0.25, 0.50, 0.75, or 1 according to the degree of abnormality as specified in the scoring guidelines. The reliability of the Thought and Language Index was established in a study in which 5 raters scored transcripts of eight 1-minute speech samples produced by each of 25 patients with schizophrenia.[25] The intraclass correlation coefficient (CC) was 0.82 for the positive FTD total (range, 0.60-0.93 for individual items).

Each 3-minute scanning run was broken down into nine 20-second epochs, and a total score for positive Thought and Language Index items was obtained for each epoch. The total number of words articulated during 20-second epochs was used as a measure of the amount of speech produced in patients and control subjects.

20-second epoch) ranged from 0 to 59 (mean [SD], 29.3 [14.7]) in patients and from 11 to 76 (mean [SD], 45.8 [13.1]) in controls (difference, $U=5.5$; $P=.04$).

The mean (SD) maximum amount of head movement during data acquisition in the *x, y,* and *z* dimensions (in the 2 runs analyzed per subject) was as follows: *x*, 0.6 (0.2) voxels; *y*, 0.6 (0.3) voxels; and *z,* 1.6 (1.5) voxels in patients and *x*, 0.3 (0.2) voxels; *y*, 0.4 (0.4) voxels; and *z*, 0.9 (0.7) voxels in controls.

In patients, the severity of positive FTD was positively correlated with the BOLD response in the cerebellar vermis, the right body of caudate, and the right precentral gyrus. Extensive negative correlations were evident in the left superior temporal gyrus and to a lesser extent in the posterior part of the middle temporal gyrus (**Table 2**, **Figure**).

The severity of FTD in controls was low, and there was little variation over time, precluding detection of significant correlations with the BOLD response.

In the control group, the amount of speech articulated was positively correlated with the BOLD response in the left superior temporal gyrus (Brodmann area [BA] 22 according to the atlas of Talairach and Tournoux[31] [Tal]; Tal *x*, –49; Tal *y,* 0; and Tal *z,* –2; number of activated voxels, 8). Negative correlations were evident in the fusiform gyri bilaterally (BA 18/19; Tal *x,* 23; Tal *y,* –69; Tal *z,* –13; number of activated voxels, 15; and Tal *x,* –26; Tal *y,* –58; Tal *z,* –7; number of activated voxels,

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IMAGE ACQUISITION AND ANALYSIS

Gradient-echo echoplanar MRIs were acquired using a 1.5-T GE Signa System (General Electric, Milwaukee, Wis) fitted with Advanced NMR hardware and software (Advanced Nuclear Magnetic Resonance Systems, Wilmington, Mass). A quadrature birdcage head coil was used for radiofrequency transmission and reception. In each of 14 noncontiguous planes parallel to the intercommissural (AC-PC) plane, 60 T2-weighted MRIs depicting BOLD contrast[26] were acquired (echo time, 40 milliseconds; repetition time, 3000 milliseconds; θ, 90°; in-plane resolution, 3.1 mm; slice thickness, 7 mm; and slice skip, 0.7 mm). Head movement was limited by foam padding within the head coil and a restraining band across the forehead. A 43-slice, high-resolution inversion recovery echoplanar image of the whole brain was acquired in the AC-PC plane (echo time, 73 milliseconds; inversion time, 180 milliseconds; repetition time, 16 000 milliseconds; in-plane resolution, 1.5 mm; slice thickness, 3 mm; and slice skip, 0.3 mm).

Before analysis, the effects of small amounts of subject motion during data acquisition were corrected using a 2-stage process involving realignment and regression.[27] In computing the correlation between behavioral and imaging data, it was necessary to minimize the possibility of spurious correlations leading to type I errors. Such effects are most likely to occur if the behavioral data show a simple monotonic trend, which could show apparent correlations with drifts in image intensity. To deal with this possibility, the seven 3-minute runs of behavioral data (amount of positive FTD and number of words produced) obtained from each individual were examined, and the 2 runs with the highest intrarun variance and at least 2 maxima and 2 minima were selected for correlational analysis. Two runs were used because all subjects had at least this number of runs showing clearly nonmonotonic time and behavior characteristics.

The behavioral data were interpolated using a cubic spline to produce smooth changes between discrete observations (20-second epochs) and obtain an estimate of the behavioral value corresponding to each fMRI volume acquired (one value per repetition time, 3 seconds). In the first analysis, the time series at each voxel was correlated with the vector of the Thought and Language Index score in patients, covarying for the number of words articulated per epoch. Covariation was performed to control for activation related to speech articulation and word retrieval. In the second analysis, applied in patients and controls, the time series was correlated with the number of words produced per epoch. In this analysis, we covaried for long speech pauses (>3 seconds) because we were interested in the correlates of speech production as it varied during continuous discourse (as opposed to the production of brief bursts of speech).[28,29]

After computing the correlation coefficient (CC) from the observed data, correlational analysis was repeated 10 times after random permutation of the time series at each voxel.[30] This process resulted in 10 estimates of the CC at each voxel for each individual after eliminating the observed relationship between the behavioral and imaging data by the permutation procedure. Ten was chosen as the number of randomizations to yield a null distribution of sufficient size to test at all necessary *P* values. A typical image contains approximately 20 000 intracerebral voxels. Ten permutations per voxel, after combining data across voxels, yields approximately 200 000 estimates of CC using the null hypothesis that there is no behaviorally determined change in fMRI signal intensity (BOLD effect). The minimum testable *P* value with this distribution is then 1 per 200 000, or .000005. The probability of any CC occurring using the null hypothesis can be obtained by sampling this distribution at the appropriate point. For example, for a *P* value of .001, the value of the CC is found that is only exceeded by 0.1% of all the values in the distribution control (20 error voxels over the whole brain). Brammer[27] and Bullmore[30] and their colleagues showed that such techniques permit excellent nominal type I error in fMRI activation mapping. The observed and permuted CC maps for each of the 2 runs selected from each subject were then transformed into the standard space of Talairach and Tournoux[31] and smoothed by a 2-dimensional gaussian filter with full width at half maximum of 7 mm. After smoothing, the mean of the 2 CC estimates for each subject at each voxel in standard space was calculated.

Finally, as a measure of the overall group CC, the median of these subject means was determined. Median statistics were chosen to minimize outlier effects in small groups.[27,30] A null distribution of median CCs was calculated by using identical computational steps on the permuted data. Activated voxels (those exceeding the critical CC for the desired *P* value [see above]) were color coded according to a negative or positive correlation and superimposed on an inversion recovery echo planar imaging data set.[27]

13) and in the posterior cingulate cortex (BA 29/30; Tal *x*, 0; Tal *y*, –50; Tal *z*, 9; number of activated voxels, 11).

In patients, the amount of speech was positively correlated with signal changes in the right superior temporal gyrus (BA 42; Tal *x*, 46; Tal *y*, –25; Tal *z*, 9; number of activated voxels, 17; BA 22; Tal *x*, 58; Tal *y*, –25; Tal. *z*, 4; number of activated voxels, 11) and inferior temporal gyrus (BA 20; Tal *x*, 40; Tal. *y*, –6; Tal. *z*, –24; number of activated voxels, 17) and the right cerebellar cortex (Tal *x*, 9; Tal *y*, –69; Tal *z*, –13; number of activated voxels, 17). There was a negative correlation in the left medial frontal (BA 10; Tal *x*, –14; Tal *y*, 42; Tal *z*, –7; number of activated voxels, 18) and inferior frontal gyrus (BA 44/45; Tal *x*, –40; Tal *y*, 31; Tal *z*, 20; number of activated voxels, 7) and the right inferior frontal gyrus (BA 44/45; Tal *x*, 46; Tal *y*, 19; Tal *z*, 9; number of activated voxels, 15) and cingulate gyrus (BA 24; Tal *x*, 9; Tal *y*, 47; Tal *z*, 9; number of activated voxels, 9).

COMMENT

Schizophrenia is a phenomenologically heterogeneous disorder, and abnormal brain activation could be related to a variety of different symptoms and cognitive processes. In this study, we tried to minimize the impact of heterogeneity by selecting a symptomatologically homogeneous group and by measuring a single phenomenon as it varied over time within each subject. The patient thus

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served as his own control, reducing potentially confounding effects of between-subject differences in other symptoms, cognitive deficits, illness duration, medication status, or IQ. Because the severity of FTD can vary with the amount of speech produced, we also covaried for the number of words per epoch in the analysis; the findings are thus independent of fluctuations in the rate of speech.

To our knowledge, this is the first study to use fMRI to examine brain activity while subjects produced thought-disordered speech "on-line." Functional MRI is associated with significant scanner noise, but all our participants reported that they were able to hear themselves speak during the tasks. Although we acquired hundreds of images in each participant, the total number of subjects was small because such patients are difficult to recruit, and our results should still be regarded as preliminary. Moreover, our patients are meant to represent only a subset of the population with schizophrenia, and our results might be specific to the production of FTD rather than the disorder as a whole. Overt speech responses during fMRI might be associated with head movement,[32] and artifacts in the orbital frontal cortex can be introduced by changes in the pharynx during phonation (susceptibility induced signal loss at the air-tissue border). However, (1) the main areas of activation were far from this region; (2) we quantified head movement, and this was minimal; and (3) at 1.5 T, when overt responses are continuous, these effects on grouped data are likely to be small.[33]

The results confirmed our main prediction, that the severity of positive FTD was negatively correlated with blood oxygenation level in the left superior temporal gyrus. This observation, and the finding of positive correlations in the right caudate, replicates the results from a previous positron emission tomography study,[10] which used a similar, although less sophisticated, design. They are also consistent with data from structural imaging studies (for a review, see Shapleske et al[34] and Rajarethinam et al[35]), which described volumetric anomalies in the left superior temporal gyrus in schizophrenia[36,37] and correlated the magnitude of the reduction in left superior temporal gyrus volume with the severity of FTD.[12,33,38-40]

We also found a strong positive correlation between the severity of FTD and signal changes in the cerebellar vermis. The cerebellum has been implicated in normal somatosensory[41] and verbal[42] self-monitoring. Increased activation in the cerebellum with increasing severity of FTD might be related to the detection of linguistic errors in the patient's speech. However, because patients often seem to be unaware of such errors,[43] this neural response might not be accompanied by detection of anomalies at the conscious level.

Key components of coherent discourse are discourse planning and self-monitoring for (and correction of) verbal errors.[44] In controls, the amount of speech produced was positively correlated with activity in the left superior temporal gyrus, consistent with its normal involvement in these processes.[45] This correlation between speech production and left temporal activity was not evident in patients. Moreover, when patients were articulating thought-disordered speech, they showed a negative correlation with activity in the left superior temporal region—opposite to what occurs during production of coherent speech. This is consistent with the effects of lesions in this area, which lead to Wernicke (jargon) aphasia, involving fluent but paragrammatical speech that bears some resemblance to FTD. Cognitive models propose that defects in discourse planning and verbal self-monitoring underlie the production of thought-

Table 1. Sociodemographic and Clinical Characteristics of Patient and Control Groups

	Patients With Formal Thought Disorder (n = 6)	Control Subjects (n = 6)	*P*
Age, mean (SD), y	34.3 (11.5)	34.0 (7.9)	.95
National Adult Reading Test IQ, mean (SD)	101.2 (10.7)	107.6 (9.6)	.28
Digit Span, mean (SD), digits	6.0 (1.9)	7.7 (1.9)	.13
Continuous Performance Test, mean (SD), errors	3.3 (1.6)	1.9 (0.9)	.15
Years of full-time education, mean (SD)	11.7 (1.7)	13.3 (2.7)	.24
Educational achievement, median (range)*	3 (1-4)	3 (1-5)	.8
Best-ever occupation, median (range)*	3 (3-4)	3 (1-3)	.7

*Rated according to Goldthorpe and Hope.[17]

Table 2. Cerebral Areas That Correlate With the Severity of Positive Formal Thought Disorder in 6 Patients With Schizophrenia ($P \leq .001$)*

Cerebral Area	BA	Hemisphere	Dimension, mm *x*	*y*	*z*	Activated Voxels, No.
Positive Correlations						
Cerebellar vermis	. . .	Left	–3	–61	–13	33
Body of caudate	. . .	Right	20	6	26	8
	. . .	Right	20	3	20	7
Precentral gyrus	6	Right	46	–6	37	6
Negative Correlations						
Superior temporal gyrus	22	Left	–55	–33	15	30
	. . .	. . .	–52	–36	20	19
Middle temporal gyrus	37	Left	–52	–61	4	12

*Only clusters of greater than 5 voxels are shown. BA indicates Brodmann area, according to the atlas of Talairach and Tournoux.[31]

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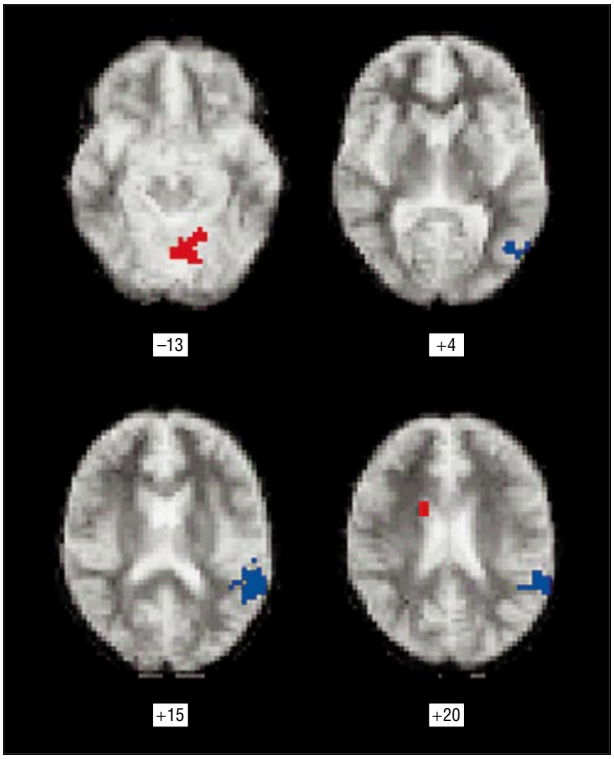

Brain areas in which signal changes in 6 patients with schizophrenia were correlated with positive formal thought disorder. Red voxels indicate positive correlations (cerebellum and caudate); blue voxels, negative correlations (middle and superior temporal gyri) ($P<.001$). The left side of the brain is shown on the right side of the image. Talairach and Tournoux[31] *z* coordinates are shown at the bottom of each slice.

disordered speech in schizophrenia.[46,47] Malfunction of the left superior temporal gyrus during continuous discourse might thus be associated with impairment of these processes and articulation of the linguistic anomalies that characterize thought-disordered speech.

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Corresponding author: Tilo T. J. Kircher, MD, PhD, Department of Psychiatry, University of Tuebingen, Osianderstr. 24, D-72076 Tuebingen, Germany (e-mail: tilo.kircher@uni-tuebingen.de).

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Correction

Error in Figures and Legends. In the article titled "Age-Related Changes in Frontal and Temporal Lobe Volumes in Men: A Magnetic Resonance Imaging Study," published in the May issue of the ARCHIVES (2001;58:461-465), **Figure 2** and **Figure 3** appeared in reverse order. Below are the corrected figures and legends. The ARCHIVES regrets the error.

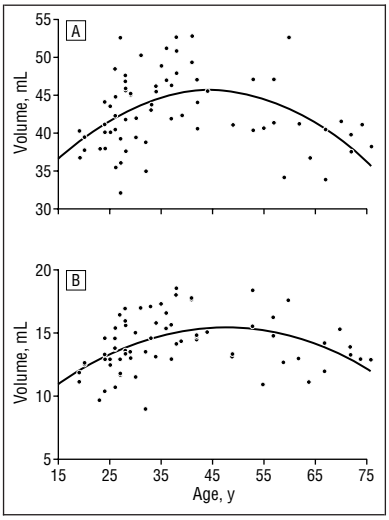

Figure 2. Regression of frontal (A) and temporal (B) lobe white matter volume on age in a sample of 70 normal adult men.

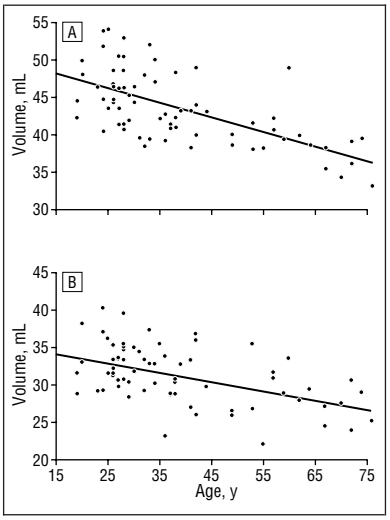

Figure 3. Regression of frontal (A) and temporal (B) lobe gray matter volume on age in a sample of 70 normal adult men.

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