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## Factors in Sensory Processing of Prosody in Schizotypal Personality Disorder: An fMRI Experiment

Chandlee C. Dickey, M.D.<sup>a,b,c,\*</sup>, Istvan A. Morocz, M.D.<sup>d</sup>, Daniel Minney, B.A.<sup>c</sup>, Margaret A. Niznikiewicz, Ph.D.<sup>b,c</sup>, Martina M. Voglmaier, PhD<sup>b,e</sup>, Lawrence P. Panych, Ph.D.<sup>d</sup>, Usman Khan, B.S.<sup>c</sup>, Rayna Zacks, B.A.<sup>b</sup>, Douglas P. Terry, B.S.<sup>c</sup>, Martha E. Shenton, Ph.D.<sup>b,c</sup>, and Robert W. McCarley, M.D.<sup>b</sup>

<sup>a</sup>Serious Mental Illness Program, VA Boston Healthcare System, Psychiatry 116A-7, 940 Belmont St., Brockton, MA 02301

<sup>b</sup>Laboratory of Neuroscience, VA Boston Healthcare System, 940 Belmont St., Brockton, MA 02301

<sup>c</sup>Psychiatry Neuroimaging Laboratory, Brigham & Women's Hospital, 1249 Boylston St, Boston, MA 02215

<sup>d</sup>Medical Physics Group, Department of Radiology, Brigham & Women's Hospital, 75 Francis St., Boston, MA 02215

<sup>e</sup>Cambridge Health Alliance, 1493 Cambridge St., Cambridge, MA 02139

### Abstract

**Introduction**—Persons diagnosed with schizophrenia demonstrate deficits in prosody recognition. To examine prosody along the schizophrenia spectrum, antipsychotic-naïve

\* **Corresponding Author:** Chandlee Dickey, M.D., Medical Director, Serious Mental Illness Program, VA Boston Healthcare System, Psychiatry 116A-7, 940 Belmont St., Brockton, MA 02301, chandlee\_dickey@hms.harvard.edu, Cell: (857) 225-0093, Fax: (857) 364-4408

All at Harvard Medical School

Morocz: pisti@bwh.harvard.edu

Minney: daniel.minney@gmail.com

Niznikiewicz: Margaret\_niznikiewicz@hms.harvard.edu

Voglmaier: Martina\_voglmaier@hms.harvard.edu

Panych: panych@bwh.harvard.edu

Khan: usman@bwh.harvard.edu

Terry: dougt@bwh.harvard.edu

Zacks: Rayna\_zacks@hms.harvard.edu

Shenton: Shenton@bwh.harvard.edu

McCarley: Robert\_mccarley@hms.harvard.edu

**Contributors**

Dickey: designed the study, wrote the protocol, performed statistical analyses, wrote the manuscript

Morocz: aided in the fMRI analyses

Minney: drew the STS on structural images

Niznikiewicz: contributed to the manuscript

Voglmaier: interviewed all subjects, performed neuropsychological tests

Panych: reviewed the manuscript

Khan: processed fMRI images, aided in fMRI data collection

Terry: aided in graph and image production

Zacks: recruited subjects, aided in data preparation

Shenton: contributed to manuscript

McCarley: contributed to manuscript

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schizotypal personality disorder (SPD) subjects and healthy control subjects were compared. It was hypothesized that SPD subjects would perform more poorly; with cognitive and demographic factors contributing to the poor performance. The superior temporal gyrus (STG) was selected as the region-of-interest (ROI) given its known abnormalities in SPD and its important role in the processing of prosody.

**Methods**—SPD and healthy comparison (HC) subjects were matched on age, IQ, and parental social-economic status (PSES). Cognitive measures included the Speech Sound Perception Test (SSPT) to examine phonological processing (SPD = 68, HC = 74) and the Verbal Fluency task to examine executive functioning (SPD = 129, HC = 138). The main experiment was a novel fMRI task of prosody identification using semantically neutral sentences spoken with emotional prosody (SPD = 16, HC = 13). Finally, volumetric measurement of the superior temporal sulcus (STS), a key region for processing prosody, and partially overlapping with the STG, was performed (SPD = 30, HC = 30).

**Results**—Phonological processing and executive functioning were both impaired in SPD subjects compared with HC subjects. Contrary to the prediction, SPD subjects, as a group, were similar to HC subjects in terms of correctly identifying the emotion conveyed and reaction time. Within the SPD group, prosody identification accuracy was influenced by executive functioning, IQ and perhaps PSES, relationships not found with HC subjects. Phonological perception aided prosody identification in both diagnostic groups. As expected, both groups activated the STG while performing the prosody identification task. However, SPD subjects may have been less “efficient” in their recruitment of STG neurons. Finally, SPD subjects demonstrated a trend toward smaller STS volumes on the left, particularly the lower bank.

**Conclusions**—These data suggest that subtle differences between SPD and controls in phonological processing, executive functioning, IQ, and possibly PSES, contributed to difficulty in processing prosody for some SPD subjects.

## Keywords

schizotypal personality disorder; schizophrenia; prosody; social cognition; superior temporal gyrus; fMRI; attention; superior temporal sulcus

## 1.0 INTRODUCTION

SPD subjects exhibit many of the features of schizophrenia, including unusual perceptual experiences, odd speech, odd behavior and few friends (1994,Dickey et al. 2005). SPD subjects are also impaired occupationally and socially, as well as having many of the cognitive deficits seen in schizophrenia (Dickey et al. 2005) (Voglmaier et al. 2000,Voglmaier et al. 1997) (Trestman et al. 1995). Indeed, as with schizophrenic patients, “affective impoverishment” in SPD was noted early in SPD (Meehl 1962). In addition, SPD and schizophrenic subjects share many endophenotypic markers in anatomical, functional, electrophysiological, and neuropsychological domains (Siever et al. 2002,Siever 1985,Siever et al. 1993,Siever et al. 1984,Siever and Davis 2004,Downhill et al. 2001,Nakamura et al. 2005,Niznikiewicz et al. 2002,Niznikiewicz et al. 1999b,Niznikiewicz et al. 2000,Shenton et al. 2001,Voglmaier et al. 2000,Voglmaier et al. 2005,Buchsbaum et al. 1997a,Buchsbaum et al. 2002,Buchsbaum et al. 1997b,Byne et al. 2001,Downhill et al. 2000a,Downhill et al. 2000b,Gunderson and Siever 1985,Haznedar et al. 2004,Keefe et al. 1997,Kirrane and Siever 2000,Koenigsberg et al. 2003,Mitropoulou et al. 2002,Roitman et al. 1997,Siever 1994,Siever et al. 1991,Trestman et al. 1995,Cadenhead et al. 2000,Cadenhead et al. 1999,Cadenhead, Geyer and Braff 1993). The schizophrenia continuum or the schizophrenia spectrum is further supported by epidemiologic data linking schizophrenia and SPD in families (Kendler et al. 1993,Kety 1983). The importance of

studying SPD is thus three-fold: (1) SPD is a common disorder with a prevalence of 3.9% (Pulay et al. 2009); (2) it is intrinsically interesting to explore aspects of disease along a spectrum; and finally, (3) to the extent that SPD and schizophrenia symptomatology lie along a spectrum, it can be studied without the confounding effects of antipsychotic medication known to affect neuroanatomy, cognition and aspects of social cognition such as prosody (Keshavan et al. 1998, Bartzokis et al. 1998).

One area of impairment exhibited in the schizophrenia spectrum is social cognition. Social cognition comprises the complex and interwoven cognitive and emotional functions that serve to guide an individual in his/her social environment. It includes the perception of a socially meaningful stimulus such as prosody, encoding the stimulus, comparing the stimulus with memories of similar stimuli, evaluating its salience, incorporating one's visceral responses to the stimulus, interpreting the intentions of the source of the stimulus, predicting future stimuli, and then selecting, planning, and executing an appropriate response (Lieberman and Rosenthal 2001, Baum and Nowicki 1998, Frith 2007, Gallese 2007, Bellack et al. 1994, Niedenthal 2007, Green and Leitman 2008, Ochsner 2008, Olsson and Ochsner 2008). Fine-tuned orchestration of these functions is central to social interaction. Indeed, "the ability to interact effectively in social environments is essential to success in everyday life" (Lieberman and Rosenthal 2001), is highly heritable (Constantino and Todd 2000) and affects longevity (Avlund, Damsgaard and Holstein 1998). Unfortunately, many individuals with schizophrenia and SPD evince deficits in social cognition.

This report focused on one aspect of social cognition, the interpretation of prosody, to explore whether the deficits seen in schizophrenia extended across the spectrum into SPD subjects. Although the definition of prosody differs in the literature, there is consensus that it refers to paralinguistic aspects of utterances and includes pitch, pitch variability, intensity, stress, and duration. Linguistic prosody such as word stress or intonation signals a question or a statement, which helps to convey nuances of meaning while affective prosody helps to convey attitudes regarding the meaning. Correctly interpreting prosody is so vital to successful social interactions (Baum and Nowicki 1998) (Frazier, Carlson and Clifton 2006) that it has a prominent role in development, with six month old infants learning to distinguish stress syllables, one aspect of prosody, in order to understand new words (Johnson and Seidl 2009). The current study focuses on affective or emotional prosody processing.

Findings regarding the neuroanatomy underlying prosody processing have differed. Major areas include the superior temporal gyrus (STG), superior temporal sulcus (STS), middle temporal gyrus (MTG), frontal, and parietal lobe cortices (Mitchell et al. 2003, van Rijn et al. 2005, Hesling et al. 2005, Beaucois et al. 2006, Buchanan et al. 2000, Wildgruber et al. 2005) (Wildgruber et al. 2006). It is also thought that there is a right hemisphere advantage for emotional (non-semantic) aspects of prosody (Ross and Monnot 2008) (Mitchell and Crow 2005), particularly in the right STG, STS, and MTG, whereas more semantic aspects of language recruit more left-sided regions (Mitchell et al. 2003, van Rijn et al. 2005) (Eckstein and Friederici 2005). More refined anatomic specialization is associated with many factors including the type of emotion heard, gender, pitch variation, and attentional demand (Buchanan et al. 2000) (Bozikas et al. 2006, Schirmer et al. 2004) (Hesling et al. 2005, Sander et al. 2005).

Patients diagnosed with schizophrenia have been shown to have deficits in processing of prosody across a range of experimental paradigms (Hooker and Park 2002, Mitchell and Crow 2005, Huang et al. 2009, Bach et al. 2009a, Bach et al. 2008) (Bach et al. 2009b) with a large effect size by meta-analysis (Cohen's  $d = -1.24$ ) (Hoekert et al. 2007). Leitman et al.

linked poor affective prosody discrimination in schizophrenic subjects to deficits in basic auditory sensory processing such as tone matching. Leitman proposed a failure of bottom-up processing, suggesting that deficits in elemental aspects of auditory processing compounded each other and culminated in prosody detection deficits (Leitman et al. 2005). Other deficits exhibited by schizophrenic patients in auditory processing germane to vocal affect processing include an overestimation of the intensity of rising tones (looming) (Bach et al. 2009b), problems with high-clarity stimuli (Bach et al. 2009a), and possible alteration of the right-hemisphere preference for processing prosody (Mitchell et al. 2004) (Bach et al. 2009c). Vocal affect recognition capabilities have also been observed to correlate with occupational success in patients with schizophrenia (Hooker and Park 2002).

Medications used to treat schizophrenia have been shown to affect prosody processing. Schizophrenic patients who received risperidone had greater prosody identification improvement over time compared with patients prescribed haloperidol, suggesting that not only can medications have an effect, but the effect was medication-specific (Bartzokis et al. 1998). Higher chlorpromazine equivalents also correlate with a larger extent of fMRI signal while subjects listened to emotional sentences (Mitchell et al. 2003). Lastly, there is evidence that medications affect the volume of the STG, the main ROI of this study (Keshavan et al. 1998).

Prosody processing has not been explored in antipsychotic-naïve SPD subjects. Basic auditory processing, pitch processing, morphometry and functional anatomy of the STG, however, have been explored in SPD (Salisbury et al. 1996) (Dickey, McCarley and Shenton 2002a). For example, the auditory P300 points to a deficit in auditory attention in SPD subjects (Kutcher et al. 1989) (Mannan et al. 2001, Niznikiewicz et al. 2000, Salisbury et al. 1996). Moreover, studies have found that higher order language processing, including processing sentence congruity in the auditory domain, is abnormal in SPD (Niznikiewicz et al. 1999a, Niznikiewicz et al. 2002). In these studies, SPD subjects were found to have deficits in using context effectively. It has been suggested (Niznikiewicz et al. 1999a) that the auditory processing deficits in SPD may be related putatively to smaller volumes in brain regions that process auditory signals. For example, several studies show smaller STG gray matter volumes including smaller Heschl's gyrus volumes in SPD (Dickey et al. 2000, Dickey et al. 2003, Dickey et al. 1999, Downhill et al. 2001). Finally, even in the setting of normal Heschl's gyrus volumes, SPD subjects demonstrate aberrant hemodynamic response while passively listening to tones differing in pitch and duration (Dickey et al. 2008). The current experimental work seeks to build on this small body of literature.

Specifically, in this report, the STG will be explored in SPD and healthy comparison subjects as they identify prosodic voice in semantically neutral sentences. The main *a priori* hypotheses are that: (1) SPD subjects will have more difficulty correctly identifying vocal affect than will comparison subjects; consistent with the spectrum concept, some SPD subjects will have more difficulties than others; (2) elements of auditory processing such as phonemic processing, will be related to performance on prosody processing; (3) the STG will play a role in the processing of affect; and (4) the comparison subjects will be more "efficient" in their recruitment of STG cortical resources than the SPD subjects. There are, however, no emotion-specific hypotheses. Instead, the goal was to explore general vocal affect processing in antipsychotic-naïve SPD subjects. To accomplish this goal SPD and HC subjects were recruited from the community and compared using behavioral, cognitive, anatomical and fMRI measures.

## 2.0 METHODS

### 2.1 Subject Recruitment

All subjects signed informed written consent forms for participation consistent with local IRB requirements. Subjects were recruited from the community and not from clinical treatment facilities (Dickey et al. 2005). Advertisements were placed in newspapers and on public transit. SPD specific advertisements targeted subjects with few friends and social anxiety. If subjects expressed interest, they participated in a telephone screen to review inclusion criteria. Inclusion criteria assessed at time of in-person interviews included (1) right-handed; (2) age 18-55; (3) native English speaker; (4) no personal history of psychosis or bipolar disorder; (5) antipsychotic-naïve; (6) no current use of psychotropic medications; (7) no medication or medical condition thought to affect brain functioning; (8) no neurological condition, and (9) no history of ECT. HC subjects had the additional criteria of no personal history of Axis I or II disorder and no family history of Axis I disorder. All subjects participated in SCID and SCID II interviews. SPD subjects were defined as those who met at least five out of the nine DSM-IV diagnostic criteria for SPD. Subjects were one-to-one matched on age and group-matched on IQ, gender, and parental socio-economic status (PSES).

### 2.2 Cognitive Measures

IQ was estimated based on the Vocabulary subscale of the WAIS (Wechsler 1997). To measure executive functioning, the Verbal Fluency Task (Benton, Hamsher and Sivan 1983) was used with the letter “c” for phonemic and “animals” for categorical word generation. Verbal fluency abnormalities are among the most common documented cognitive deficits in schizophrenia with a pooled effect size of 1.98 across over seventy studies in a meta-analysis (Johnson-Selfridge and Zalewski 2001). To assess subjects’ ability to distinguish phonological sounds, subjects underwent the Speech Sound Perceptions Task (SSPT) (Reitan). In this task, subjects listen to a recording of a nonsense word and have to match the nonsense word from four phonologically-related written nonsense words. For example, subjects heard “zeeks,” and selected “zeeks” from among “theeks zeeks theets zeets.”

### 2.3 Sentence Stimuli for the fMRI Prosody Identification Task

Fifteen reviewers carefully evaluated 67 sentences for possible inclusion in this study. Criterion for study inclusion was that no reviewer thought that a sentence could be construed as semantically emotional. The resulting 50 sentences were determined to be semantically neutral per all 15 reviewers. Examples of the semantically neutral sentences include, “She picked up her shoes” and “The flower is yellow.” The sentences were recorded by a male and a female native English speaker to control for potential gender effects. Prior to scanning, subjects familiarized themselves with all sentences by reading them silently. Subjects practiced identifying each of the emotions outside of the scanner with the same sentences and the same female speaker until they were able to identify each emotion without error. The male speaker was not available at time of scanning.

There were 50 sentences, each repeated four times, one time per emotional condition. The four emotional conditions were: happy, sad, sarcastic, and neutral. Therefore, there were 200 total sentences or stimuli heard by the subjects, 100 sentences in each of two separate runs. The order of the sentences within a run was counterbalanced across emotions to control for practice effects. The sentences were between 4-7 words in length and approximately 2 sec in duration (Fig 1). Sentences were recorded using a sound editor (Boersma and Weenink 2005). Stimulus onset asynchrony (SOA) was randomized between 4.5 and 5.5 sec with a mean of 5.0 seconds in order to avoid anticipation effects.



## 2.4 Stimulus Presentation

In order to reduce the potential confound of sensory processing of scanner noise (Amaro et al. 2002), particularly for SPD subjects, subjects inserted ear plugs and used sound-insulating earphones (Silent Scan, Avotec, Jensen Beach, FL, avotec.org). Recordings were played at approximately 80 db (individually determined for maximum comfort and ease of hearing) using locally derived software (Howe et al. 2009).

## 2.5 Behavioral Response

Subjects were asked to indicate the emotion heard (happy, sad, sarcastic, or neutral) using a response pad corresponding to a visually presented smiley face cartoon of the emotion to minimize working memory demands. Responses were collected via a fiber optic button box (Current Designs, Philadelphia, PA). The dependent measures, reaction time and number of correct responses, were compared using an ANOVA. Note that the “neutral” response button malfunctioned for one SPD and one HC subject so that neutral and total correct data were not available for those two subjects.

## 2.6 Image Acquisition

fMRI data were collected with a GE 3.0 Tesla Signa System (GE Medical Systems, Milwaukee, WI). Functional images were acquired using a gradient-recalled BOLD sensitized EPI pulse sequence (parameters: 35 slices oriented parallel to AC-PC plane, 5 mm thick, Flip angle=90 degrees, TE=40msec, TR=2 sec, FOV 22 cm, matrix size= 64 × 64, 285 acquisitions). T1-weighted SPGR low-resolution anatomical images were acquired using the same slice orientation/thickness purposes. Total scan time was 23 minutes.

## 2.7 Image Preprocessing

EPI raw data were reconstructed, realigned, motion corrected, normalized, and smoothed converted to analyze format (.img files in analyze format) and smoothed with an 8 mm FWHM Gaussian filter. SPM5 was used throughout (www.fil.ion.ucl.ac.uk/spm/software/spm5/).

## 2.8 fMRI Statistical Analysis

The beginning of each sentence was used for the onset time vector in an event-related analysis (Fig 1). First-level analysis involved grouping the hemodynamic responses in contrast files for each emotional condition per subject. Family-wise error correction was applied on the first-level analysis. The main analytic approach focused on the STG as the region of interest (ROI). The STG was hypothesized *a priori* to be critically involved in the processing of prosody as well as an area of vulnerability among SPD subjects (Dickey et al. 2000, Dickey et al. 2003, Dickey et al. 1999, Downhill et al. 2001, Dickey et al. 2008). To examine activation patterns in this region, at the second level, the left and right STG were masked using the SPM plug-in PickAtlas ([http://www.fmri.wfubmc.edu/downloads/WFU\\_PickAtlas\\_User\\_Manual.pdf](http://www.fmri.wfubmc.edu/downloads/WFU_PickAtlas_User_Manual.pdf)). To control for multiple comparisons, the alpha level for accepting statistical significance was lowered by dividing 0.05 by the number of resels (resolution elements) within the left (12.7) and right (12.8) STG. As a result, clusters of activation reaching the lowered alpha level of 0.003 were considered statistically significant. Extent and magnitude of activation for those clusters surpassing the reset alpha level of 0.003 within the left and right STG on a per subject basis were used in Pearson correlation procedures with cognitive and demographic measures. These measures were IQ, Verbal Fluency, SSPT, and PSES. Emotion-specific activation maps were created for the purpose of future hypothesis generation only.

As this was the first experiment to explore prosody using fMRI in a population of SPD subjects, an exploratory and secondary whole brain analysis was performed. The purpose of this exploratory analysis was to provide guidance for hypothesis development in future studies. This analysis was a random effects analysis, with the threshold set at 0.001. This exploratory analysis, therefore, did not correct for multiple comparisons, thus, results need to be interpreted with caution.

## 2.9 Structural Imaging of STS

The STS is the sulcus which links the STG and MTG. The STG has been shown to be abnormal in SPD (Dickey et al. 2003) (Dickey et al. 2002b) (Dickey et al. 2003) (Downhill et al. 2001), and it is the most common region studied morphometrically in SPD. The upper bank of the STS overlaps with the inferior aspect of the STG. The STS itself has not been specifically explored in SPD. It was selected for examination in this study as it has been shown to be involved in processing of prosody (Wildgruber et al. 2006, Wildgruber et al. 2005) and thus is potentially germane for the interpretation of the fMRI results.

To examine this region high-resolution SPGR images 1.5 mm thick were acquired on a 1.5T GE magnet. The STS was manually delineated on these images using the image analysis tool, 3-D Slicer 2.6 ([www.slicer.org](http://www.slicer.org)). The anterior and posterior boundaries of the STS were the coronal slices containing the mamillary bodies and the temporoccipital notch, respectively. The superior and inferior boundaries were defined by the lateral extent of gray matter rim seen on coronal images. Note that the STS in this report extends more posteriorly than our laboratory's usual posterior boundary (Dickey et al. 1999), the complete crux of the fornix, because the literature suggests that prosody can be processed more posteriorly in the STS (Kriegstein and Giraud 2004) (Fig 2a). Upper and lower banks of the STS were separated by drawing a line from the cortical edge to the white matter at the most medial aspect of the sulcus.

Four measures of volume, left hemispheric upper and lower banks and right hemispheric upper and lower banks, were determined. Volumes were corrected for total intracranial contents with a linear regression procedure with unstandardized residuals used in a subsequent ANOVA. For this analysis, structural images were randomly selected from a cohort of subjects (SPD = 30, NC = 30), of which SPD = 10 and NC = 7 overlap with the fMRI study. Note that the gyral sulcal pattern varies among individuals so that warping to a common template such as in VBM may not faithfully represent individual anatomic variation (Park et al. 2004). Thus we choose the approach of manual drawing.

## 2.10 Correlations

The behavioral measure of total number correct on the fMRI task was correlated with IQ, verbal fluency, SSPT, and PSES scores, in order to explore contributory factors to vocal affect processing. To assess the "efficiency" of brain activation, that is, the tightness of the coupling between activation and performance, correlations were performed between the extent and magnitude of activation per ROI and number of emotions correctly identified. All were Pearson correlations with an alpha level set at  $p < 0.05$  and not Bonferroni corrected. Therefore, all correlations must be considered exploratory and require replication.

## 2.11 Note on Subject N

Subject N differed across tasks due to the duration of task implementation in the laboratory. Cognitive measures and structural MRI have been longstanding in the laboratory whereas the fMRI task was given to subjects who were currently involved with the laboratory. As the laboratory was not linked to a treatment program, subjects, in general, did not remain as



connected to the laboratory as they might have had there been a treatment component. Therefore, subject N differed among experiments.

### 3.0 RESULTS

#### 3.1 Subject Demographics

Groups did not differ on age, gender, PSES, IQ, or years of education (Table 1).

#### 3.2 Cognitive Measures

SPD subjects performed worse than HC subjects on SSPT (Table 1, Fig 3) and verbal fluency (Table 1, Fig 4). Note a potential ceiling effect on the SSPT.

#### 3.3 fMRI Behavioral Measures of Emotional Prosody Identification

The *a priori* hypothesis was that SPD subjects would have more difficulty correctly interpreting vocal affect. Contrary to that hypothesis, groups did not differ in number correct across all conditions (total correct). Some SPD subjects had more difficulty than others, however, as predicted and consistent with the spectrum hypothesis (Fig 5a). There was no statistically significant difference between groups for any individual prosodic condition (Table 1, Fig 5b). For the sad condition there was a small effect size, (.36), with smaller effect sizes for happy (.26), and sarcastic and neutral conditions (.2) (total correct effect size was small, .27). There was no difference between groups in reaction time (Table 1).

#### 3.4 Correlations among Cognitive and Behavioral Measures

For both groups, the better they were able to distinguish subtle phonological differences (SSPT), the better they were at distinguishing prosodic differences (SPD,  $r = .708$ ,  $p = 0.003$ ,  $N = 15$ ; HC,  $r = .582$ ,  $p < 0.05$ ,  $N = 12$ ) (Fig. 6a). This was consistent with the hypothesis that the ability to process other aspects of auditory and language signals, namely phonemes, correlated with the processing of more complex prosody.

For SPD subjects, the more words produced on verbal fluency, the higher the number of correct responses in the fMRI task (“c”  $r = .661$ ,  $p = 0.007$ ,  $N = 15$ ; “animals”  $r = .525$ ,  $p = 0.04$ ,  $N = 15$ ) (Fig 6b). This relationship did not hold for HC subjects (“c”  $r = .345$ ,  $p < 0.3$ ,  $N = 12$ ; “animals”  $r = .127$ ,  $p < .7$ ,  $N = 12$ ) (Fig 6b).

IQ played a significant role in the ability of SPD subjects to correctly identify prosodic voice ( $r = .567$ ,  $p < 0.03$ ,  $N = 15$ ), but not for HC subjects ( $r = .206$ ,  $p = 0.5$ ,  $N = 12$ ) (Fig. 6c).

Although in neither group was the correlation between PSES and total number correct on the fMRI task statistically significant (for SPD,  $r = .421$ ,  $N = 15$ ,  $p = 0.1$ ; for NC,  $r = -.489$ ,  $N = 12$ ,  $p = 0.1$ ), correlations were in opposite directions. Moreover, Fisher Z transformation demonstrated a significant difference between correlation coefficients ( $Z = 2.23$ ,  $p = 0.01$ ) (Fig. 6d).

To view these same data from a different perspective, both groups were separated into split halves using the mean number correct for the HC subjects as the dividing line (mean = 154.8, see Fig 5a). Those SPD subjects who performed worse on prosody identification compared to those who performed better, also had lower Vocabulary scores ( $F(1,14) = 13.989$ ,  $p = 0.002$ ); lower Verbal Fluency “c” ( $F(1,14) = 11.353$ ,  $p = 0.005$ ) with a trend toward fewer “animals” produced ( $F(1,14) = 3.396$ ,  $p < 0.09$ ); more auditory processing deficits on the SSPT ( $F(1,13) = 18.828$ ,  $p = 0.001$ , if exclude subject outliers); and lower PSES ( $F(1,14) = 21.197$ ,  $p < 0.0005$ ). There were no differences on any of these measures between HC subjects scoring higher than 154.8 and those scoring lower: Vocabulary

( $F(1,11) = 2.468, p = 0.1$ ); “c” ( $F(1,11) = .003, p < 1.0$ ) and animals ( $F(1,11) = .181, p < 0.7$ ); SSPT ( $F(1,11) = 1.477, p < 0.3$ ); or PSES ( $F(1,10) = .606, p < 0.5$ ).

Taken together, these exploratory analyses suggest that while phonological processing correlated with emotion identification for both groups of subjects, for SPD subjects more factors may have had influence. Specifically, for SPD subjects only, prosody identification may have been somehow affected by IQ, executive functioning and possibly PSES.

### 3.6 fMRI Activation Maps for ROI Analysis of the STG

*Overall Activation Maps* Consistent with the *a priori* hypothesis, one-sample t tests demonstrated that both SPD and HC subjects activated the predicted STG region bilaterally (Fig 7a, 7b). The HC subjects activated additional small regions of the STG bilaterally compared with SPD subjects, whereas the SPD subjects did not recruit additional areas beyond those employed by HC subjects (Fig 7c and notation 7d).

### 3.7 Extent and Magnitude of Activation and Behavioral Measure of Number Correct Across All Conditions

For the HC subjects, there appeared to be a pattern of tight coupling between the hemodynamic response maps and accuracy: the larger the activation, the more correct responses, for the right STG (extent of activation:  $r = .712, p = 0.009$ ; magnitude of activation:  $r = .573, p = 0.05$ ), and for the left STG (extent of activation:  $r = .614, p = 0.03$ ; magnitude of activation:  $r = .507, p = 0.09$ ). This was not the case for SPD subjects, for the right STG (extent of activation:  $r = -.053, p < 0.9$ ; magnitude of activation:  $r = .002, p < 1.0$ ); nor for the left STG (extent of activation:  $r = -.085, p < 0.8$ ; magnitude of activation:  $r = -.024, p = 0.9$ ) (Fig 8). These data suggest that for the group of HC subjects, the STG was effectively used to complete the task; the group of SPD subjects lacked such efficiency. The correlation coefficient for the correlation between right STG extent of activation and accuracy was compared between groups using a Fisher Z transformation and was found to be statistically different (Fisher Z transformation: extent right STG  $Z = 2.24, p < 0.03$ ).

### 3.9 FMRI Activation Maps for Secondary, Exploratory ROI Analysis of the STG for each Emotion Separately

For the purpose of generating hypotheses for future work, a secondary, exploratory whole brain analysis was performed. Note that we did not have *a priori* emotion-specific hypotheses as this is the first fMRI experiment with SPD subjects examining vocal affect processing. The t scores were not statistically significantly higher for the SPD subjects than the HC subjects.

### 3.10 FMRI Activation Maps for Secondary, Exploratory Whole Brain Analysis

For the purpose of generating hypotheses for future work, a secondary, exploratory whole brain analysis was performed. The alpha level for considering a finding statistically significant was arbitrarily set at 0.001. Note that correction for multiple comparisons was not performed so that these data needed to be viewed within that context. SPD subjects recruited extensive frontal and temporal areas including the parahippocampus to perform the task whereas comparison subjects recruited frontal, parietal, and insular regions (Table 2).

### 3.11 STS Volumes

Although the volumes of the right STS were nearly identical between groups, there was a trend toward SPD subjects having smaller left STS, particularly in the lower bank (Table 1). When volumes from the subset of subjects involved in the fMRI experiment were compared (SPD = 10, NC=7), the results did not differ.

## 4.0 DISCUSSION

The findings in this report span multiple domains of testing. Cognitively, SPD subjects as a group compared with controls had poorer phonological processing as measured by the SSPT and poorer executive functioning as measured by the Verbal Fluency Task both in the phonemic and somatic sections. In the behavioral measure of emotional prosody identification from the fMRI task, some—but not all—SPD subjects had difficulties with emotional prosody identification and that ability to process prosody may have been affected by several cognitive and demographic measures. HC subjects' ability to process prosody correlated only with their phonological processing. Functionally, both subject groups activated the predicted STG, with HC subjects activating small regions of the STG bilaterally not recruited by the SPD subjects. HC subjects also demonstrated a tight coupling of hemodynamic response and behavioral responses particularly in the right STG. This was not seen in SPD subjects. Note that there is a right hemisphere specialization for prosody interpretation (Ross and Monnot 2008). Morphometrically, there was a trend toward smaller volumes of the lower bank of the left STS in SPD subjects compared with HC subjects. Combined, these data suggest that some SPD subjects have multiple deficits in the cognitive, functional, and morphometric domains which may have affected some SPD subjects' ability to process vocal affect.

As SPD subjects exhibit “affective impoverishment” (Meehl 1962) and suffer from social and language deficits (Dickey et al. 2005, Niznikiewicz et al. 1999a, Voglmaier et al. 2000), it was originally hypothesized that SPD subjects as a group would perform poorly on a task of prosody identification. This hypothesis was not substantiated. As a group SPD subjects scored equally well compared with healthy control subjects. However, behavioral performance was not uniform across SPD subjects. Some SPD subjects performed well and had preserved functioning in this domain (Dickey et al. 2005, Siever and Davis 2004) whereas other subjects had more difficulty interpreting prosody. Note that preserved vocal affect recognition had been demonstrated for some schizophrenic subjects (Ross et al. 2001).

What factors influenced whether a given SPD subject was able to identify emotional prosody? Poorer executive functioning, lower IQ, possibly lower PSES, and poorer phonological processing all may have contributed to whether SPD subjects were able to identify emotional prosody. The finding that executive functioning and IQ may have affected prosody identification in some SPD subjects is consistent with the schizophrenia literature (Scholten, Aleman and Kahn 2008, Pijnenborg et al. 2007, Bozikas et al. 2004) (Edwards et al. 2001) (Poole, Tobias and Vinogradov 2000, Addington and Addington 1998) (Murphy and Cutting 1990). Altered executive functioning and IQ have been associated with poorer psychosocial adjustment and prosody identification in schizophrenic patients (Simon et al. 2003, Bozikas et al. 2004). Finally, social class of origin may have affected some SPD subjects' ability to process prosody. PSES has been shown in children to affect executive functioning and language skills (Hackman and Farah 2009, Stevens, Lauinger and Neville 2009). Precisely how the lower PSES in some of the SPD subjects affected their ability to process prosody could not be determined from the current data. Note, however, that the richness of the home environment may not have been the important variable. Alternatively, genetics may have been the critical factor (Skuse 2006).

Phonological processing was impaired in SPD compared with HC subjects. Moreover, phonological processing ability correlated with performance across subject groups. In SPD the potential linkage among abnormal basic auditory signal processing (Dickey et al. 2008, Niznikiewicz et al. 2009), abnormal phonological processing, and prosody identification may be important. Although this link had not been shown previously for SPD subjects, SPD subjects, compared with controls, have demonstrated aberrant simple auditory processing

(Dickey et al. 2008, Niznikiewicz et al. 2009). Specifically, SPD subjects had a greater hemodynamic response than comparison subjects in the STG while passively listening to simple tones of differing pitch and duration (Dickey et al. 2008). Taken together these data may suggest a basic auditory processing “factor” independently influencing downstream phoneme and prosody processing, consistent with evidence in schizophrenia (Leitman et al. 2005) (Leitman et al. 2007).

Basic auditory signals are processed by the STG (Yoo et al. 2005, Wible et al. 2001, Dickey et al. 2008). In the current study, as predicted, prosody identification required the recruitment of the STG in both subject groups. However, SPD subjects were less “efficient” in their ability to process prosody than are HC subjects: HC subjects demonstrated a tight coupling between STG cortical activation and performance particularly on the right, which SPD subjects did not. Prior work suggested that SPD subjects compared with controls may have either inefficient processing, that is, recruit more cortical resources, or have an exaggerated response in the STG to changes in simple auditory signals (Dickey et al. 2008). In both reports, SPD subjects appeared to ineffectively recruit the STG to process auditory stimuli, both simple tones and complex vocal affect.

Whole brain exploratory analyses (Table 2, Fig 10) suggest that the SPD subjects also utilized large frontal regions to perform the task. In contrast, the HC subjects recruited clusters with peak hemodynamic responses in the STS, with no peak seen in SPD subjects. These analyses need to be interpreted with caution as they were not corrected for multiple comparisons. However, they may guide future hypotheses generation regarding the relative roles of the STS and frontal lobes in prosody interpretation by SPD subjects.

Structural manual drawings of the STS suggested at the trend level that the left lower bank of the STS was smaller in SPD compared with HC, consistent with other reports of smaller left temporal regions in SPD and schizophrenic subjects (Dickey et al. 2000, Dickey et al. 2003, Dickey et al. 1999) (Onitsuka et al. 2004) (Downhill et al. 2001)(reviewed in (Shenton et al. 2001)). Whether the trend toward the smaller lower bank of the STS in SPD affected their ability to effectively process prosody cannot be determined from this study given the lack of complete subject overlap, but this is an intriguing possibility requiring further investigation.

One strength of this study is the use of antipsychotic-naïve SPD subjects. The involvement of medication-free subjects suggested that fMRI signal abnormalities in schizophrenic subjects documented in other prosody experiments were not solely iatrogenic. Limitations to this report were several. The subject N was small given the inherent difficulty of recruiting SPD subjects from the community, thus limiting the ability to generalize findings to the larger SPD population. There are known gender effects on social interactions and in the processing of vocal affect specifically (Schirmer et al. 2004), which were not explored here given the subject N. In addition, voice recordings used were not obtained from professional actors, which some argue was preferred (Hoekert et al. 2007). Finally, several exploratory correlations were performed and the alpha level for determining significance was not adjusted. Therefore, the conclusions drawn in those cases need to be interpreted cautiously within that context.

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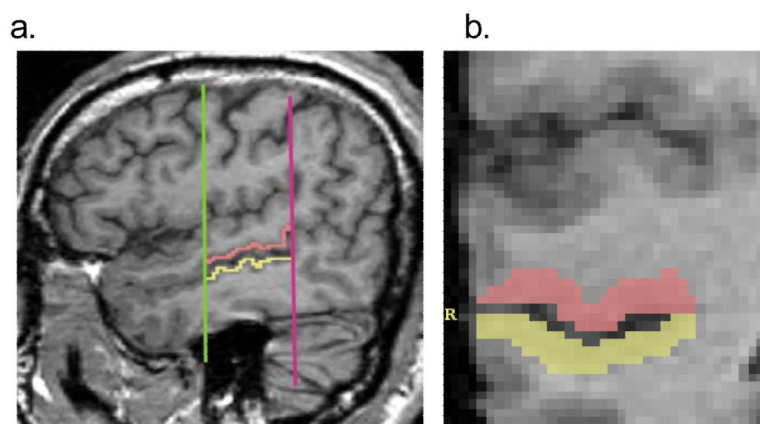
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**Figure 1. fMRI Experimental Design**

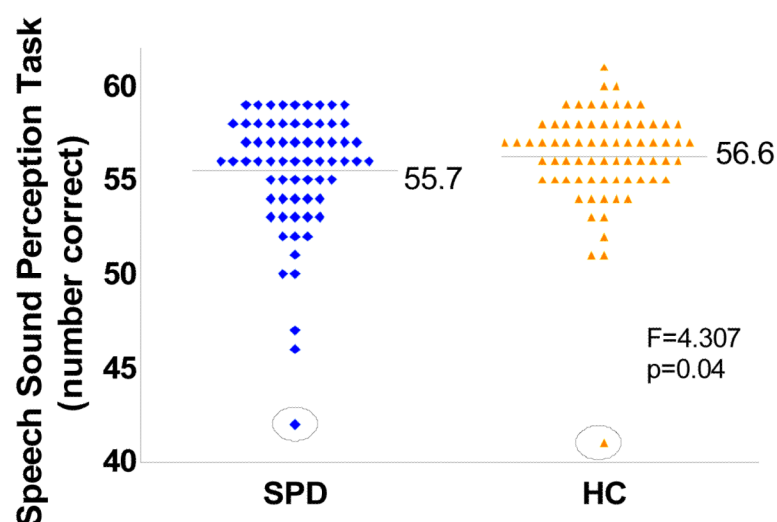
The onset vector begins with the first phoneme of the sentence (arrow) and the epoch continues to the onset of the next sentence in the series. SOA = stimulus onset asynchrony.



**Figure 2. Manual Tracing of STS**

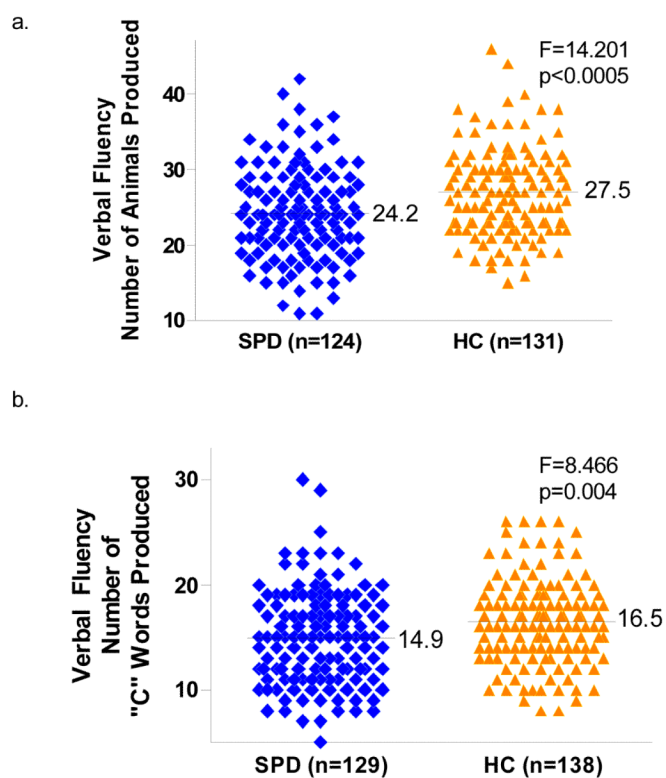
(a). Vertical lines on the sagittal image demarcate the anterior (green) and posterior (magenta) boundaries of STS drawing. (b). The coronal image shows the segmented right STS upper bank (salmon) and the lower bank (yellow).





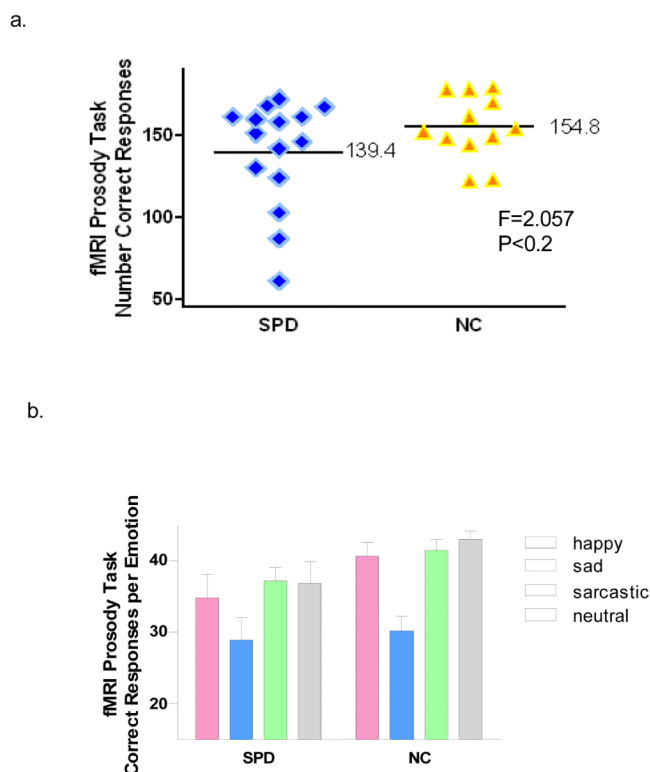
**Figure 3. Speech Sound Perception Test (SSPT)**

SPD subjects demonstrated deficits in phonemic processing when the two subjects who were outliers on this measure were removed from the analysis (one SPD and one HC, data points circled). When their data was included, the difference in performance was statistically significant at the trend level ( $F(1,139) = 2.930$ ,  $p < 0.09$ ). Bars and numbers represent mean values.



**Figure 4. Verbal Fluency**

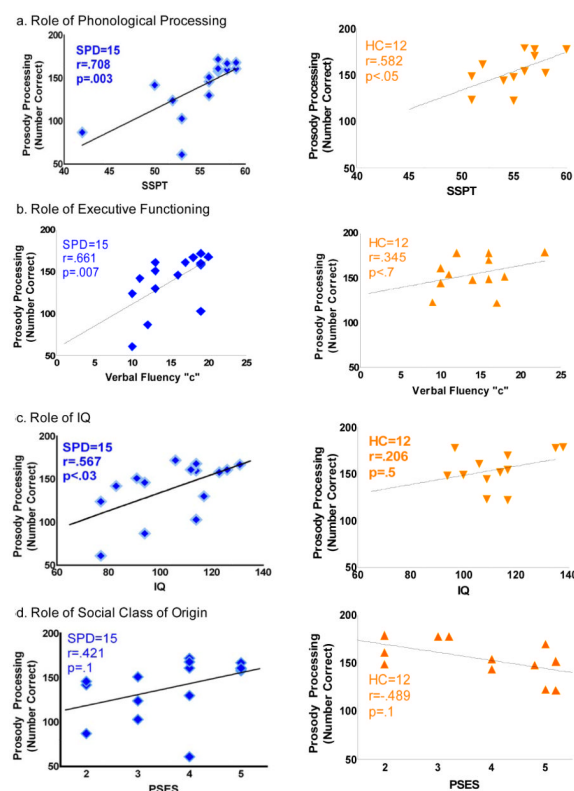
(a). Semantic Fluency. (b). Phonemic Fluency. SPD subjects have executive functioning deficits as measured by the Verbal Fluency task in both the semantic and phonemic domains. Bars and numbers represent mean values.



**Figure 5. fMRI Behavioral Measure of Number Correctly Identified Prosodic Emotions**

(a). Total number of sentences correctly identified. There was no difference between groups on this measure. Some SPD subjects, however, appeared to have difficulty. To examine those subjects more closely, both groups were examined with split-half comparisons. The mean number of correctly identified sentences for the HC subjects (154.8) was used to separate each diagnostic group into two groups, higher performers and lower performers.

(b). Number of correctly identified sentences by prosodic emotion condition. There were 50 sentences per condition. There were no statistically significant differences between groups although there was a trend toward SPD subjects having more difficulty with “sad”.



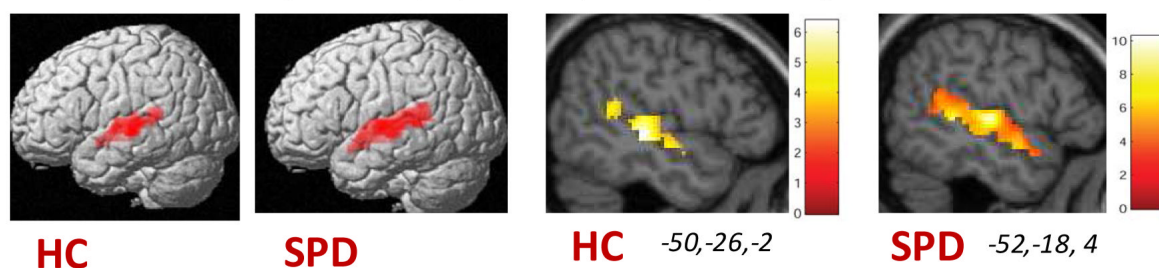
**Figure 6. Correlations among Cognitive and Behavioral Measures: Factors Influencing Prosody Processing**

(a). Role of Phonological Processing. Phonological processing was significantly correlated with prosody processing for both SPD and HC subjects. (b). Role of Executive Functioning. Executive function significantly affected SPD subjects only. (c). Role of IQ. IQ significantly affected SPD subjects only. (d). Role of Social Class of Origin. There was a positive correlation for SPD subjects but a negative correlation for HC subjects. Neither correlation in this case reached the significance level, but there was a statistically significant difference in the correlation coefficient between groups.

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**7a. All Conditions, ROI analysis, Left STG, one-sample t test, threshold 0.003**

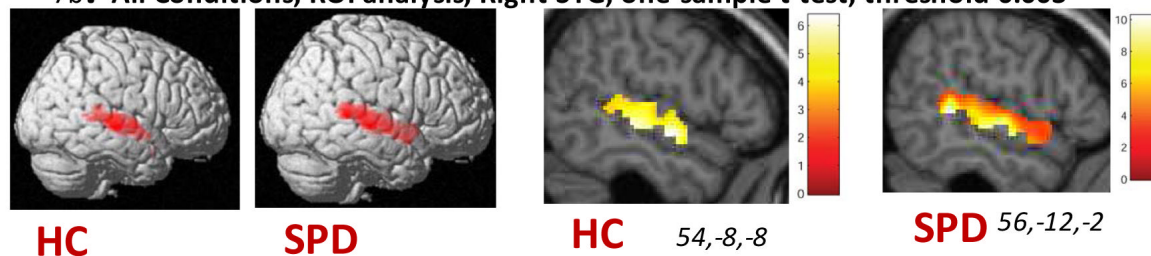

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**7b. All Conditions, ROI analysis, Right STG, one-sample t test, threshold 0.003**

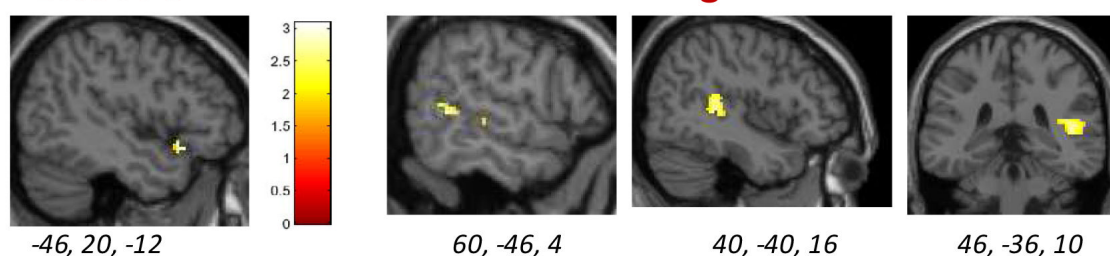

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**7c. All Conditions, ROI analysis, STG, HC > SPD, Two-sample t test, threshold 0.003**


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**Left STG****Right STG**


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**7d. All Conditions, ROI analysis, STG, SPD > HC, Two-sample t test, threshold 0.003**

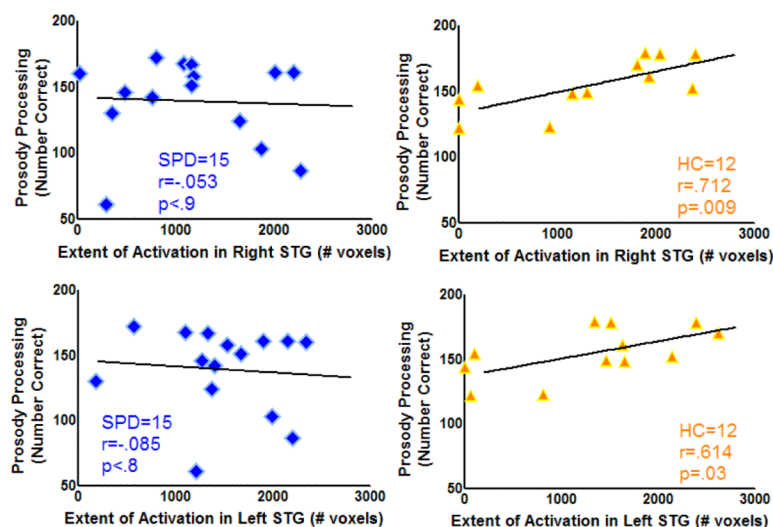

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*No suprathreshold clusters in left or right STG*

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**Figure 7. fMRI Parametric Maps for ROI Analysis across All Conditions, Threshold = 0.003**

Using the one-sample t test both groups demonstrated activation in the (a) left STG and (b) right STG. When the two groups were directly compared with a two-sample t test there were areas of both the left and the right STG seen in the HC > SPD analysis (c). However, with the two-sample t test there were no super-threshold voxels in the SPD>HC comparison (d). MNI x, y, z coordinates given for voxel of peak magnitude activation as well as color bar for t score significance.



**Figure 8. Correlations between the Extent of Activation in STG and Behavioral Measure of Number Correct Across All Conditions**

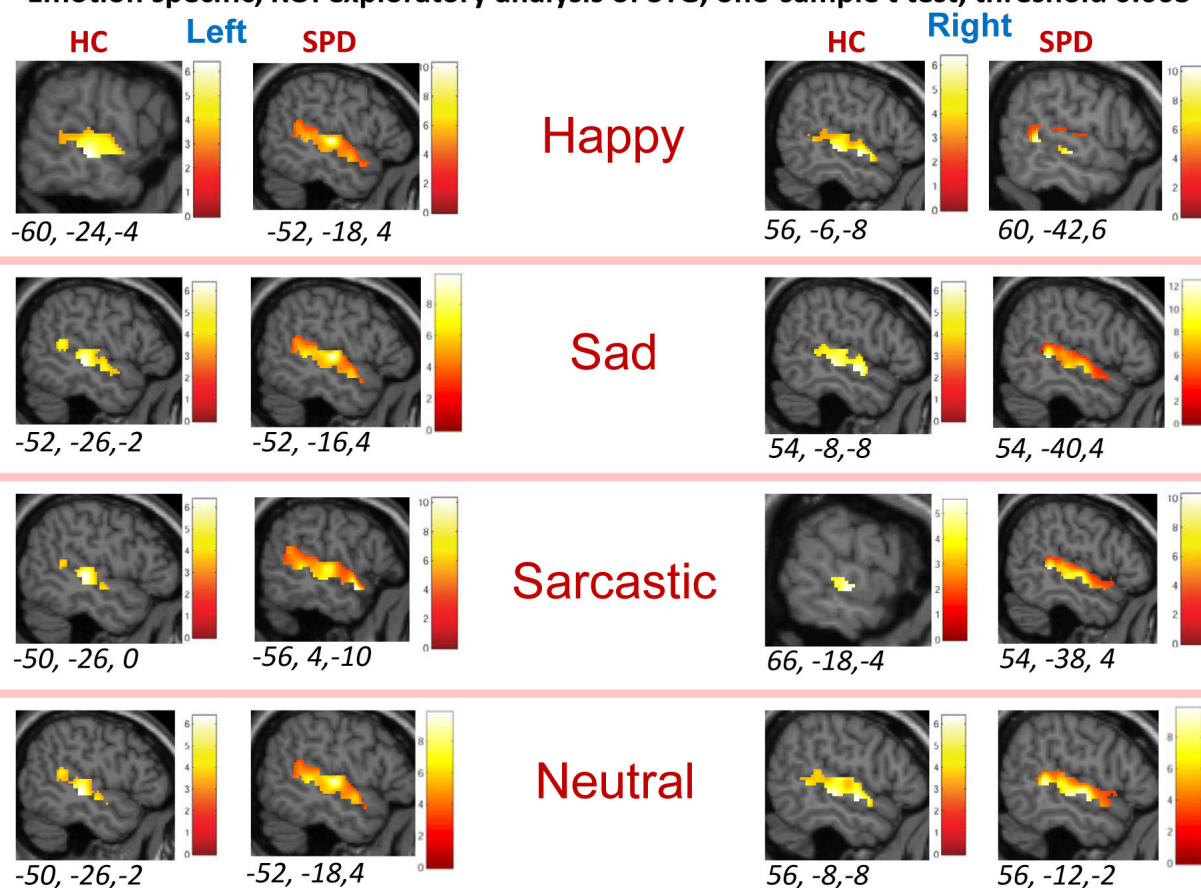
For the healthy control subjects there was a tight coupling between ROI activation bilaterally and accuracy of prosodic emotion identification (orange graphs). SPD subjects did not display such tight coupling (blue graphs). Top: right STG data. Bottom: left STG data.



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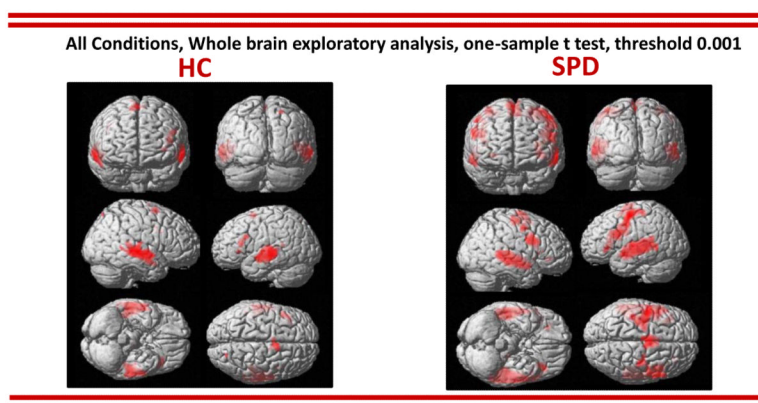
**Emotion specific, ROI exploratory analysis of STG, one-sample t test, threshold 0.003**


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**Figure 9. fMRI Parametric Maps for Exploratory ROI Analysis for Each Separate Emotion, Threshold = 0.003**

Using one-sample t tests, the left (left-sided images) and the right STG (right-sided images) parametric maps are displayed for each emotion separately for HC and SPD subjects. Note that these analyses are *post-hoc* as there were no emotion-specific hypotheses. MNI *x, y, z* coordinates given as well as color bar for *t* score significance.



**Figure 10. fMRI Parametric Maps for Secondary, Exploratory Whole Brain Analysis across All Conditions, Threshold 0.001**

These whole brain parametric maps were produced using one sample t tests and are included for further hypothesis generation. The results suggest that SPD subjects have large hemodynamic responses in frontal regions while the HC have little. The areas in red are those where the significance threshold of 0.001 was exceeded. Specific regions are noted in Table 2.

**Table 1**  
**Subject Demographics, Cognitive Measures, STS Volumes, Reaction Times, Number of Correct Responses**

+ Chi Square distribution was performed on gender distribution. Subjects were one-to-one matched on age and group matched on PSES, years of education and IQ. The SPD subjects had smaller left STS volumes in the lower bank and total STS at the trend level compared with HC. There was no difference between groups in reaction time on the prosody identification fMRI task. SPD subjects had more difficulty than did HC subjects identifying sad emotion at the trend level in an exploratory analysis (Fig 5b).

(N=SPD, HC)	SPD	CONTROL		F,	P
Subject Demographics					
Gender +	male=13, female=3	male=9, female=4			
Age (16, 13)	39.1 (11.0)	35.2 (12.3)		.566, .925,	<0.5 0.3
PSES (16, 12)	3.6 (1.2)	3.7 (1.2)		.053, 2.905	0.8 0.1
SES (15, 11)	3.2 (1.0)	3.8 (.8)		.287, .675,	0.6 .4
Education (16, 13)	14.7 (2.1)	15.1 (1.6)			
Vocabulary (IQ) (16, 13)	11.9 (4.4)	13.1 (3.2)			
Cognitive Measures					
Verbal Fluency “c” (129,138)	14.9 (4.6)	16.5 (4.0)		8.466	0.004
Verbal Fluency “animals” (124,131)	24.2 (6.1)	27.5 (5.7)		14.201,	<0.0005
SSPT total correct (67,73)	55.7 (2.8)	56.6 (2.2)		4.307	0.04
STS Volumes (absolute volumes in mls) (SPD=30, NC=30)					
Left Upper STS	3.5 (1.0)	3.7 (1.0)		2.069	<0.2
Left Lower STS	3.3 (1.0)	3.6 (.8)		3.932	0.052
Total Left STS	6.8 (1.8)	7.4 (1.7)		3.454	<0.07
Right Upper STS	4.2 (1.3)	4.3 (1.1)		.321	<0.6
Right Lower STS	4.1 (1.3)	4.1 (1.1)		.011	0.9
Total Right STS	8.4 (2.5)	8.4 (2.2)		.118	0.7
Reaction Time (in seconds)					
Time: Happy (16/14)	2.5 (.3)	2.5 (.2)		.054,	0.8
Time: Sad (16/14)	2.8 (.2)	2.7 (.1)		.487,	<0.5

(N=SPD, HC)	SPD	CONTROL		F,	P
Time: Sarcastic (16/14)	3.1 (.1)	3.0 (.1)		.666,	0.4
Time: Neutral (15/14)	2.8 (.2)	2.7 (.2)		.155,	<0.7
Time: Total (15/14)	11.1 (.7)	10.9 (.4)		.153,	<0.7
<b>Number of Correct Responses</b>					
Correct: Happy (16/14)	35.4 (11.2)	40.5 (7.1)	81%	2.023,	<0.2
Correct: Sad (16/14)	37.06 (9.7)	42.7 (7.4)	85%	3.804,	0.06
Correct: Sarcastic (16/14)	29.0 (10.7)	30.9 (5.8)	61%	.279	0.6
Correct: Neutral (15/13)	37.9 (9.7)	40.7 (7.6)	81%	1.108,	0.3
Correct: Total (15/13)	139.4 (32.8)	154.8 (7.0)	77%	2.057,	<0.2

**Table 2**  
**Exploratory whole-brain analysis across conditions, uncorrected  $p = 0.001$ , one-sample t tests**

HC subjects demonstrated a peak in the hemodynamic response curve in the left STS and left insula, not seen in SPD subjects. Note that the SPD subjects activated additional frontal and left hippocampal regions not seen in HC subjects (Fig 10). These analyses were for exploratory purposes only.

<i>Region</i>	<i>Cluster size</i>	<i>T</i>	<i>P (uncorrected)</i>	<i>x</i>	<i>y</i>	<i>z</i>
<b>Healthy control subjects</b>						
<i>Temporal lobe</i>						
<i>Right STG</i>	1541	6.84	<0.0005	64	-20	-8
<i>Left STG</i>	1207	6.37	<0.0005	-50	-26	-2
<i>Left STS</i>	15	4.29	0.001	-52	-44	14
<i>Parietal lobe</i>						
<i>Right superior parietal gyrus</i>	11	6.19	<0.0005	24	-74	58
<i>Frontal lobe</i>						
<i>Left inferior frontal gyrus</i>	159	4.71	<0.0005	-46	16	26
<i>Right superior frontal gyrus</i>	154	4.91	<0.0005	10	6	62
<i>Insula</i>						
<i>Left short insular gyrus</i>	46	4.83	<0.0005	-34	26	2
<b>SPD subjects</b>						
<i>Temporal lobe</i>						
<i>Right STG</i>	1756	10.95	<0.0005	56	-40	4
<i>Left STG</i>	2871	10.25	<0.0005	-52	-10	4
<i>Left parahippocampus</i>	13	4.45	<0.0005	-18	-26	-20
<i>Frontal lobe</i>						
<i>Left middle frontal gyrus</i>	2071	10.38	<0.0005	-46	-6	52
<i>Left superior frontal gyrus</i>	691	8.17	<0.0005	-2	-4	66
<i>Right precentral gyrus</i>	665	7.29	<0.0005	56	4	28
<i>Right precentral gyrus</i>	139	5.50	<0.0005	42	-6	46
<i>Right precentral gyrus</i>	247	5.42	<0.0005	38	-20	60
<i>Left inferior frontal gyrus</i>	338	6.09	<0.0005	-38	30	-4