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ScienceDirect
Schizophrenia Research 103 (2008) 26–39
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Auditory processing abnormalities in schizotypal personality disorder: An fMRI experiment using tones of deviant pitch and duration

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Received 31 January 2008; received in revised form 18 April 2008; accepted 24 April 2008
Available online 13 June 2008

Abstract

Background: One of the cardinal features of schizotypal personality disorder (SPD) is language abnormalities. The focus of this study was to determine whether or not there are also processing abnormalities of pure tones differing in pitch and duration in SPD.

Methods: Thirteen neuroleptic-naïve male subjects met full criteria for SPD and were group-matched on age and parental socio-economic status to 13 comparison subjects. Verbal learning was measured with the California Verbal Learning Test. Heschl's gyrus volumes were measured using structural MRI. Whole-brain fMRI activation patterns in an auditory task of listening to tones including pitch and duration deviants were compared between SPD and control subjects. In a second and separate ROI analysis we found that peak activation in superior temporal gyrus (STG), Brodmann Areas 41 and 42, was correlated with verbal learning and clinical measures derived from the SCID-II interview.

Results: In the region of the STG, SPD subjects demonstrated more activation to pitch deviants bilaterally ($p<0.001$); and to duration deviants in the left hemisphere ($p=0.005$) (two-sample t). SPD subjects also showed more bilateral parietal cortex activation to duration deviants. In no region did comparison subjects activate more than SPD subjects in either experiment. Exploratory correlations for SPD subjects suggest a relationship between peak activation on the right for deviant tones in the pitch experiment with odd speech and impaired verbal learning. There was no difference between groups on Heschl's gyrus volume.

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0920-9964/$ - see front matter. Published by Elsevier B.V.
doi:10.1016/j.schres.2008.04.041

Conclusions: These data suggest that SPD subjects have inefficient or hyper-responsive processing of pure tones both in terms of pitch and duration deviance that is not attributable to smaller Heschl's gyrus volumes. Finally, these auditory processing abnormalities may have significance for the odd speech heard in some SPD subjects and downstream language and verbal learning deficits.
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Keywords: Schizotypal personality disorder; Auditory; Schizophrenia; fMRI; MRI; Imaging; Tone processing; Evoked potential; ERP; Mismatch negativity; Pitch; Frequency; Duration; MMN

1. Introduction

Auditory sensory processing has been found to be impaired in schizophrenia (Salisbury et al., 1998; Javitt et al., 2000) and correlate with clinical features, particularly negative symptoms (Javitt et al., 2000), (Kasai et al., 2002) (Leitman et al., 2005) and cognitive impairment (Baldeweg et al., 2004). Abnormalities in the superior temporal gyrus (STG) have been implicated in the processing of pure tones, a fundamental element of complex sounds and language, using fMRI (Wible et al., 2001) and event-related potentials (Salisbury et al., 1998). Hallucinations, which may be considered an error in auditory sensory processing, have been associated with the STG (Dierks et al., 1999) (Cleghorn et al., 1992), with the STG more activated during hallucinations than actual speech (David et al., 1996). The STG has also been implicated in verbal learning deficits in schizophrenia using PET (Ragland et al., 2001). However, research in schizophrenia has been confounded by potential modulating effects of neuroleptic medications on fMRI signal (Stephan et al., 2001; Brassen et al., 2003). Neuroleptic-naïve subjects are needed to ensure that research findings are due to underlying neuropathology rather than iatrogenic effects.

Subjects with schizotypal personality disorder (SPD) may provide an ideal population of neuroleptic-naïve subjects for fMRI studies. Although SPD shares many features with schizophrenia, it is not a direct proxy for schizophrenia, as SPD subjects are not psychotic. Nonetheless, SPD and schizophrenia have traditionally been considered part of the schizophrenia spectrum disorders based on epidemiological data (Kety et al., 1967) (Kendler et al., 1993), shared clinical features such as thought disorder (Dickey et al., 1999) and paranoia (Dickey et al., 2005), similar biological markers (Siever and Davis, 2004), comparable cognitive deficits in verbal learning (Voglmaier et al., 1997) (Voglmaier et al., 2000) (Voglmaier et al., 2005), and overlapping morphometric abnormalities (Dickey et al., 2002a,b).

Indeed, one brain region critical for early sensory auditory processing, Heschl's gyrus (Yoo et al., 2005), has been shown to have reduced volumes in subjects with SPD (Dickey et al., 2002a,b), similar to what has been shown in schizophrenia (Hirayasu et al., 2000). Heschl's gyrus lies on the plane of the STG, a region found to have small volumes in males with SPD (Dickey et al., 1999; Downhill et al., 2001), and in females with SPD with a family history of mental illness (Dickey et al., 2003). Of particular interest to this report, however, Heschl's gyrus is noted to have marked inter-subject morphometric volume and shape variability (Leonard et al., 1998; Knaus et al., 2006), thus complicating the interpretation of volume data (Knaus et al., 2006).

As in schizophrenia, abnormalities of auditory processing at multiple stages have been shown in SPD including the P50 (Cadenhead et al., 2000), P300 (Salisbury et al., 1996), and N400 (Niznikiewicz et al., 1999). Similarly, in subjects with high scores of schizotypal features but not frank SPD, auditory abnormalities have been shown in the P300b (Klein et al., 1999), N400 (Kimble et al., 2000), and in phonemic discrimination (Li et al., 2003). Finally, in one paper examining mismatch negativity (MMN) in subjects clinically diagnosed with schizotypy but for whom a formal diagnostic interview was not performed, schizotypal subjects were found to have increased amplitudes in the Fz and Cz electrodes to pitch deviants (Liu et al., 2007). Hence, it appears that in the schizophrenia spectrum there is a range of auditory processing abnormalities, albeit with some negative findings (Brenner et al., 2003). The current report seeks to build on this literature by examining tone processing of pitch and duration deviance in SPD subjects using fMRI.

One question in the literature is how to best measure deficits in early auditory sensory processing in schizophrenia and SPD, whether through event-related potential (ERP) or fMRI studies. The ERP methodology affords good temporal resolution while fMRI offers a good spatial resolution. ERP components often used to examine processing auditory pre-attentive and attentive abnormalities in schizophrenia are mismatch negativity (MMN) and P300. A MMN ERP paradigm, which

elicits an early negative deflection following a deviant stimulus, results in a less negative deflection in schizophrenic subjects and has been used frequently to assess subjects' pre-attentive ability to detect changes in tone features (e.g.:Salisbury et al., 1998). In contrast, to our knowledge (Medline search 1/10/08), there have been only two published fMRI experiments utilizing the mismatch design in patients with schizophrenia (Wible et al., 2001; Kircher et al., 2004). Adequate numbers of deviants are required to produce a detectable contrast-to-noise ratio, yet this must be balanced with experimental length, as subjects' tolerance to long scanning session is limited. For these reasons, we employed a significantly modified mismatch experiment with larger differentials between standard and deviant tones and more frequent deviants as compared with prototypic mismatch paradigms.

Therefore, whether the STG in SPD exhibits normal functioning as measured by hemodynamic response to early auditory sensory information is the central question driving the current report. Structural MRI and neuropsychological testing procedures are also included. The possible relationship between early auditory processing and downstream language and other cognitive functions, as well as the highly complex clinical manifestations of SPD, is also evaluated in an exploratory fashion. These questions are important to ask in SPD subjects as they are neuroleptic-naïve, thus, a complicated confound in similar studies of auditory function with schizophrenic subjects is removed (Umbricht et al., 1998).

2. Methods

2.1. Subject recruitment

All subjects were male; right-handed; between 18 and 55 years old; neuroleptic-naïve; on no psychotropic medications; had no history of ECT, neurologic disorder, substance abuse in the last 1 year or substance dependence in the last 5 years; and were recruited from the community through newspaper and subway advertisements (for recruitment specifics, see Dickey et al., 2005). Note that data for past psychotropic use of any kind or substance dependence beyond five years ago was not available. SPD subjects met DSM-IV criteria for SPD using the SCID and SCID-II interviews and had no personal history of bipolar disorder nor psychosis. Thirteen SPD subjects were group-matched on age, parental socio-economic status, and estimated IQ to 13 comparison subjects who had additional exclusionary criteria of no personal history with Axis I or Axis II disorder as determined by SCID, or first-degree relative history of Axis I disorder.

2.2. Clinical measures

SPD criteria were from SCID-II interview. IQ was assessed through the WAIS-R Vocabulary and Block Design sub-scales (Brooker and Cyr, 1986). Verbal learning was assessed using the California Verbal Learning Test (CVLT), total words learned trials 1–5 (Delis et al., 1987). This test was selected as a test of verbal working memory and because it has been shown by our laboratory to be abnormal in SPD subjects (Voglmaier et al., 1997; Voglmaier et al., 2000; Voglmaier et al., 2005).

2.3. Structural MRI

Heschl's gyrus was manually delineated on resolution SPGR images obtained within a year of the fMRI protocol, except one SPD subject for which no structural MRI was available. The protocol for the drawing resembled that of a previously published report on Heschl's volumes (Dickey et al., 2002a,b). The anterior boundary was the temporal stem; the posterior boundary was the complete crux of the fornix; the lateral boundary was determined by a horizontal line extending laterally from the superior most white matter track of the STG. There was one major methodological difference in the drawing between the two reports, however. In this report axial views were used initially to guide the definition of the extent of Heschl's. Axial views were not available previously. With the use of Slicer software (www.slicer.org) one could now visualize whether there was a single transverse gyrus, a common medial stem branching to two more laterally in which case both would be included per Steinmetz's criteria (Steinmetz et al., 1986), or two medial stems joining more laterally in which case only the more anterior portion would be selected. This ability to visualize and draw in three dimensions represents a significant technological advancement compared with previous capabilities and is important given the marked inter-subject and even inter-hemispheric variability of this gyrus (Knaus et al., 2006). Volumes were corrected for total intracranial contents using a regression procedure (Dickey et al., 2002a,b). Inclusion of Heschl's volume measurement was important for the interpretation of the functional data.

2.4. fMRI acquisition and post processing

Whole-brain images were acquired on a 3.0T GE system in the oblique axial plane parallel to the superior

temporal plane prescribed from the localizer images. Functional image parameters included whole-brain coverage, 30 slices, 5 mm thick with 1 mm gap, 162 acquisitions the first 6 of which were removed, FOV 24, matrix 64x64, TR 2.5, TE 35. The same prescription (orientation/slice thickness) was applied to obtain a low-resolution SPGR sequence. These low-resolution SPGR images were reoriented, realigned, and normalized to the Montreal Neurological Institute (MNI) T1 template with the resulting matrix files applied to the functional images using SPM2. Functional images were subsequently smoothed (using 12 FWHM 3-dimensional Gaussian kernel).

2.5. Stimuli

Two experiments were employed to activate the auditory cortex, one using the pitch deviants and the second using the duration deviants. Tones were transmitted via sound-insulated and cushioned earphones (Silent Scan, Avotec, Jensen Beach, FL) at 80 db SPL (Sound Pressure Level). All tones had 10 ms rise and fall times and an interstimulus interval of 300 ms and were played at 80 db. *Experiment 1: Pitch*. The standard tone was 500 Hz and the deviant tone was 2000 Hz, all tones 100 ms in duration (Fig. 1a). *Experiment 2: Duration*. The standard tone was 50 ms in duration, the deviant tone was 200 ms in duration, with a frequency of 500 Hz for all tones (Fig. 1b and c). Presentation was block design with 30 s blocks of tones alternating with 30 s rest (Fig. 1d). Each tone block consisted of 100 tone presentations, alternating between blocks of 100% standard tones and mixed blocks of 75% standard tones and 25% deviant tones. In the mixed standard and deviant blocks the order of standard and deviant tones was randomly determined. Only one deviant (pitch or duration)

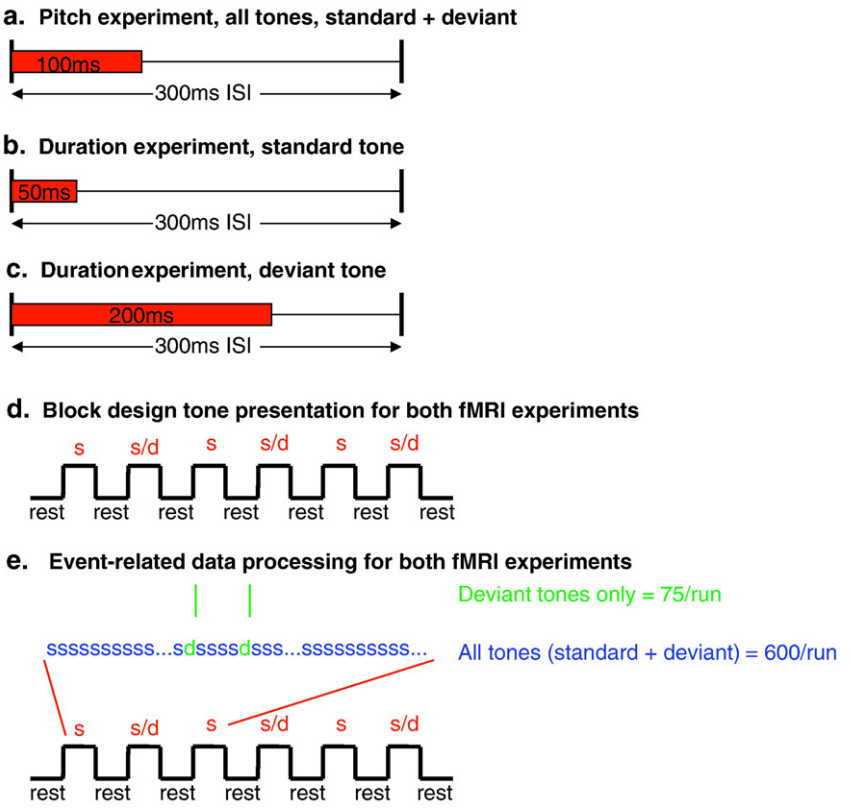


Fig. 1. Diagrams of stimuli presentation and processing. a. For the pitch experiment all tones are 100 ms in duration with 200 ms of silence before the next tone. b. For the duration experiment, the standard tone is 50 ms in duration with 250 ms of silence before the next tone. c. For the duration experiment the deviant tone is 200 ms in duration with 100 ms of silence before the next tone. This variation decreases the expectancy factor. d. Tones were presented in block design. e. Hemodynamic response curves were generated for all tones together (both standard and deviant, all tone condition) and for only the deviant tones (deviant condition). ISI = interstimulus interval; ms = milliseconds; s = standard; s/d = standard and deviant tones intermixed; rest = silence.

was presented in a given run. Run duration was 6′45″. There were two runs for pitch and two for duration for a total of four runs, order counterbalanced among subjects. Subjects heard 1050 standard tones and 150 deviant tones for a total of 1200 tones per experiment (Fig. 1e). For technical reasons, data were acquired on only 11 SPD subjects for the duration experiment, therefore, the sample size differs in the two fMRI experiments. Task for both experiments was passive listening with eyes closed. Following each run subjects were queried as to whether they heard the tones to ensure adequate hearing and wakefulness. All subjects affirmed that they did indeed hear the tones after each run. Subjects were not asked nor expected to differentiate between the tones.

Table 1
Subject demographics and absolute Heschl's gyrus volumes in milliliters

	SPD	NC	*p*
N	13	13	
Age	36.8 (10.8)	30.4 (11.4)	<0.2
PSES	4.0 (1.2)	3.8 (1.4)	0.08
SES	3.0 (1.4)	3.2 (1.4)	0.7
IQ	116 (9.7)	120.4 (12.4)	<0.4
Education	15.2 (1.9)	18.0 (3.8)	0.02
SSPT score	55.2	56.2 (N=8)	<0.5
Left Heschl's gyrus [a]	2.23 (0.9)	2.35 (0.6)	0.74
Right Heschl's gyrus [b]	1.95 (0.51)	1.92 (0.2)	0.29

Note that statistics were performed on regressed not absolute volumes in order to account for confounding effect of head size. PSES = parental socio-economic status, SES = socio-economic status, SSPT = Speech Sound Perception Test.
[a] $F(1,24)=0.109$.
[b] $F(1,24)=1.128$.

2.6. fMRI statistical methods

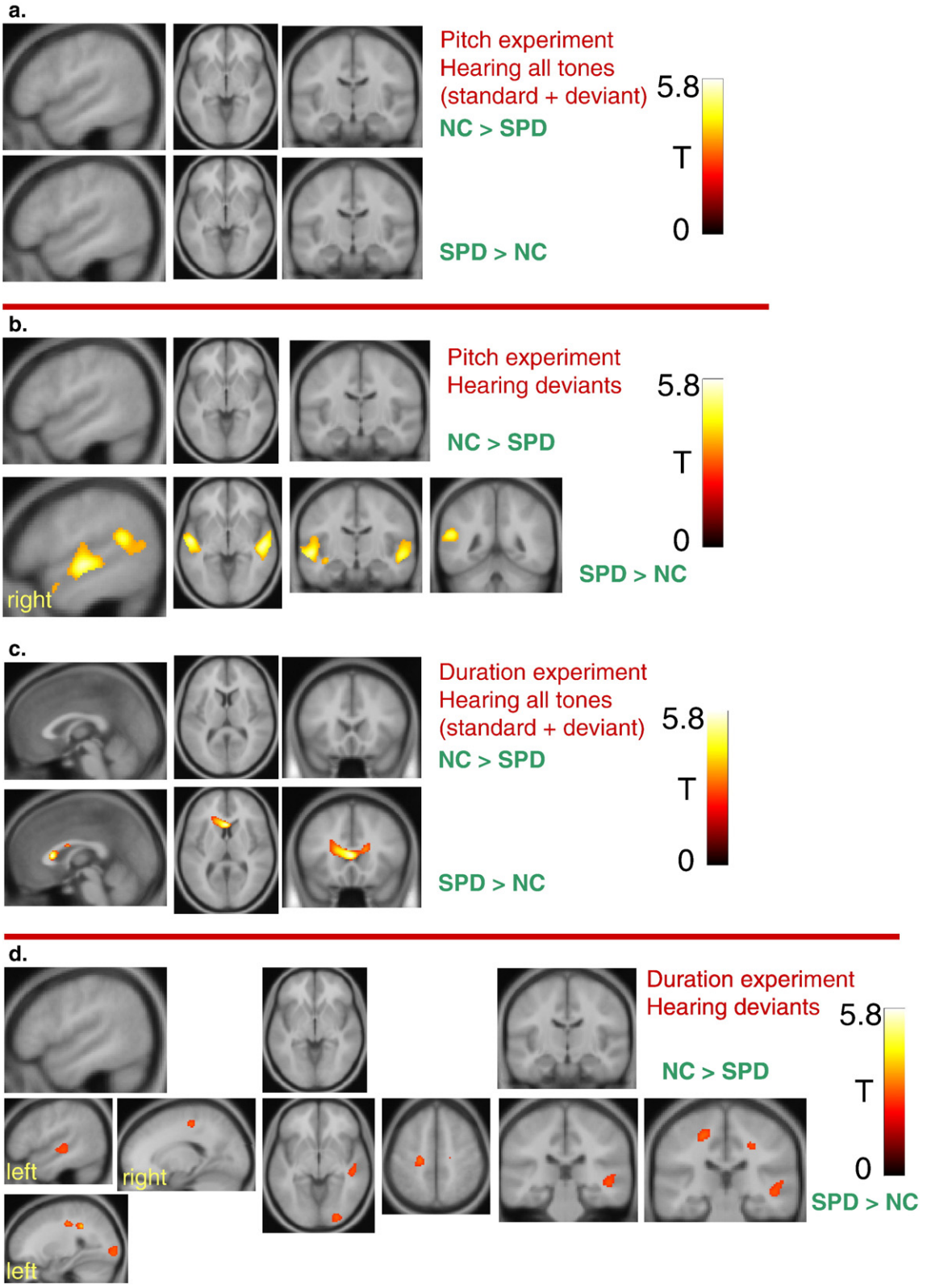
2.6.1. Whole-brain analysis

This was the primary statistical analysis for the pitch and duration fMRI experiments. Whole-brain event-related procedures were employed statistically in order to single out the effect of all tones (standard+deviant), and in a separate analysis, the differential effect of hearing only deviant tones. Restated, the hemodynamic responses were modeled first in order to examine the effect of being in the scanner and hearing all tones, both standard and deviant, regardless of block type (main effect) (Fig. 1e, in blue and green). Subsequently, the hemodynamic effect of hearing only deviant tones (parametric effect) was modeled (Fig. 1e, in green). This isolates the effects of hearing deviant tones "on top of" the effect of hearing all tones, that is, standard and deviant (green only "on top of" green and blue). Specifically, the main effect of hearing all tones (standard+deviant, regardless of block) vs. rest were modeled using one regressor (effect of hearing deviant tones only) in the General Linear Model for each subject. Second, the differential effect of hearing the deviant tones was modeled as a parametric regressor (deviant tones as 1 and standard tones with value 0) in order to measure the deviant-related modulation of the BOLD signal time course for each subject. Thus the effect of hearing all tones (both standard and deviant combined, the effect of being in a scanner and hearing tones, the main effect) could be compared as well as the effect of only hearing deviant tones (parametric effect). Subject specific whole-brain contrast images from the two groups were pooled and were compared using one-sample (all tone and deviant tone conditions for both experiments) and two-sample *t* tests (all tone and deviant tone conditions for both experiments) for the random-effects analysis. Note that these analyses were whole-brain analyses.

2.6.2. Secondary ROI analysis

In order to perform exploratory correlations with clinical/cognitive measures, a second procedure, a second analysis, a voxel-wise restricted ROI analysis, was employed in order to isolate peak activation in the region of the STG for individual subjects. Note that this *secondary ROI analysis was used for correlations only* and that the main fMRI analysis used a whole-brain analysis. Therefore, for secondary and exploratory

Fig. 2. Whole-brain statistical parametric maps with consistent *p* scale shown. Note that regardless of experiment (pitch or duration) and regardless of tone set heard (all tones or deviants only), there is no area of the brain in which control subjects activated more than SPD subjects. a. Pitch experiment, all tones (standard+deviant) heard analyzed together. b. Pitch experiment deviant condition. Note significantly more activation in SPD subjects compared with control subjects in the region of the STG bilaterally. Thresholded at the $p<0.001$ level with an extent of activation cluster size limit set at 240 voxels. MNI coordinates and cluster significance by two-tailed *t* tests were: (−52, −22, −2, $T=5.3$, $p<0.001$), (54, −46, −2, $T=5.3$, $p<0.001$), (54, −46, 18, $T=4.85$, $p<0.001$). c. Duration experiment, all tones (standard+deviant) condition. Thresholded at the $p<0.01$ level with an extent of activation cluster size limit set at 0 voxels to ensure all visible super-threshold activation. MNI coordinates and cluster significance by two-tailed *t* tests were: (2, 22, 10, $T=5.67$, $p<0.0005$) and (−14, 4, 24, $T=5.3$, $p<0.0005$). d. Duration experiment, deviant condition. SPD subjects activated more to deviant tones than comparison subjects in left temporal and bilateral parietal regions. Thresholded at the $p<0.01$ level with an extent of activation cluster size limit set at 240 voxels for temporal lobe regions, 0 voxels for parietal regions in order not to lose relevant findings in that area. MNI coordinates and cluster significance by two-tailed *t* tests were: for temporal lobe regions, (−48, −28, −4, $T=2.83$, $p=0.005$ and −22, −88, 2, $T=3.1$, $p=0.003$); for parietal lobe regions, (−26, −42, 38, $T=4.0$, $p<0.001$), (−24, −20, 42, $T=3.2$, $p=0.002$), (28, −40, 38, $T=3.36$, $p=0.001$). Note standardized color bars across images reflect relative *T* scores. Neurological convention (left is left).


a.
Pitch experiment
Hearing all tones
(standard + deviant)
NC > SPD
SPD > NC
5.8
T
0
b.
Pitch experiment
Hearing deviants
NC > SPD
SPD > NC
5.8
T
0
right
c.
Duration experiment
Hearing all tones
(standard + deviant)
NC > SPD
SPD > NC
5.8
T
0
d.
Duration experiment
Hearing deviants
NC > SPD
SPD > NC
5.8
T
0
left
right
left

correlations, ROI were selected as defined by WFU PickAtlas (www.fmri.wfubmc.edu). Specifically, PickAtlas defined ROI masks were applied and peak *t* values were generated for left and right Brodmann Areas 41, 42, and STG for the deviant condition (three regions of interest (ROI) per side per experiment, 12 in total). These regions were selected a priori as they likely are the regions involved in tone processing (Yoo et al., 2005; Kropotov et al., 1995; Alho, 1995). Note that Brodmann Area 41 derived from PickAtlas does not directly correspond to the manual Heschl's drawing above. They are slightly different measurements but both roughly correspond to presumed areas of pure tone processing. Threshold was set at 0.05 corrected.

2.7. Clinical/cognitive/functional correlations

Exploratory Pearson correlations with peak *t* values and clinical measures were obtained. The clinical measures that included the nine SPD diagnostic criteria and CVLT were correlated with the 12 ROI for a total of 120 correlations. To limit the number of correlations considered significant *post hoc*, only those which were significant in two of the three regions per side in a single condition were accepted (one of the two regions could have a correlation significant at the trend level). For example, a significant correlation with a clinical measure and right Brodmann Areas 41 and 42 would be accepted, but not right 41 and left 42, nor just right 41. We appreciate that even with these more stringent rules, a large number of correlations were performed. However, given that this is the first fMRI paper on auditory processing in SPD to our knowledge (Medline search performed 1/10/08), an attempt to understand the clinical significance of the potential findings was important.

3. Results

3.1. Subject demographics

There were no group differences in age, parental socio-economic status (PSES) (scale 1–5, with 5 as highest PSES), personal socio-economic status (SES), or IQ although SPD subjects had fewer years of education (Table 1). SPD subjects met criteria for additional co-morbid personality disorders including: avoidant ($N=1$), paranoid ($N=6$), borderline ($N=2$), obsessive compulsive ($N=3$), narcissistic ($N=2$), passive aggressive ($N=1$), and schizoid ($N=1$), similar to what others (McGlashan, 1986) and our laboratory previously published (Dickey et al., 2005) with the exception of a higher percentage of paranoid subjects here (46%). The mean number of DSM-IV SPD criteria met for the SPD group was 5.62 (S.D. = 0.768) out of a possible nine criteria.

Table 2
Clinical/cognitive/functional correlations

	Condition	ROI	RHO	*p*
SPD criteria of odd thinking or speech	Pitch	Right 41	0.639	<0.02
		Right 42	0.534	<0.06
CVLT	Pitch	Right 41	−0.633	<0.03
		Right 42	−0.670	<0.02
		Right STG	−0.830	0.001

Correlations between peak *t* activation values for the ROI, namely, STG, Brodmann Areas 41 and 42, with clinical criteria, and verbal learning (CVLT) are given.

3.2. Heschl's volumes

There were no group differences in left or right Heschl's gyrus gray matter volumes manually drawn on high-resolution SPGR images and corrected for intracranial contents using a regression procedure (Dickey et al., 1999) (Table 1). Indeed the effect size on the left was small, effect size = 0.18, the effect size on the right was 0.03. The lack of volume difference, however, strongly suggested that differences in functional activation were not due to a primary volume difference.

3.3. Pitch experiment

There were no areas in which comparison subjects demonstrated statistically significantly more activation than SPD subjects in neither the all tones (standard + deviant) condition nor the deviant tone condition. For the differential effect of deviance, there were three areas in which SPD subjects demonstrated more activation (two-sample *t* test) all in the region of the STG bilaterally (Fig. 2a and b).

3.4. Duration experiment

There were no areas in which comparison subjects demonstrated statistically significantly more activation than SPD subjects in neither the all tones (standard + deviant) nor the deviant tone condition. For the additive effect of hearing deviant tones only, there were areas of significantly more activation in both the temporal and parietal lobes in SPD subjects compared with controls (Fig. 2c and d).

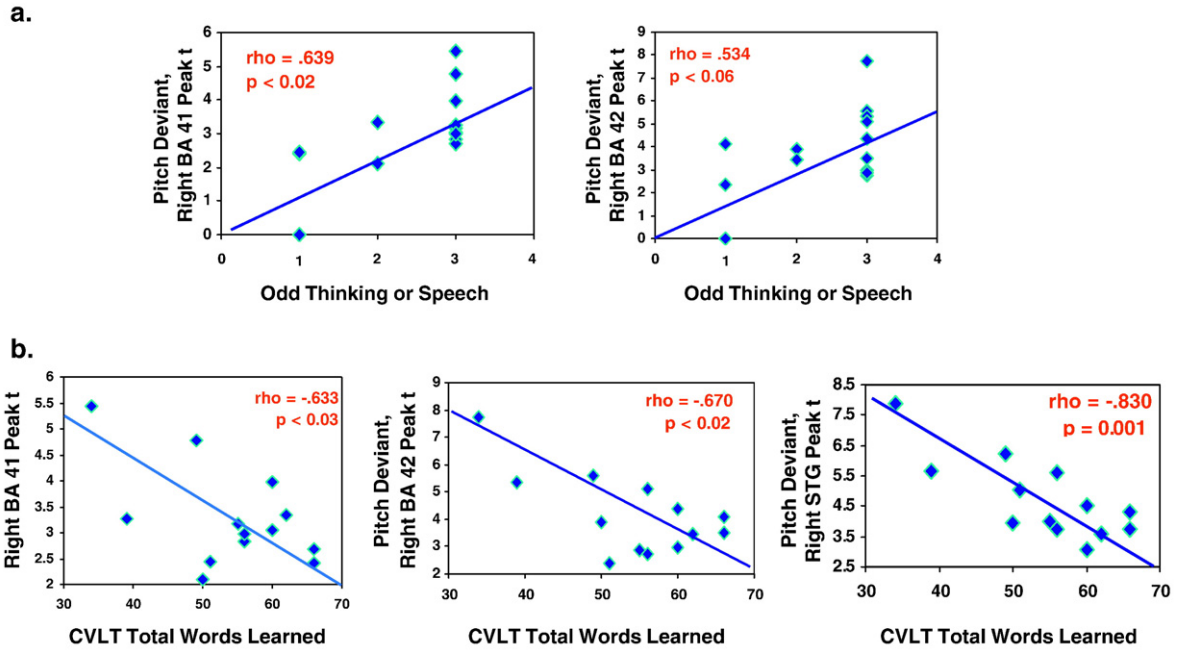


Fig. 3. Scatterplots of peak activation and clinical and cognitive measures. a. SPD subjects with greater impairment due to odd thinking or speech (higher score) demonstrated more activation while passively hearing tones in BA 41 and 42 on the right. b. SPD subjects who learned fewer words on the CVLT had greater peak activation in the right BA 41, 42, and STG. BA = Brodmann Area.

3.5. Clinical correlations with fMRI activation patterns in the duration experiment

Of note, correlations were found on the right side between the clinical symptom of odd thinking/speech in the pitch experiment (Table 2). The more abnormal the activation (*t*-score) while hearing deviant pitch tones, the more the impairment due to the clinical symptom. Verbal learning, a key abnormality in SPD, correlated with all right-sided regions such that the fewer words learned in trials 1–5, the more abnormal the activation while hearing deviant pitch tones. The number of correlations performed was high given the exploratory nature of the study and results would not have withstood a Bonferroni correction. However, they are included here to generate future hypotheses regarding the functional/anatomic relationships in SPD. As stated in the Methods section, included in Table 2 are only those correlations which were found in at least 2/3 regions/side (Fig 3).

4. Discussion

The main finding of this report is increased activation in the region of the STG bilaterally in SPD subjects compared with controls while subjects heard deviant tones regardless of whether the deviance was in the pitch or duration. In the whole-brain analysis, in no region of the brain did comparison subjects activate more than SPD subjects. These findings suggest that SPD subjects compared with controls had inefficient or hyper-responsive processing of two of the most basic aspects of auditory sensory stimuli. These data cannot unequivocally address the question as to whether the SPD subjects have inefficient processing and, thus, needed to recruit more neurons to process the tones with a resulting larger hemodynamic response, or, the reverse, that SPD subjects have an exaggerated response to subtle changes in sensory inputs with a resulting larger hemodynamic response curve. More basic research is required to differentiate those two possible interpretations. Nonetheless, these current findings cannot be attributed to small Heschl's gyrus volume as the groups did not differ on that measure.

Deficits in early auditory sensory processing, including N1, MMN, and P300, have been shown using ERP in schizophrenic subjects (Baldeweg et al., 2004; Kasai et al., 2002; Salisbury et al., 1998; Javitt et al., 2000; Javitt et al., 1995; Elvevag et al., 2004), in prodromal subjects (Brockhaus-Dumke et al., 2005), and in SPD subjects (Salisbury et al., 1996; Niznikiewicz et al., 2000; Liu et al., 2007). Moreover, progressive changes in schizophrenic subjects can be indexed using a MMN paradigm in the ERP environment (Salisbury et al.,

2007). Indeed, ERP has certain advantages in testing auditory sensory processing in that tones can be played in sound-proof laboratories with little to no extraneous noise, experimental design allows for a large number of deviants, greater than 160 in most studies (Shelley et al., 1991; Javitt et al., 1995; Umbricht et al., 1998; Michie et al., 2000; Baldeweg et al., 2004; Brockhaus-Dumke et al., 2005) (exception, Kirino and Inoue, 1999) and allows for precise time recordings on the order of milliseconds at the expense of poor spatial resolution.

In contrast, fMRI allows for more accurate anatomic localization at the expense of poor time resolution and high ambient scanner noise, although some have utilized the scanner noise as stimuli (Mathiak et al., 2002; Kircher et al., 2004). Applying a prototypic mismatch paradigm has been challenging in the fMRI environment resulting in few papers on schizophrenia (Wible et al., 2001; Kircher et al., 2004). Even using scanner noise as the stimulus causes limitations as variation in pitch cannot be tested (Mathiak et al., 2002; Kircher et al., 2004).

How one might measure the effect of tone deviants also differs between ERP and fMRI. ERP MMN studies rely on traditional subtraction of waveforms (i.e.: waveforms from standard tones subtracted from waveforms from deviant tones) (Javitt et al., 1995; Umbricht et al., 1998). Unfortunately, in fMRI aberrant activation patterns can result from subtraction. These areas of unusual activation may reflect "spontaneous neuronal activity", that is, areas not predicted by task demands, which cannot be experimentally controlled (Binder et al., 1999). A mismatch task is not cognitively demanding, in fact it is arguably pre-attentive (Naatanen 1990), possibly allowing for more "task-unrelated thoughts" (Binder et al., 1999). These "task-unrelated thoughts" can result in changes in blood flow detected by BOLD method (Binder et al., 1999). In fact, the hemodynamic effect of such thoughts using the subtraction method has been demonstrated in a tone task (Binder et al., 1999). Moreover, depending on the statistical approach, subtraction or other, results can differ markedly (Friston et al., 1996). The subtraction method assumes "pure insertion", that the cognitive process is "irrespective of the cognitive or physiological context" (Friston et al., 1996), an assumption which may not be valid. Indeed, the two fMRI papers in schizophrenia compared groups on standard and deviant tones separately, thus avoiding the difficulties of the subtraction method in an fMRI environment (Wible et al., 2001; Kircher et al., 2004).

In the current fMRI study the effect of deviants was measured using a parametric analysis. Specifically, the differential processing of deviant tones against the background of hearing all tones was measured (i.e.: the first parameter is the effect of hearing all tones, both standard and deviant; and the second parameter is the effect of hearing deviant tones only) (Fig. 1e). This has the benefit of making no assumption of "pure insertion" (Friston et al., 1996) and isolates the effect of hearing deviant tones "on top of" hearing all tones. In addition, this method may possibly minimize the hemodynamic effect of "task-unrelated thoughts" (Binder et al., 1999).

Another aspect of this study which differed from the MMN ERP literature was the use of disparate frequencies and durations between the standard and deviant tones. Stimuli used across studies have varied with differences between standard and deviant pitches as small as 24 Hz (1000–1024 Hz) (Javitt et al., 1995) to as large as 1000 Hz (1000–2000 Hz) (Kirino and Inoue, 1999) and differences in duration as small as 25 ms (25–50 ms) (Baldeweg et al., 2004). Nonetheless, the presence of the MMN-like deflection in both conditions suggests that these experimental parameters engage the early auditory sensory processing stream. Indeed, stimulus presentation features including probability and degree of separation of the deviants, and interstimulus interval, are all important variants which may affect the results (Michie et al., 2000). However, as SPD has demonstrated less severe abnormalities than schizophrenia on electrophysiological measures (Trestman et al., 1996), more extreme differences in terms of pitch and duration between the standard and deviant tones were selected to amplify the fMRI signal. Moreover, a larger differentiation between standard and deviant tones would help to compensate for any potential deficit in tone discrimination processing described in the schizophrenia literature (Javitt et al., 2000; Leitman et al., 2005). Although a lower percentage of deviant tones would have similarly increased an electrophysiological signal (Javitt et al., 2000), in order to achieve enough trials for an adequate hemodynamic response, a higher percentage of deviant tones was selected.

Although the paradigm used in this study is not standard mismatch, evidence from the MMN literature may inform the current findings. For example, generators for the MMN are thought to be from the auditory cortex (Kropotov et al., 1995) with physical separation of foci for processing of pitch and duration (Molholm et al., 2005), similar to the current findings. Some workers have also noted activation from frontal generators thought to reflect a shift of attention toward the deviant, although recent work suggests that the role of the frontal generator may not depend on attention requirements (Shalgi and Deouell, 2007). Indeed, a recent review by Naatanen et al. (2007) suggests that

frontal activity may be due to the sum of supratemporal generators (Naatanen et al., 2007). Our report did not find evidence of fMRI activation in either group in the frontal lobe, possibly due to the use of largely disparate standard and deviant tone features (Shalgi and Deouell, 2007). The activation of the parietal lobe in the duration experiment is consistent with the hypothesis that the parietal lobe is important for time perception (Harrington et al., 1998) and change-detection (Molholm et al., 2005). Indeed, bilateral activation has been demonstrated with deviants in duration (Molholm et al., 2005). Finally, abnormalities in MMN have been documented in clinically diagnosed patients with SPD (Liu et al., 2007).

In this report, in contrast to our previous report (Dickey et al., 2002a,b), we did not show any difference in Heschl's gray matter volume. We would argue, however, that, in general, in the peri-Heschl's/ STG region, SPD subjects likely have smaller volumes (Dickey et al., 2002a,b, 2003, 1999; Downhill et al., 2001 {Koo, 2006 #3366}). There are several differences between our two reports on Heschl's gyrus ((Dickey et al., 2002a,b) and current) and that volumes measured depend on many factors including subject demographics, co-morbidity, subject *N*, image viewing tools which can affect landmark detection, and inter-subject and inter-hemispheric variability of Heschl's morphology, particularly in schizophrenia spectrum disorders. First, in the earlier report there was a significant difference between IQ and personal socio-economic status between groups suggesting that cohort may have represented a more impaired group of SPD subjects. Second, and delving deeper into the issue of subject characteristics, the percentage of subjects meeting DSM-IV criteria for other Axis II disorders differs between samples. In the prior report there were more borderline personality disorder subjects (31% vs. 15% in current sample) and fewer who met criteria for paranoid personality disorder (37.5% vs. 46% in current report). Little is known about brain morphology of the STG region in paranoid and borderline personality disorders (no papers found per PubMed search performed 4/17/08). Whether the presence of co-morbid personality disorders has an effect on Heschl's measurement cannot be addressed. Third, in this current sample, the subject *N* is smaller, leading to possibly less stable data. Fourth, the current study used Slicer as the image processing software tool, a more sophisticated tool than previously available (www.slicer.org) as this tool now allows for simultaneous 3D viewing. As noted under the Methods section above, the delineation of Heschl's previously may have included more peri-Heschl's area posteriorly thus leading to the differences between groups in that report (Dickey et al., 2002a,b). In the current report the more posterior transverse gyri may not have been included. Fifth, there is marked inter-subject and even inter-hemispheric variability of the STG, particularly, Heschl's gyrus (Lange et al., 1997; Leonard et al., 1998; Sweet et al., 2005; Knaus et al., 2006). To clarify, it is quite common for there to be two parallel transverse or Heschl's gyri (Knaus et al., 2006; Sweet et al., 2005). However, these parallel transverse gyri can be completely separate or partially separate. If they are partially separate they can be merged medially, part way down the gyrus, or laterally. What should one consider as Heschl's gyrus is not clear. Should one include both, part of both, or only the more anterior one? Both the prior report and this paper used Steinmetz's criteria (Steinmetz et al., 1986) as the posterior boundary. This arbitrary criteria state that if the gyri are merged medially with a common stem, then one can include both. If they are merged part way down the gyrus or laterally, then they should be divided into two separate gyri and only include the more anterior gyri as Heschl's. Note that this criteria is helpful, but arbitrary. Subtle differences in visualization abilities or in morphometry can result in significant volume differences which may not be meaningful functionally. Indeed, the functional anatomy of AI (primary auditory cortex) may not be restricted to medial Heschl's gyrus, regardless of its definition or criteria (Sweet et al., 2005). Indeed, recent work suggests that there may be two primary auditory receptive fields in the human auditory system, one more medial, one more lateral (Engelien et al., 2002). Close inspection of the receptive field maps (Engelien et al., 2002) suggests that the more lateral field may be partially located on what may be considered by Steinmetz's criteria to be the second transverse gyrus, an area more likely captured in our first report but less likely captured in this current report. That functionally important area (Sweet et al., 2005) may represent the difference in these two reports. Indeed, other workers suggest that volume asymmetries in the region of the primary auditory cortex do not correspond to functional activation while hearing tones and word pairs (Yoo et al., 2005), possibly due to the poor matching of gyral sulcal patterns and cytoarchitechtonically defined acoustic regions (Morosan et al., 2001), and marked variation in the morphology of Heschl's gyrus (Leonard et al., 1998) (Sweet et al., 2005). Furthermore, regional differences in STG volumes are more marked in schizophrenia than in controls (Park et al., 2004). In sum, the lack of replication of our previous report is likely due to a combination of factors: differences in subject demographics, presence of co-morbid disorders,

subject *N*, difference in measurement tools, and inter-subject morphometric variability of Heschl's gyrus particularly in the schizophrenia spectrum.

Despite these limitations to direct comparison between the two samples, the lack of difference between groups in Heschl's volume in this study is informative: one cannot attribute differences in activation in the current report to subtle volume differences of Heschl's gyrus per se. There may be subtle differences in volumes in the adjacent cortical regions, perhaps in areas 41 and 42 or the larger STG not measured by the current report. However, even if there were smaller volumes in the adjacent cortex in SPD subjects, one would not have predicted that smaller volumes lead to larger areas of activation, more likely, smaller volumes would predict smaller areas of activation. Therefore, we do not believe that possible volume differences in peri-Heschl's regions can account for the between group differences in activation patterns.

The possible relationship between abnormal auditory sensory processing and clinical measures was also investigated. Exploratory correlations between ROI and clinical/cognitive symptoms suggest that these early auditory sensory processing problems may have implications for downstream language functioning. Specifically, in SPD subjects, there was a correlation between abnormal activation on the right during the pitch experiment with odd speech. Odd speech and formal thought disorder likely represent a symptom continuum. Our laboratory previously demonstrated thought disorder correlating with left STG volumes in female SPD subjects (Dickey et al., 2003). Similarly, in schizophrenic subjects, correlations have been shown between thought disorder and hallucinations with bilateral measures of volume and function of temporal lobe regions (Shenton et al., 1992; Dierks et al., 1999; Kircher et al., 2001; Barta et al., 1990; Woodruff et al., 1997). In this report, however, the correlation with odd speech occurred with right-sided activation. Odd speech in SPD may be characterized by impoverished prosody (Dickey et al., unpublished data). Consensus suggests a right hemisphere advantage for emotional (non-semantic) aspects of language and prosody (Mitchell and Crow, 2005), particularly in the right STS and MTG, whereas more semantic aspects of language recruit more left-sided regions (Mitchell et al., 2003). This hemispheric pattern has been seen using fMRI (Mitchell et al., 2003) (Wildgruber et al., 2005), transcranial Doppler ultrasonography (Vingerhoets et al., 2003), repetitive transcranial magnetic stimulation (van Rijin et al., 2005), event-related potential (Eckstein and Friederici, 2005), and in lesion studies (Pell, 2006). Therefore, it is possible, that the tone processing impairment on the right in the SPD subjects is related to non-semantic aspects of their odd speech.

Other aspects of language, specifically verbal learning, also correlated with inappropriate activation of right-sided ROI for the current pitch experiment. Again, this is similar to findings in schizophrenia. Using PET, Ragland et al. demonstrated impaired verbal learning correlating with STG activation abnormalities (Ragland et al., 2001).

There are several limitations to the current study. One limitation is the large number of correlations performed as discussed in the Methods section. However, including these exploratory findings in this paper may serve to generate future hypotheses about the relationship between auditory processing and clinical features in this understudied schizophrenia spectrum disorder. Second, only male subjects were included in this study. Future work will need to include females to test whether there is a gender effect (Dickey et al., 2003; Knaus et al., 2006). This is particularly critical as our laboratory recently completed a pitch MMN investigation in a group of male and female SPD individuals and the results suggest that there is no impairment of early sensory processing as indexed by MMN in males. Instead, the significant pitch MMN reduction was found in females (Niznikiewicz et al., in submission). Third, the whole sample size is small relative to fMRI studies in schizophrenia. This reflects the inherent difficulty in recruiting SPD subjects who are not part of a clinical population for a research study. Had we had access to a larger group of SPD subjects then the findings could be more generalized to all SPD subjects. Nonetheless, these data suggest that for at least a sub-population of SPD subjects, there may be deficits in early sensory processing of tones. Fourth, there was a difference between groups in terms of education. However, we are not aware of any paper suggesting that education plays a role in simple tone processing per se. Fifth, shifting gradients in the MRI scanner are loud and theoretically may have caused more sensory interference for SPD subjects than for control subjects. Although all subjects used earphones, one cannot rule out systematic affect of scanner noise. We note that a silent event-related design, in which the scanner would not scan during stimuli presentation, would more fully remove the confound of interference from scanner noise. Unfortunately, such a design would also significantly increase the scanning time (a mean of 14 s between stimuli as proposed by Amaro et al., 2002). In addition, one cannot modulate scanner frequency or pitch, thus limiting the exploration of differential pitch discrimination in SPD subjects. Sixth, there is no behavioral output measure during the experiments. This limits the ability to determine what the subject is doing while hearing the tones and, therefore, limits the ability to draw firm interpretations of the results.

That is, one cannot definitively conclude that the SPD subjects exhibit inefficient processing vs. exaggerated responses to deviant tones. However, one can state that it appears that SPD subjects recruit more neurons while hearing simple tones than comparison subjects. Having a behavioral response, however, would have added a layer of complexity by introducing other potential confounds such as SPD subjects' ability to make decisions, processing speed, and motor speed. Finally, one limitation common to the fMRI literature is that data were collected for each subject on only one time point. Recent work has shown marked intersession variability for the extent of activation emanating from listening to tones or word pairs (Yoo et al., 2005).

Nonetheless, these data suggest that neuroleptic-naïve SPD subjects, compared with matched comparison subjects, demonstrate inefficient or hyper-responsive early processing of pure tones. This atypical processing may be correlated with some of the core features of SPD, namely, odd speech and impairment in verbal learning.

Role of funding source

This study was funded by awards to CCD (VA Advanced Career Development Award and Brigham & Women's Hospital Translational Neuroscience Award), and to RWM (NIMH RO1 MH52807). The VA, BWH, and NIMH had no involvement in the study design, data collection or interpretation, nor in the writing or submitting of the report.

Contributors

Dickey: designed the study, collected the fMRI data, analyzed the clinical and fMRI data, and wrote the manuscript.

Morocz: analyzed the fMRI data.

Niznikiewicz: collected and analyzed the ERP data, and contributed to the manuscript.

Voglmaier: collected and analyzed CVLT data, and performed SCID interview.

Dreusicke: analyzed the fMRI data.

Toner: aided in fMRI data collection.

Yoo: aided in initial fMRI data collection.

Khan: aided in final fMRI data presentation.

Shenton: reviewed the manuscript.

McCarley: reviewed the manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

Acknowledgements

We thank Dr. Dean Salisbury for his careful review of this manuscript. We thank Marie Fairbanks, Nancy Maxwell, and Lori Benjamin for their administrative support.

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