

# Do you hear what I hear? Neural correlates of thought disorder during listening to speech in schizophrenia

Sara Weinstein <sup>a,\*</sup>, Janet F. Werker <sup>b</sup>, Athena Vouloumanos <sup>c</sup>,  
Todd S. Woodward <sup>d</sup>, Elton T.C. Ngan <sup>a</sup>

<sup>a</sup> Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, BC, Canada V8T 2A1

<sup>b</sup> Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC, Canada V6T 1Z4

<sup>c</sup> Department of Psychology, McGill University, 1205 Dr. Penfield Avenue, Montreal, QC, Canada H3A 1B1

<sup>d</sup> Department of Research, Riverview Hospital, 2601 Lougheed Highway, Coquitlam, BC, Canada V3C 4J2

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## Abstract

Thought disorder is a fundamental symptom of schizophrenia, observable as irregularities in speech. It has been associated with functional and structural abnormalities in brain regions involved in language processing, including left temporal regions, during language production tasks. We were interested in the neural correlates of thought disorder during receptive language processing, as this function is relatively preserved despite relying on the same brain regions as expressive language. Twelve patients with schizophrenia and 11 controls listened to 30-s speech samples while undergoing fMRI scanning. Thought disorder and global symptom ratings were obtained for each patient. Thought disorder but not global symptomatology correlated positively with the BOLD response in the left posterior superior temporal lobe while listening to comprehensible speech (cluster-level corrected  $p = .023$ ). The pattern of brain activity associated with thought disorder during listening to comprehensible speech differs from that seen during language generation tasks, where a reduction of the leftward laterality of language has often been observed. As receptive language is spared in thought disorder, we propose that the increase in activation reflects compensatory processing allowing for normal performance.

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## 1. Introduction

Thought disorder is a fundamental symptom of schizophrenia, expressed as disturbance in the organization and coherence of speech. Functional brain imaging studies in thought disordered subjects have

found abnormal patterns of activity during the production of speech and performance of language-based tasks. These abnormalities suggest a deviation from the normal pattern of hemispheric lateralization of language functions. Specifically, severity of thought disorder has been observed to correlate negatively with activation in the left posterior superior temporal gyrus (McGuire et al., 1998; Kircher et al., 2001b, 2002) and positively with activation in the right superior and middle temporal gyri (Kircher et al., 2002) during continuous speech

\* Corresponding author. Tel.: +1 604 822 7070; fax: +1 604 822 7756.

E-mail address: [saraw@interchange.ubc.ca](mailto:saraw@interchange.ubc.ca) (S. Weinstein).

production. A similar reduction in the normal leftward functional lateralization of language has also been observed in schizophrenia during the performance semantic decision and verbal fluency tasks (Sommer et al., 2001; Weiss et al., 2004).

Abnormal lateralization in thought disorder is also reflected in the anatomy of the cortex. One of the more consistent morphological findings in schizophrenia is reduced posterior superior temporal lobe asymmetry, and severity of thought disorder is inversely related to the degree of grey matter volume reduction in this area (Shenton et al., 1992; Rossi et al., 1994). Posterior superior temporal lobe is one of the classic language processing regions, incorporating Wernicke's area, and is important for both speech comprehension and production (Binder et al., 1997, 2000; Moore and Price, 1999; Buchsbaum et al., 2001; Crinion et al., 2003). The linguistic nature of this symptom coupled with these and other findings have led to the proposal that thought disorder reflects abnormality in language function, marked by a decrease in the normal leftward structural and functional asymmetry of brain regions involved in language processing (Crow, 1997; Kircher et al., 2002).

Neuroimaging investigations of language and thought disorder have focused on productive language tasks as this is the domain in which disorder is observed. However, receptive and productive language functions rely largely but not entirely on the same brain regions, a key difference being a greater reliance of receptive language on the right hemisphere, particularly at the level of discourse comprehension (St George et al., 1999; Robertson et al., 2000). As both functions involve posterior superior temporal lobe processes, the same region in which grey matter density and activation during producing language correlate with severity of thought disorder, it is interesting that thought disorder is not also evident in receptive language. Working memory is also affected in schizophrenia. Increased brain activation has been observed to accompany normal performance on working memory tasks by subjects with schizophrenia; this is thought to reflect compensatory processing (Callicott et al., 2003; Manoach, 2003).

We hypothesized that a similar process may underlie the preservation of receptive language in thought disorder, that is, that compensatory processing allows for maintenance of this function. If this postulation is correct, severity of thought disorder should be associated with increased brain activation in receptive language processing regions. We imaged subjects as they listened to comprehensible speech to test this hypothesis; specifically, that activity in receptive language processing areas would be positively correlat-

ed with the severity of thought disorder in patients with schizophrenia.

## 2. Methods

### 2.1. Subjects

Eleven healthy control subjects and 12 patients with schizophrenia were recruited. Groups were matched for age, IQ as estimated with the Quick Test (Ammons and Ammons, 1962; Nelson, 1982), and parental socioeconomic status (SES) as determined with the Hollingshead Index (Hollingshead, 1957). Summary statistics for these and other sample characteristics are given in Table 1. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), and were native English speakers with no history of head injury, substance abuse or neurological disorder. Three patients were receiving typical and 8 atypical antipsychotic medication and all were stable outpatients with no recent changes to their medication. Patients with schizophrenia were recruited from the Schizophrenia Day Program at Vancouver Hospital or through their primary care physician. Diagnosis according to DSM-IV criteria was confirmed by one of the authors (E.N.). Control subjects were recruited via advertisement from the University of British Columbia campus. All subjects received 10 dollars per hour remuneration; subjects were screened for MRI compatibility and provided informed written consent before participating. Experimental procedures were approved by the University of British Columbia Clinical Research Ethics Board.

### 2.2. Procedure

Stimuli were thirty 30-s blocks of speech: 10 English (comprehensible), 10 Mandarin (non-comprehensible),

Table 1  
Sample characteristics

	Control subjects (n=11)	Schizophrenic subjects (n=12)
Gender (male/female)	7:4	7:5
Age	34.0±12.0	35.9±12.6
IQ (Quick Test)	111.6±14.1	102.7±5.2
Education (years)	18.4±2.3	15.1±2.4*
Parental SES	3.0±1.6	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

\*  $t(21)=3.35, p=.003$ .

and 10 reversed English (control). The English and Mandarin speech was recorded from a bilingual male speaker fluent in both languages reading trivia about the physical world; the reversed English stimuli were created by reversing the English stimuli using conventional sound editing software. Stimuli were presented pseudorandomly, alternating with 30 s of silence and counterbalanced across three 10-min runs, through insert earphones contained within 30-dB sound attenuating MRI-compatible headphones. As the three conditions were likely to be differentially engaging—comprehensible commanding more attention than either non-comprehensible or reversed speech—a tone detection task was incorporated in an attempt to balance attention. Three or four 1000 Hz tones were embedded in each speech sample at random intervals and subjects were instructed to listen to the auditory stimuli and press a response button when they heard a tone. Although this task may have been distracting during the comprehensible speech, we hoped that it would increase attention during the other two conditions. As this task was simply intended to maintain attention across the three conditions, it was not included in analysis. We considered including a post-scan memory task to assess whether subjects were listening to the stimuli, but as this would

be useful for only one of three conditions we chose not to. The difficulty in assessing memory of non-comprehensible speech reinforced our decision to use the tone task to maintain attention. Thought disorder was assessed with the Thought and Language Index (TLI) (Liddle et al., 2002a) and overall symptom severity with the Signs and Symptoms of Psychotic Illness (SSPI) rating scale (Liddle et al., 2002b).

### 2.3. Image acquisition

Echo-planar images were collected on a standard clinical GE 1.5 T system fitted with a Horizon Echo-speed upgrade. Conventional spin-echo  $T_1$ -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,  $90^\circ$  flip angle, FOV  $24 \times 24$  cm,  $64 \times 64$  matrix, 62.5 kHz bandwidth,  $3.75 \times 3.75$  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  $T_1$  saturation effects.

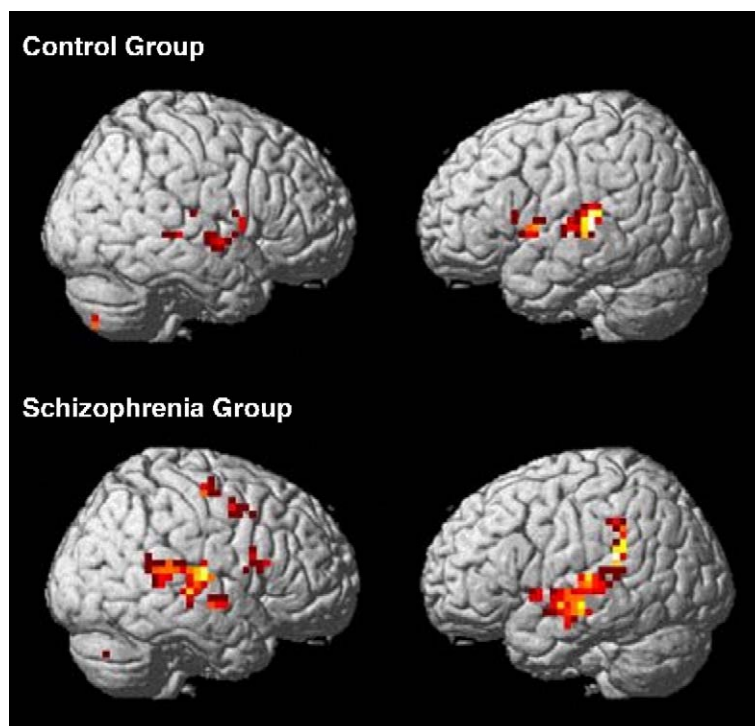


Fig. 1. Regions of activation observed during listening to English for the control group and patient group, corrected  $p < 0.05$ .

Table 2  
Localization of activation during listening to English,  $p < 0.05$  corrected

Group	Region	MNI coordinates ( <i>x, y, z</i> )	No. of voxels	<i>p</i> =
Controls	Left:	Superior temporal gyrus	54	.000
		Inferior frontal gyrus and insula	39	.000
		Cerebellum	4	.005
	Right:	Superior temporal gyrus	35	.000
		Middle temporal gyrus	10	.000
		Cerebellum	5	.010
Patients	Left:	Superior and middle temporal gyri	142	.000
		Hippocampus	13	.000
		Inferior frontal gyrus	3	.003
	Right:	Superior and middle temporal gyri	200	.000
		Precentral gyrus, inferior frontal gyrus	62	.001
		Mid cingulate gyrus	30	.000
		Caudate nucleus	17	.003
		Precentral gyrus	9	.003
		Cerebellum	7	.003
		Inferior temporal gyrus	3	.003

#### 2.4. Image processing

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 s box-car with a synthetic hemodynamic response function composed of two gamma functions. Beta weights associated with the modelled hemodynamic responses were computed to fit the observed BOLD-signal time course in each voxel using the General Linear Model as implemented in SPM2. Contrasts against baseline were calculated

Table 3  
Localization of activation for English > Mandarin,  $p < 0.00001$  uncorrected

Group	Region	MNI coordinates ( <i>x, y, z</i> )	No. of voxels	<i>p</i> =
Controls	Left:	Postcentral gyrus	62	.001
		Middle temporal gyrus	61	.004
		Superior temporal gyrus	56	.001
		Insula	12	.002
		Supramarginal gyrus	10	.024
	Right:	Insula, superior temporal gyrus	219	.000
		Postcentral gyrus	126	.000
		Middle temporal gyrus	33	.008
		Paracentral lobule	19	.002
		Inferior temporal gyrus	15	.011
Patients	Left:	Inferior frontal gyrus	3	.014
		Middle temporal gyrus	22	.030
		Hippocampus	15	.002
		Thalamus	8	.016
	Right:	Superior temporal gyrus	4	.030
		Insula, middle temporal gyrus	80	.000
		Superior temporal gyrus	57	.006
		Thalamus	16	.003
		Middle frontal gyrus	10	.016
		Postcentral gyrus	8	.007
Cerebellum	5	.002		

separately for all three conditions in each subject. These contrasts were brought forward to a 2nd level analysis (random effects) to determine the regions of activation for each condition in the two groups.

### 3. Results

All three conditions produced similar patterns of activation relative to baseline in the patient and control groups: posterior superior and middle temporal gyri bilaterally, lateralized to the left. Fig. 1 shows the activation observed during listening to English relative to baseline for patients and controls, random effects  $p < .05$  corrected for multiple comparisons; cerebral regions, MNI coordinates and voxel-level  $p$ -values are given in Table 2. English was associated with greater activation than Mandarin and reversed English for both groups at  $p < 0.00001$  uncorrected; cerebral regions, MNI coordinates and voxel-level  $p$ -values for the English–Mandarin and English–reversed English contrasts are given in Tables 3 and 4, respectively. Neither of the control conditions was associated with increased activity relative to English at this threshold. No significant differences between groups were observed for the baseline or between conditions contrasts.

A whole-brain regression analysis with TLI score entered as a covariate was conducted to identify regions active during listening to English that correlated with

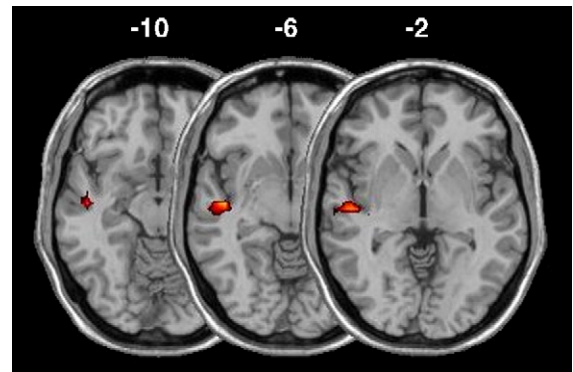


Fig. 2. Region of correlation between TLI score and brain activation in patients with schizophrenia during listening to English, cluster-level corrected  $p < 0.05$ .

thought disorder in patients. This identified a single significant cluster of 54 voxels, spanning the left posterior superior temporal sulcus and middle temporal gyrus (maximum at  $x\ y\ z$ :  $-48\ -12\ -8$ , cluster-level corrected  $p = 0.023$ ; see Fig. 2). No other regions were found to correlate with TLI score, even when the threshold was lowered to  $p < 0.05$ . The correlation between TLI score and activation (mean beta) in this region while listening to English was  $r = .93$ . The mean beta value in this region was 2.40 for the patients and 2.02 for the controls, a slight but not significant increase

Table 4  
Localization of activation for English > reversed English,  $p < 0.00001$  uncorrected

Group	Region	MNI coordinates ( $x, y, z$ )	No. of voxels	$p =$
Controls	Left:	Inferior parietal lobule	28	.001
		Mid cingulate	18	.001
		Postcentral gyrus	11	.012
	Right:	Putamen, globus pallidus	65	.007
		Superior frontal gyrus	24	.000
		Precentral gyrus	23	.002
		Superior temporal gyrus	14	.001
		Inferior frontal gyrus	8	.026
		Middle temporal gyrus	8	.050
Patients	Left:	Superior temporal gyrus	48	.002
		Parahippocampal gyrus	41	.001
		Middle temporal gyrus	27	.003
		Middle frontal gyrus	10	.020
	Right:	Superior frontal gyrus	7	.019
		Inferior frontal gyrus	4	.043
		Parahippocampal gyrus	50	.001
		Precentral gyrus, inferior frontal gyrus	50	.007
		Superior temporal gyrus	40	.007
		Insula	31	.004
		Superior medial frontal gyrus	19	.010
		Angular gyrus	11	.000
		Caudate nucleus	6	.001

( $p=0.16$ ). The regression analysis was repeated for the acoustic control conditions, Mandarin and reversed English, but identified no significant correlations. To test for an association between both overall symptom levels and positive symptom levels with activation during any of the three conditions, SSPI total and SSPI positive scores were separately entered as covariates in regression analyses; no correlations were found.

#### 4. Discussion

In this study, while listening to comprehensible English speech, severity of thought disorder in patients with schizophrenia correlated with increased activation in left posterior superior temporal sulcus and middle temporal gyrus. Activation in this region was not associated with thought disorder when listening to either Mandarin or reversed English, or with overall symptomatology. This result contrasts with previous studies of language production, in which thought disorder was associated with decreased activation in this region (McGuire et al., 1998; Kircher et al., 2001b) or increased activation in the homologous right hemisphere region (Kircher et al., 2002) during continuous speech. A study of speech detection, however, found severity of thought disorder correlated positively with activation in the left temporo-parietal junction (Ngan et al., 2003), while a sentence completion paradigm showed reductions in right temporal and increases in left inferior frontal activation in thought disordered patients (Kircher et al., 2001a). This disparity suggests that a reduction in the functional laterality of language may not fully explain this symptom, and that patterns of language-related activation associated with thought disorder are likely task-dependent.

The concept of reduced efficiency in schizophrenia has been introduced in the working memory literature, where in low memory load conditions patients with schizophrenia show greater prefrontal activity than controls and normal performance, whereas at high load conditions patients show a reduction in prefrontal activity with impaired performance (Manoach et al., 1999; Cairo et al., *in press*). This is explained as a shift in the normal inverted-U relationship between memory load and prefrontal activation: in healthy subjects, activity increases commensurate with load until memory capacity is exceeded, at which time both activity and performance drop (Goldberg et al., 1998b; Callicott et al., 1999). In schizophrenia however, the memory system operates at a higher intensity to maintain normal performance at lower load levels and so reaches the capacity threshold earlier; increased activation observed

at lower load levels reflects compensatory processing and is a sign of inefficiency in the system.

It is possible that a similar mechanism could explain the apparent preservation of comprehension in patients with thought disorder. Simple speech comprehension is a fundamental element of language, with lower cognitive demands than most productive language functions. An (in)efficiency model would predict that, for this relatively undemanding function, increased activation could compensate for processing deficits resulting in preserved comprehension, while for higher-demand generative language functions such as speech production capacity threshold would be exceeded resulting in reduced activation and impaired performance. Thus, increased left temporal activation in thought disordered subjects during speech comprehension may reflect the compensatory processing necessary to perform normally with an impaired language system. While this group of patients had a slightly higher mean activation than controls in the region correlating with thought disorder, the difference was not significant. This may reflect the symptomatic heterogeneity of this group. Under the inefficiency model, subjects who are not disordered would not be expected to show greater than normal activation—only those exhibiting the symptom would need to compensate for the underlying functional disturbance.

Our results suggest that thought disorder is associated with abnormal activity when listening to speech; however, these data do not allow direct assessment of between-group differences. The within-groups contrasts of English relative to the control conditions produced roughly similar patterns of activation with both groups showing activation in bilateral temporal cortices. This likely reflects semantic processing, and is consistent with previous findings contrasting speech and non-speech stimuli (Demonet et al., 1992; Binder et al., 1997, 2000). The common focus of activation for all three conditions was the left posterior superior temporal gyrus, a region known to be involved in acoustic and phonological processing (Demonet et al., 1992; Binder et al., 2000; Scott and Johnsrude, 2003). Previous research has found activation in posterior superior temporal gyrus for meaningless speech sounds comparable to that seen in response to comprehensible speech (Wise et al., 1991; Hirano et al., 1997; Binder et al., 2000). While reversed speech stimuli are intended to control for non-phonological acoustic features of speech, there is evidence of partial preservation of phonological information in the acoustic signal. It has been shown, for example, that subjects can phonologically transcribe reversed words with a notable degree of

intra-subject consistency (Binder et al., 2000), and that segment-reversed speech can be comprehensible (Saber and Perrott, 1999).

If activity observed during the control conditions is primarily due to acoustic or phonological processing, the current correlation between thought disorder and activation when listening to English may reflect abnormal semantic processing. The region of correlation lies almost entirely within the section of left posterior superior temporal lobe implicated in semantic processing, lateral and inferior to the region involved in phonological processing. Both verbal and nonverbal semantic tasks have been found to activate cortex of the left posterior superior temporal sulcus and middle temporal gyrus (Vandenburghe et al., 1996; Binder et al., 1997). Increased semantic priming (Manschreck et al., 1988; Spitzer et al., 1993; Moritz et al., 2002; Quelen et al., 2005) suggests that semantic processing is abnormal in thought disorder, and there is evidence that the organization of the semantic network may be disturbed. Unlike healthy subjects, thought disordered subjects fail to use semantic category dimensions to generate words in a verbal fluency task (Aloia et al., 1996; Paulsen et al., 1996; Goldberg et al., 1998a).

It remains unclear whether temporal lobe functional abnormalities, including semantic processing deficits, are the source of thought disorder or whether they are both secondary to higher level dysfunction. Studies of semantic processing in schizophrenia have observed reduced inferior frontal activity in addition to over-activation of posterior temporal lobe (Kubicki et al., 2003), and there is evidence of a disconnection between frontal and temporal semantic processing regions (Kim et al., 2005). Recent behavioural studies suggest the strongest predictor of thought disorder is executive dysfunction (Kerns and Berenbaum, 2002; Barrera et al., 2005), but possible interactions between higher-level cognition and language have yet to be explored.

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