

Brain activation mediates the association between structural abnormality and symptom severity in schizophrenia

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Thought disorder is a symptom of schizophrenia expressed as disorganized or incoherent speech. Severity of thought disorder correlates with decreased left superior temporal gyrus grey matter volume and cortical activation in posterior temporal regions during the performance of language tasks. The goal of this study was to determine whether language-related activation mediates the association between thought disorder and left superior temporal lobe grey matter volume. 12 patients with schizophrenia were assessed for thought disorder. fMRI images were acquired for each subject while they listened to English speech, along with a high resolution structural image. Thought disorder was used as a covariate in the functional analysis to identify brain regions within which activation correlated with symptom severity. Voxel based morphometry was used to calculate grey matter volume of the planum temporale. A mediation model was tested using a four-step multiple regression approach incorporating cortical volume, functional activation and symptom severity. Thought disorder correlated with activation in a single cluster within the left posterior middle temporal gyrus during listening to speech. Grey matter volume within the planum temporale correlated significantly with severity of thought disorder and activation within the functional cluster. Regressing thought disorder on grey matter volume and BOLD response simultaneously led to a significant reduction in the correlation between grey matter volume and thought disorder. These results support the hypothesis that the association between decreased grey matter volume in the left planum temporale and severity of thought disorder is mediated by activation in the posterior temporal lobe during language processing.

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Introduction

Schizophrenia is a psychiatric illness characterized by delusions, hallucinations, disordered thought and negative symptoms. Brain morphological and neuroimaging studies have reported subtle and wide-ranging irregularity in schizophrenia,

frequently associated with specific symptom profiles. Among the few consistent anatomical findings reported in schizophrenia is abnormality of left posterior superior temporal cortex (Barta et al., 1997; Falkai et al., 1995; Menon et al., 1995; Rossi et al., 1992; Shenton et al., 1992), including the planum temporale (Barta et al., 1997; Falkai et al., 1995; Rossi et al., 1992). The planum temporale is the horizontal aspect of the posterior temporal lobe, it has a leftward asymmetry (Geschwind and Levitsky, 1968), overlapping with Wernicke's area, and is classically associated with language function. The planum temporale largely consists of auditory association cortex; lesion and imaging research indicates involvement in early auditory and phonological processing (Binder et al., 1997; Binder et al., 1996; Caplan et al., 1995; Petersen et al., 1988; Wise et al., 1991). In his review of the structural, functional and clinical literature regarding the planum temporale, Shapleske points out that the planum temporale likely engages in language tasks as a functional unit and is not inherently linguistic (Shapleske et al., 1999).

Reduced gray matter volume in left superior temporal cortex, including planum temporale, is associated with an increased severity of thought disorder in schizophrenia (Menon et al., 1995; Rajarethinam et al., 2000; Rossi et al., 1994; Shenton et al., 1992; Vita et al., 1995). The finding is robust, despite methodological variation in the measurement of cortical abnormality, anatomical definition of brain regions, and assessment of thought disorder. In a recent fMRI study we observed a correlation between left posterior temporal activation during listening to speech and severity of thought disorder in schizophrenic patients (Weinstein et al., 2006). Other investigators have described correlations between activation in temporal cortex and thought disorder during the performance of generative language tasks (Kircher et al., 2001a; Kircher et al., 2001b, 2002; McGuire et al., 1998).

Although thought disorder has been linked with both temporal lobe function and gray matter volume separately, the possibility that these three variables may be interrelated has not been tested. The planum temporale operates at an earlier linguistic level than that of posterior superior and middle temporal gyri; therefore, the relationship between planum temporale structural abnormality and

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Table 1
Sample characteristics

Gender (male:female)	7:5
Age	35.9±12.6
Estimated IQ (quick test)	102.7±5.2
Education (years)	15.1±2.4
Parental SES	3.1±1.7
Age of onset	24.3±6.3
SSPI (total score)	9.5±5.7
TLI (total score)	5.0±3.7
Chlorpromazine equivalent of antipsychotic dose (mg)	412.9±271.4

thought disorder may be arbitrated by the degree of activation in the posterior temporal lobe. Specifically, our hypothesis is that the association between decreased left planum temporale gray matter volume and greater severity of thought disorder is mediated by increased activation in left posterior temporal cortex during receptive language processing.

Mediation implies a very specific type of statistically testable relationship that extends beyond the concept of a partial correlation. True mediation suggests that an intermediate variable functions as a mechanism by which an independent variable exerts its influence on a dependent variable. Although this concept is widely recognized and tested in the social sciences, we are unaware of any investigation to date that has applied the methodology to neuroimaging data. In this study, we used a conventional mediation analysis procedure (Baron and Kenny, 1986) to directly investigate the proposal that temporal lobe functioning is the mechanism by which planum temporale structural abnormality influences severity of formal thought disorder.

Methods

Subjects

Twelve patients with a DSM-IV diagnosis of schizophrenia were recruited from the Schizophrenia Day Program at Vancouver Hospital or through the primary care physician. Subjects were selected according to psychopathology to produce a sample with a range of thought disorder (from none detectable to severe). Diagnosis according to DSM-IV criteria was confirmed by one of the authors (EN). All were right-handed (Annett, 1967) native English speakers with no history of head injury, hearing loss, substance abuse or neurological disorder. Sample characteristics are described in Table 1. These subjects were recruited to participate in an fMRI study reported elsewhere (Weinstein et al., 2006); the current paper presents a novel analysis of data from one condition of the original experiment.

Thought disorder was assessed with the Thought and Language Index (TLI) (Liddle et al., 2002a). Subjects were also assessed with the Signs and Symptoms of Psychotic Illness (SSPI) rating scale, a measure of general symptom severity (Liddle et al., 2002b). Three subjects were receiving typical and nine atypical antipsychotic medication and all were stable outpatients with no recent changes to their medication. After complete description of the study to the subjects, written informed consent was obtained. Subjects received 10 dollars per hour remuneration. Experimental procedures were approved by the University of British Columbia Clinical Research Ethics Board.

Functional imaging

All imaging was performed on a 1.5 T General Electric SIGNA scanner. Subjects listened to 30-second blocks of continuous speech stimuli while in the scanner. There were 10 blocks for each of three conditions, English, Mandarin and reversed English. The speech stimuli were recorded from a bilingual male speaker, fluent in both English and Mandarin, reading trivia-type facts about the physical world. Stimuli were presented pseudorandomly, counter-balanced across three 10-minute runs in a block design and alternating with 30 s of silence, through insert earphones contained within 30 dB sound attenuating MRI compatible headphones. These functional data are described in greater detail elsewhere (Weinstein et al., 2006); only data from the English condition are reported here. Echo-planar images were collected on a standard clinical GE 1.5 T system fitted with a Horizon Echo-speed upgrade. Conventional spin-echo T₁-weighted sagittal localizers were used to view head position and to graphically prescribe the functional image volumes. Functional image volumes sensitive to the blood oxygen level-dependent (BOLD) contrast signal were collected with a gradient echo sequence (TR/TE 3000/40 ms, 90° flip angle, FOV 24×24 cm, 64×64 matrix, 62.5 kHz bandwidth, 3.75×3.75 mm in plane resolution, 5.00 mm slice thickness, 29 slices, 145 mm total brain coverage). The first 4 volumes (12 s) collected in each run were discarded to avoid T₁ saturation effects. Functional images were reconstructed offline. Statistical Parametric Mapping software (SPM2, Wellcome Institute of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm/>) was used for image reorientation, realignment, normalization into Talairach stereotaxic anatomical space, and smoothing with a Gaussian kernel (8 mm FWHM) to compensate for inter-subject anatomical differences and optimize the signal to noise ratio. Maximum rotation and translation estimates from realignment were 4 mm and 4°, respectively. The BOLD response for each block of auditory stimuli was modeled as the convolution of a 30-second box-car with a synthetic hemodynamic response function composed of two gamma functions. Beta weights associated with the modeled hemodynamic responses were computed to fit the observed BOLD signal time course in each voxel using the General Linear Model as implemented in SPM2.

Structural imaging

High resolution T₁-weighted anatomical images were acquired with a three-dimensional spoiled gradient recall acquisition sequence (124 sagittal slices, thickness 1.5 mm, TR 11.2, TE 2.1 ms fractional echo, flip angle 20°, FOV 26×26 cm, NEX 1, matrix 256×256, 15.6 kHz bandwidth). Structural images were processed following an optimized voxel based morphometry (VBM) protocol (Ashburner and Friston, 2000; Good et al.,

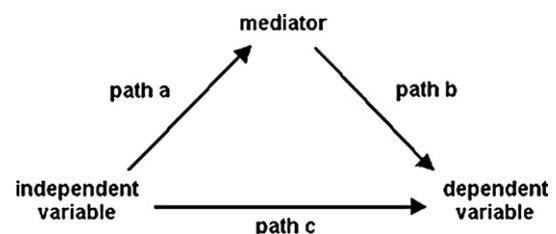


Fig. 1. The mediation model.

2001). VBM is an automated technique that allows for whole brain voxel-wise estimation of tissue volume or concentration. Images were processed on a Linux workstation using SPM2 (SPM2, Wellcome Institute of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm/>) running in Matlab 6.0 (MathWorks, Natick, MA). Images were segmented into gray matter, white matter and CSF, normalized to a T1 template, smoothed with a 12 mm FWHM kernel and then modulated to reverse the effect of normalization on the voxel intensities. The prior probability maps and MNI template provided in SPM2 were used for segmentation and normalization, respectively. A mask of the left planum temporale was created in MNI space with MRIcro, using the template the structural images were normalized to (Rorden and Brett, 2000). The planum temporale was defined as the horizontal aspect of the left posterior temporal lobe. The anterior boundary was defined as the transverse sulcus, which separates the planum temporale from Heschl's gyrus; the posterior boundary was the onset of the posterior ascending ramus. The lateral border was taken to be the superolateral margin of the superior temporal gyrus. As the planum temporale is of a roughly triangular shape, the medial border was defined, of necessity, as the confluence of the transverse sulcus (heading posteromedially) and the posterior border (heading anteromedially). The mask incorporated 25 sagittal slices, from $x=-38$ to -62 , ($z=0$ to 16 , $y=-5$ to -35) with a volume of 3.045 cm^3 , and is illustrated in Fig. 2.

Mediation analysis

A mediation model, illustrated in Fig. 1 (figure from Baron and Kenny, 1986), was tested to assess the associations among gray matter volume, brain activation and symptom severity following the multiple regression approach described by Baron and Kenny (1986). There are four steps to establishing mediation. First,

demonstrate that the independent variable is correlated with the dependent variable (path c). Second, show that the independent variable is correlated with the mediator (path a). Third, show that the mediator affects the dependent variable (path b). Fourth, demonstrate that the effect of the independent variable on the dependent variable (path c) is significantly reduced or eliminated when the mediator is controlled for. This analysis is accomplished with three regression equations: the dependent variable is regressed on the independent variable; the mediator is regressed on the independent variable; and the dependent variable is regressed on both the mediator and independent variables. Perfect mediation is defined as the case where the independent variable is found to have no effect in the third equation (i.e. regression coefficient=0); partial mediation is the case where there is a significant reduction in the effect of the independent variable on the dependent variable in the third equation. The Aroian version of the Sobel test is commonly used to assess the indirect effect of the independent variable on the dependent variable via the mediator (Baron and Kenny, 1986). The Sobel test gives a z score reflecting effect size and an associated p value. In this study, gray matter volume served as the independent variable, BOLD response during listening to English as the mediator variable, and thought disorder ratings as the dependent variable.

Results

TLI scores ranged from 1.50 to 12.75 ($M=5.01$, $SD=3.67$). SSPI scores ranged from 0 to 19 ($M=9.50$, $SD=5.70$). A whole-brain regression analysis of the fMRI data, with TLI score entered as a covariate, was conducted to identify regions active during listening to English speech in which BOLD correlated with thought disorder (cluster-level corrected $p < 0.05$). One cluster of 54 voxels was significant at this criterion, spanning the left middle–posterior

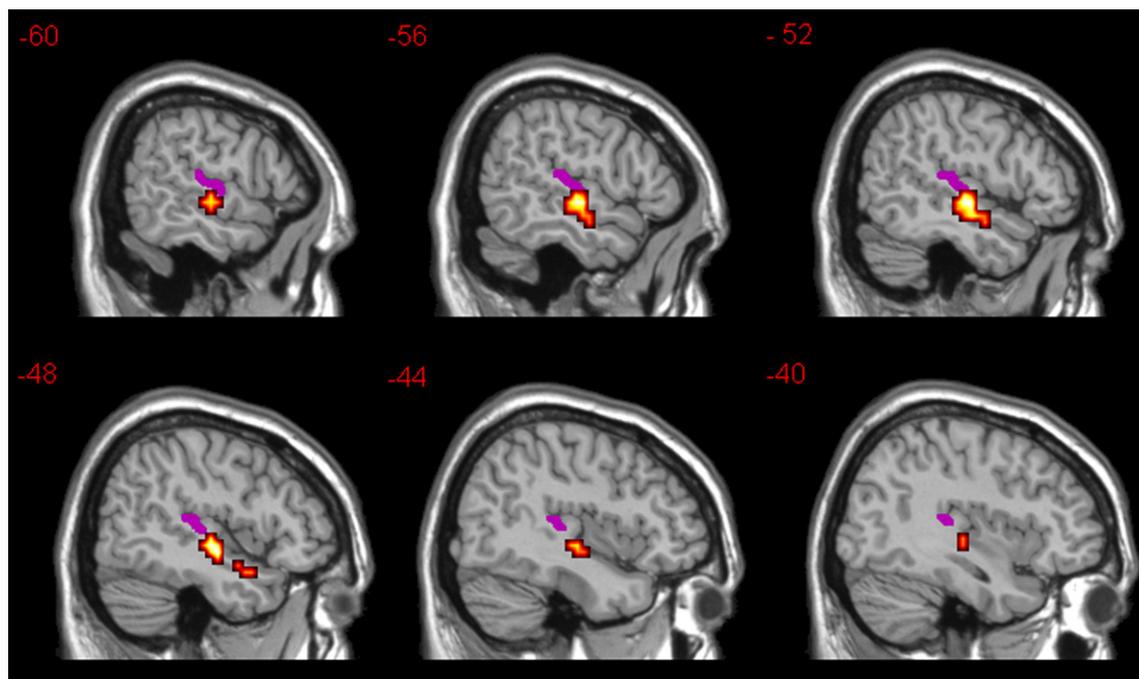


Fig. 2. The two brain regions used in the mediation analysis: the mask of the planum temporale is shown in solid purple and the functional cluster is shown in red scale. Brain slice label is given in the x plane of the Talairach system.

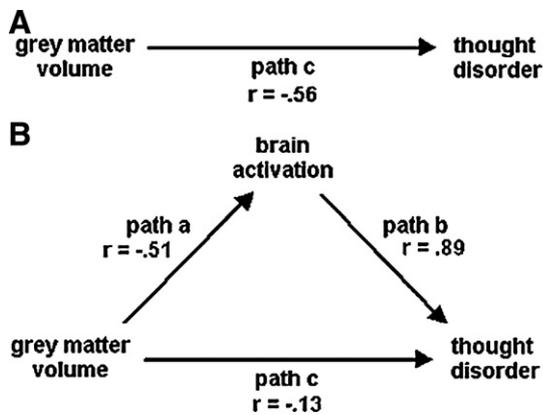


Fig. 3. The correlation between gray matter volume within the left planum temporale and severity of thought disorder before brain activation is included in the mediation model is given in (A) the correlations between gray matter volume within the left planum temporale, severity of thought disorder and brain activation when all three variables are included in the model are given in (B).

superior and middle temporal gyri (maximum at $-48 -12 -8$, $p=0.02$). No brain regions were associated with thought disorder while listening to Mandarin or reversed English. The regression analysis was repeated, first with SSPI total score as a covariate and again with SSPI positive symptoms subscale score as a covariate, to determine if either overall or positive symptom severity was associated with activation during any of the three conditions; no significant associations were found. A detailed description of the analysis of these functional data, including comparison with healthy controls, is given elsewhere (Weinstein et al., 2006).

Mean activation (beta) in the left posterior temporal cluster identified in the TLI regression analysis was extracted for each subject and ranged from 0.99 to 4.16 ($M=2.44$, $SD=1.02$). Mean gray matter volume (voxel intensity) within the left planum temporale mask was extracted from each subject's normalized gray matter structural image. Values ranged from 0.32 to 0.62 ($M=0.44$, $SD=0.09$) and indicate the average proportion of gray matter within each voxel in the mask. The functional cluster and planum temporale mask are shown in Fig. 2. As with activation in the functional cluster, gray matter volume within the mask did not correlate significantly with either the SSPI total score, $r=-0.19$, $p=0.55$, or SSPI positive subscale score, $r=-0.19$, $p=0.55$. Independent samples t -tests conducted to test for sex differences in this mixed sample found no significant differences in mean activation, $t(10)=0.13$, $p=0.90$, gray matter volume, $t(10)=1.47$, $p=0.17$, or TLI score, $t(10)=0.17$, $p=0.87$.

The mediation analysis procedure was followed as described in the Methods section above. Gray matter volume within the planum temporale was a significant predictor of severity of thought disorder, $r=-0.56$, $p=0.03$ (Fig. 3A), as well as activation in the functional cluster, $r=-0.51$, $p=0.04$ (Fig. 3B, path a). As found in the functional analysis, mean activation in the functional cluster was also a significant predictor of severity of thought disorder, $r=0.89$, $p<0.001$ (Fig. 3B, path b). The correlations between TLI score and both functional activation and gray matter volume are illustrated in Fig. 4. When thought disorder was regressed on gray matter volume and mean activation simultaneously, the regression coefficient for gray matter volume was reduced to $r=-0.13$, $p=0.45$ (Fig. 3B, path c), a significant reduction (from $r=-0.56$)

according to the Aroian version of the Sobel test, recommended by Baron and Kenny (1986), $z=-1.73$, $p=0.04$. Effect size is exactly equivalent to a z score of a standard normal distribution, thus our z score of 1.73 shows that the reduction we saw is 1.73 standard deviations above the null hypothesis of no reduction. To assess the possibility of reciprocity within the mediation model, i.e. that gray matter volume mediates the association between functional activation and thought disorder, we tested the mediation model with functional activation as the independent variable and gray matter volume as the mediator. The regression coefficient for activation, with TLI score as the dependent variable, dropped slightly from $r=0.89$, $p<0.001$, to $r=0.82$, $p=0.001$. The Sobel test found this decrease to be insignificant, $z=0.65$, $p=0.51$. In this sample, gray matter is not a significant mediator of the association between functional activation and severity of thought disorder.

Discussion

The objective of this study was to investigate whether the association between decreased left planum temporale gray matter volume and severity of thought disorder is mediated by increased activation in left posterior temporal cortex during language processing. Until now, the relationships among these three variables had only been investigated with a pair-wise approach. Brain activation during a simple listening task correlated positively with thought disorder in this sample, and we replicated the negative correlation between gray matter volume in the left planum temporale and severity of thought disorder described in earlier reports. We also observed a significant correlation between planum temporale gray matter volume and posterior temporal lobe activation, which has not been previously reported.

The mediation hypothesis was confirmed by a significant reduction in the strength of the association between gray matter volume and severity of thought disorder when functional activation was taken into account. This suggests that the structure–symptom association is partially mediated by the degree of activation in left posterior superior temporal gyrus during language processing. In other words, neural activation acts as a mechanism by which cortical volume changes are expressed in thought disorder. A limitation of the study is the small sample size—low power means that the mediation effect may not hold up with larger samples as the correlation that reduced to nonsignificance may become significant when power is increased. On the other hand, the

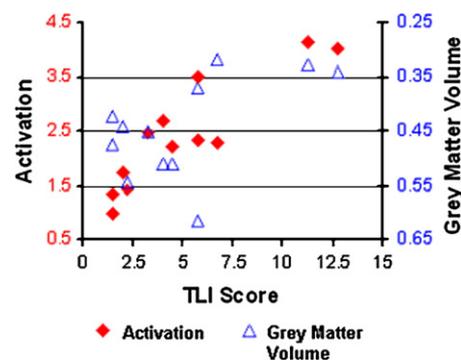


Fig. 4. The correlations between TLI score and both functional activation and gray matter volume prior to mediation analysis. Note that the scale for gray matter volume is inverse.

correlations that were significant were so despite reduced power, possibly reflecting large effects that would be expected to replicate in larger samples. Further investigation is needed to confirm the present findings.

The two regions included in the investigation, planum temporale and the left posterior temporal cluster, are anatomically distinct. The posterior temporal cluster is anterior and inferior to the mask created of the planum temporale; there is only a very narrow region of overlap between the anterior, inferior portion of the mask and the superior, posterior edge of the posterior temporal cluster. The planum temporale is primarily engaged in acoustic and phonetic processing and does not appear to be a dedicated language region as it responds to sounds such as pure tones (Binder et al., 1996) and signal correlated noise (Wise et al., 2001).

The region of functional correlation, on the other hand, is located on the lateral posterior superior temporal gyrus, an area implicated in phonetic, phonological and lexical–semantic processing (Binder et al., 1997, 2000; Scott et al., 2000; Vandenburghe et al., 1996; Vouloumanos et al., 2001). Investigations into the neuroanatomy of auditory speech perception have found evidence of functional subdivisions within the posterior superior temporal gyrus, accounting for the ability of this region to contribute to all three aspects of speech perception (Boatman, 2004). This functional circuitry appears to be adaptable: recent primate and human neuroimaging studies have found that auditory information can be processed by different temporal lobe pathways depending on task and stimulus demands (Kaas et al., 1999; Rauschecker et al., 1995; Romanski et al., 1999; Wise et al., 2001). Furthermore, the primate literature describes direct cortical projections from an early auditory processing region analogous to the planum temporale to a secondary processing regions located within the superior temporal gyrus (Kaas et al., 1999).

There are limits to the flexibility of the auditory speech processing network. Electrocortical mapping studies indicate that the left middle–posterior portion of the superior temporal gyrus—the region of correlation with thought disorder in the current study—is essential for acoustic–phonetic processing (Boatman, 2004; Boatman et al., 1995, 1997). It may be that, as the anatomical substrate supporting early auditory processing in the planum temporale becomes compromised, an increase in neural activity is required at a later, perhaps more critical, processing stage to compensate for the deficiency and maintain normal or near-to-normal function. The correlation we observed between severity of thought disorder and functional activation within the left middle–posterior superior temporal gyrus may reflect such compensatory processing.

It is important to note that the task used was a simple listening task, a function which does not appear to be much affected in schizophrenia. The mediation relationship described would likely have a very different dynamic where generative language functions are concerned, as these have a different association with thought disorder than our receptive task. Generally speaking, generative tasks are associated with a reduction in left temporal activation in schizophrenia. In our report on these functional data (Weinstein et al., 2006), we proposed that the positive association between thought disorder and BOLD response reflected compensatory processing. As receptive language is largely spared in thought disorder, perhaps compensation for inefficient early auditory processing is possible by simply ramping up activation at later processing stages. For more complex language functions such as generative tasks, it may be that the inefficiency cannot be

overcome with a simple increase in processing power, thus the system becomes overwhelmed and reduced activation is seen.

This is, to the best of our knowledge, the first neuroimaging study to directly assess whether associations between neuroanatomy and behaviour correlates are mediated by functional activation. We believe that this type of analysis will prove useful not only for investigations into the physiology of cognitive symptom expression, as in the current report, but also more generally in clarifying the interplay between brain structure and function that determines behavior.

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