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### Authors

Shaffer, Joseph J  
Peterson, Michael J  
McMahon, Mary Agnes  
[et al.](#)

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# Neural Correlates of Schizophrenia Negative Symptoms: Distinct Subtypes Impact Dissociable Brain Circuits

Joseph J. Shaffer<sup>a</sup> Michael J. Peterson<sup>a</sup> Mary Agnes McMahon<sup>b</sup>  
 Joshua Bizzell<sup>a, c</sup> Vince Calhoun<sup>d, e</sup> Theo G.M. van Erp<sup>f</sup> Judith M. Ford<sup>h</sup>  
 John Lauriello<sup>i</sup> Kelvin O. Lim<sup>j</sup> Dara S. Manoach<sup>k</sup> Sarah C. McEwen<sup>l</sup>  
 Daniel H. Mathalon<sup>h</sup> Daniel O'Leary<sup>m</sup> Steven G. Potkin<sup>g, h</sup> Adrian Preda<sup>g</sup>  
 Jessica Turner<sup>n</sup> Jim Voyvodic<sup>c</sup> Cynthia G. Wible<sup>o, p</sup> Aysenil Belger<sup>a, c</sup>

<sup>a</sup>Department of Psychiatry, University of North Carolina, Chapel Hill, N.C., <sup>b</sup>Colorado Clinical and Translational Sciences Institute, University of Colorado, Denver, Colo., <sup>c</sup>Duke/University of North Carolina Brain Imaging and Analysis Center, Durham, N.C., <sup>d</sup>The Mind Research Network and <sup>e</sup>Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, N. Mex., <sup>f</sup>Departments of <sup>f</sup>Psychiatry and Human Behavior and <sup>g</sup>Psychiatry, University of California Irvine, Irvine, Calif., <sup>h</sup>Department of Psychiatry, University of California San Francisco, San Francisco, Calif., <sup>i</sup>Department of Psychiatry, University of Missouri, Columbia, Mo., <sup>j</sup>Department of Psychiatry, University of Minnesota, Minneapolis, Minn., <sup>k</sup>Department of Psychiatry, Massachusetts General Hospital, Charlestown, Mass., <sup>l</sup>Department of Psychology, University of California Los Angeles, Los Angeles, Calif., <sup>m</sup>Department of Neuroscience, University of Iowa, Iowa City, Iowa, <sup>n</sup>Department of Psychology, Georgia State University, Atlanta, Ga., <sup>o</sup>Department of Psychiatry, Harvard Medical School, Boston, Mass., and <sup>p</sup>Department of Psychiatry, VA Medical Center Brockton, Brockton, Mass., USA

## Key Words

Schizophrenia · Negative symptoms · Functional magnetic resonance imaging · Auditory oddball · Functional Biomedical Informatics Research Network

## Abstract

**Background:** The negative symptoms of schizophrenia include deficits in emotional expression and motivation. These deficits are stable over the course of illness and respond poorly to current medications. Previous studies have focused on negative symptoms as a single category; however, individual symptoms might be related to separate neurolog-

ical disturbances. We analyzed data from the Functional Biomedical Informatics Research Network dataset to explore the relationship between individual negative symptoms and functional brain activity during an auditory oddball task.

**Methods:** Functional magnetic resonance imaging was conducted on 89 schizophrenia patients and 106 healthy controls during a two-tone auditory oddball task. Blood oxygenation level-dependent (BOLD) signal during the target tone was correlated with severity of five negative symptom domains from the Scale for the Assessment of Negative Symptoms. **Results:** The severity of alogia, avolition/apathy and anhedonia/asociality was negatively correlated with BOLD activity in distinct sets of brain regions associated with pro-

cessing of the target tone, including basal ganglia, thalamus, insular cortex, prefrontal cortex, posterior cingulate and parietal cortex. **Conclusions:** Individual symptoms were related to different patterns of functional activation during the oddball task, suggesting that individual symptoms might arise from distinct neural mechanisms. This work has potential to inform interventions that target these symptom-related neural disruptions.

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## Introduction

Negative symptoms in schizophrenia patients include diminished motivation, affective responsiveness, speech, movement, social engagement and hedonic pleasure, and are associated with poor functional outcome and quality of life [1]. They are of particular interest due to their resistance to current antipsychotic treatments [2–4] and their persistence over the course of the illness [3, 4]. The presence of negative symptoms in unaffected first-degree relatives [3, 5] further suggests that the neural underpinnings of these deficits may be associated with a genetic liability for schizophrenia. Negative symptoms have a high internal consistency and vary in severity independently of positive symptoms such as hallucinations and delusions [2]. Although improvements in negative symptoms are associated with improved functional outcomes, including independent living skills, social functioning and role functioning [6], and as such targeting them may have significant functional benefits, identification of reliable targets for the treatment of negative symptoms remains an unmet clinical need [7–10].

While the severity of negative symptoms is often evaluated by measuring individual symptom ratings, negative symptoms tend to co-occur [2]. Some recent factor analytic studies have suggested that negative symptoms can be divided into two categories – one related to avolition, comprised of avolition/apathy and anhedonia/asociality, and a second related to emotional expressiveness, comprised of flat affect and alogia [11–14]. It remains unclear whether all negative symptoms share the same neural pathology, even when they are strongly related, as suggested by factor analytic approaches.

Elucidating the neural correlates of negative symptom severity in schizophrenia and its modulatory effects on cognitive function in schizophrenia is a vital step towards identifying relevant endophenotypes [2, 3], uncovering the pathophysiological mechanisms that underlie them and developing targeted interventions [4]. A review of 25

schizophrenia studies showed that blood oxygenation level-dependent (BOLD) activity in ventrolateral prefrontal cortex and ventral striatum was inversely associated with negative symptom severity during executive functioning and reward conditioning tasks, respectively [3]. Other studies have identified a negative correlation between the severity of negative symptoms and cortical thickness in prefrontal cortex, superior temporal cortex and medial temporal cortex, including the hippocampus [4]. Furthermore, functional magnetic resonance imaging (fMRI) studies have identified decreased functional activation and connectivity within these regions [3, 4]. As negative symptoms represent a complex aggregate of emotional and motivational deficits, we expected correlations between functional activity during the task and negative symptom severity to vary by symptom subtype. Therefore, in this study, we examined correlations between functional activation and individual negative symptom domain severity measures obtained using the Scale for the Assessment of Negative Symptoms (SANS) [15]. Few studies have addressed these component symptoms separately; however, this approach is pertinent to research efforts to identify research domains across neuropsychiatric disorders such as bipolar disorder and major depressive disorder. Clinically, the combination of these negative symptoms, when persistent, constitutes the deficit syndrome [16], which is not present in bipolar disorder or major depressive disorder; however, individual symptoms such as anhedonia are present across all three disorders. The goal of this work was therefore to compare the neural correlates of domains of negative symptoms from the SANS (flat affect, alogia, anhedonia/asociality, avolition/apathy and attention deficits) rather than their effects when grouped together.

In a retrospective analysis, we used an auditory oddball task consisting of a series of standard tones with rare target tones of a different frequency. This task has been used to investigate differences in attention related to auditory mismatch and target detection between healthy controls and patients with schizophrenia in hundreds of studies since the 1970s [17]. In electroencephalography-based studies, patients exhibit a decrease in the amplitude of the P300, which is thought to indicate identification of rare targets, during oddball tasks [17–20] and diminished mismatch negativity component thought to reflect an inability to properly shift attention [19, 21–25]. In addition to reflecting attention processes, P300 has been shown to correspond with negative symptoms in schizophrenia [19, 26, 27]. fMRI studies of schizophrenia have shown decreased activity in frontal [21, 22, 28], temporal [22, 28,

29], anterior cingulate [21], posterior cingulate [28], insula [21, 28], visual [21] and parietal cortex [21, 22] as well as in subcortical structures such as the striatum [28] and thalamus [21, 28] in response to the target tone, many of which has been found to be associated with negative symptom severity [3, 4, 30]. It is therefore highly likely that individual differences in negative symptom severity may interact with activation of neural systems engaged during attentional and executive processing.

Our goal was to identify correlates between regional brain activity and the severity of individual negative symptoms from the SANS. We expected that patients with schizophrenia with severe negative symptoms, particularly avolition and anhedonia, which form the basis of the 'avolition' factor, and attention deficit symptoms, would show decreased activity in brain regions related to attention and target detection during the oddball task, including frontal and parietal cortex as well as the striatum, insula and anterior cingulate. The large multisite Functional Biomedical Informatics Research Network (FBIRN) MRI dataset provides a unique opportunity to examine associations between brain physiology and symptom severity. Kim et al. [21] demonstrated significant group differences between patients and healthy controls during the deviant tone in several brain regions, including dorsolateral prefrontal cortex, insula, anterior and posterior cingulate, superior temporal, medial occipital and lateral parietal areas. The FBIRN group also used this task to investigate correlates of hallucinations in schizophrenia patients [29]. Ford et al. [29] reported that patients who tended to hallucinate showed decreased activity in left primary auditory cortex when compared with patients who tended not to hallucinate. To extend this work, we examined correlations between negative symptoms and the BOLD response to target stimuli in this fMRI auditory oddball dataset from the FBIRN study.

One previous study tested the relationship between negative symptom severity and brain activity during an auditory oddball task. In that study, left dorsolateral prefrontal cortex and ventral striatum activation were correlated with negative symptom severity during the response to distractor stimuli (but not targets) [30]. The FBIRN implementation of the auditory oddball task does not include distractor sounds; however, in contrast to their findings, we expected that given robust differences in brain activity between healthy control individuals and people with schizophrenia during the target task condition, this brain activity would also show correlations with clinical symptom severity, including the severity of nega-

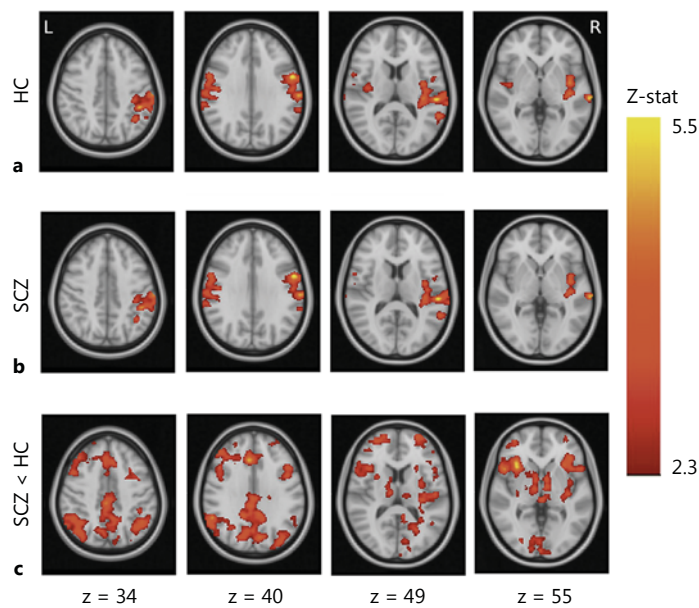
tive symptoms. It seems reasonable to expect that the Wolf et al. [30] study sample was too small ( $n = 17$ ) to measure this effect.

We hypothesized that the severity of total negative symptoms in patients with schizophrenia would correlate with reduced activation in response to target tones [31] in frontal and temporal cortex regions, striatum, limbic regions and default mode network (DMN) regions. Furthermore, we expected that the individual domains of negative symptoms would correlate with brain activity in distinct but potentially overlapping subsets of these same regions – that is, that the patterns of individual symptom-correlated brain activity would qualitatively differ between symptom domains. Overall such findings would suggest that the functional correlates of total negative symptoms are the combination of heterogeneous parts, and would therefore dispute the notion that negative symptoms are a uniform entity.

## Methods

### Participants

89 adult schizophrenia patients (67 male, 22 female; mean age 38.55 years,  $SD = 11.62$ ) and 106 healthy control individuals (68 male, 38 female; mean age 36.58 years,  $SD = 11.82$ ) were recruited at eight research sites (Duke/University of North Carolina, Brigham Women's Hospital, Massachusetts General Hospital, University of California at Los Angeles, University of California at Irvine, University of New Mexico, University of Minnesota and Yale University) as part of the FBIRN project (see online suppl. tables S1 and S2; for all online suppl. material, see [www.karger.com/doi/10.1159/000440979](http://www.karger.com/doi/10.1159/000440979)). The healthy control and schizophrenia groups did not differ in terms of age ( $t(195) = -0.6794$ ,  $p = 0.4977$ ), sex (odds ratio = 0.578,  $p = 0.0758$ ), race (odds ratio = 1.18,  $p = 0.6345$ ), ethnicity (odds ratio = 1.33,  $p = 0.627$ ) or handedness ( $p = 0.3847$ ). Healthy controls had more education than patients ( $t(180) = 6.3259$ ,  $p = 1.927 \times 10^{-9}$ ). All participants underwent the Structured Clinical Interview for DSM-IV [32] to confirm their diagnostic category. Participants were excluded for current or past substance or alcohol abuse problems, head injury, migraine treatment or an IQ  $<75$  as measured using the North American Adult Reading Test. Healthy controls were excluded if they had a first-degree family member with a diagnosed psychotic illness. Schizophrenia patients were excluded if they showed significant tardive dyskinesia; they were also required to be clinically stable without major psychotropic medication changes for the 2 months preceding their participation in the study. All subjects were asked to abstain from drinking coffee for 2 h and from smoking for 40 min previous to the scanning session. Participants were also asked to refrain from consuming more than one alcoholic beverage the night before and were asked to get a good night's sleep. Institutional review board approval was obtained at each site and participants provided written consent prior to study participation. Severity of negative symptoms was assessed using the SANS during a clinical interview [15].



**Fig. 1.** **a, b** Voxels showing significantly increased activation to the deviant tone in healthy controls (**a**) and schizophrenia patients (**b**). **c** Voxels that were significantly more active during the deviant tone in healthy controls than in schizophrenia patients ( $p < 0.05$ ).

#### Auditory Oddball Task

Participants were presented with a two-tone auditory oddball task consisting of a 1,000-Hz standard tone and a 1,200-Hz target tone. Stimulus duration was 100 ms with an approximately 500-ms inter-stimulus interval. Target stimuli were rare, occurring in only 5% of trials or about every 6–15 s. A black fixation cross was presented in the center of a gray screen. Volume was adjusted by the experimenter to 85 dB SPL at the headset to ensure that the stimuli could be heard binaurally over scanner noise. Participants underwent two practice runs and four experimental runs, each lasting 280 s. Runs were preceded and followed by a 15-s fixation period. Participants were instructed to press a button with their right index finger in response to the target tone and to do nothing in response to the standard tone. Responses occurring faster than 200 ms were excluded from the behavioral analysis. Response times were not available from one site participating in the study, but are reported for the others. Discrimination was assessed using the  $d'$  statistic and was available from all sites. The  $d'$  statistic measures target discrimination by utilizing the difference between hit rate and false-positive rate.

#### Imaging Parameters

Imaging parameters were standardized between sites based on prior work carried out as part of the FBIRN project [33–37]. Functional imaging slice orientation was along the AC-PC line using a single-shot EPI sequence at all sites except for Duke, which used a spiral echo sequence (TR = 2,000 ms, TE = 30 ms (3 T); 40 ms (1.5 T), flip angle = 90°, matrix = 64 × 64, FOV = 22 cm, slices = 27, thickness = 4 mm, gap = 1 mm). The scanner hardware for each site is listed in online supplementary table S1.

#### Image Processing

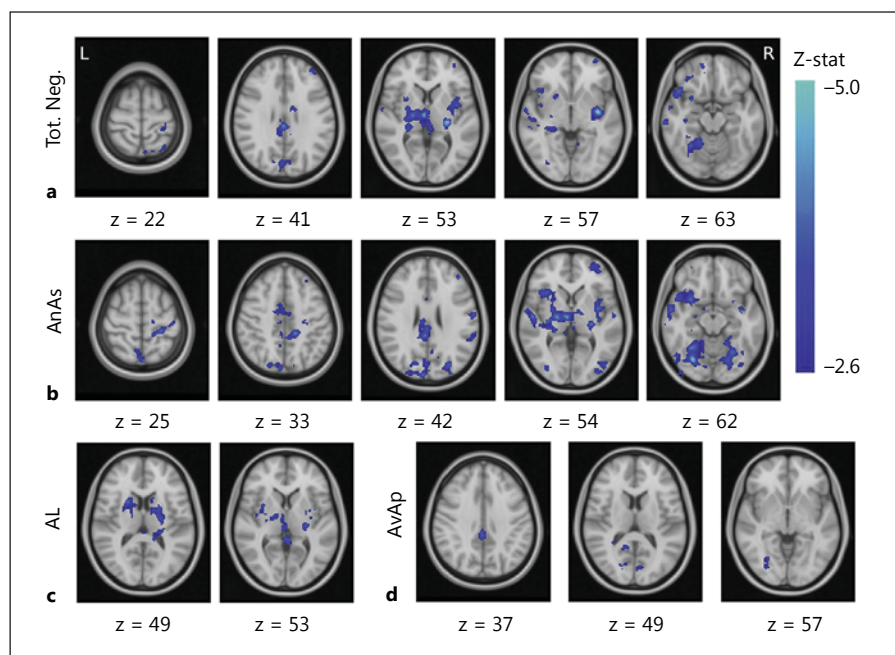
Image data were processed using the FBIRN Image Processing System (FIPS), which relies on functions from the FMRIB Software Library (FSL, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)) [38–40]. Images were cor-

rected for motion, b0 field irregularities and slice timing. Brain extraction was carried out using FSL, and 8-mm full-width at half maximum Gaussian smoothing was carried out using FreeSurfer so that images from all sites were consistently smooth.

fMRI data processing was carried out using FMRI Expert Analysis Tool (FEAT) version 5.98, part of FSL. Activation to the task was analyzed in an event-related design by contrasting equal numbers of deviant and standard tone events. Only correct trials were used in order to identify regions that were significantly activated in the deviant tone condition. Imaging data were first analyzed to identify regions that were correlated with the deviant tone within each individual. Then, a general linear model was used in order to analyze our data in two parts. First, we carried out a group contrast between patients and healthy controls. The results of this analysis are shown in figure 1. Second, we tested the correlation between total negative symptoms, and individual symptom domains and functional activation within the patient group only. Because of the correlation between negative symptom domains, separate models were created for each symptom category (total negative, flat affect, avolition/apathy, anhedonia/asociality). Site, gender and age were included in these models as covariates in order to control for their effects. Multiple comparisons correction was carried out using cluster-based family-wise error with an initial threshold of  $z = 2.3$  and  $p = 0.05$  for the group contrast and for each symptoms correlation model separately. In order to account for the five separate models generated for the negative symptoms correlation analysis, we performed a Bonferroni correction which increased our threshold to  $z = 2.6$ . This threshold was applied to the images shown in figure 2.

#### Statistical Analysis

The statistical analysis of demographic data was carried out using the Welch two-sample t test for continuous variables and Fisher's exact test for categorical data. Between-group behavioral results were also tested using the Welch two-sample t test.



**Fig. 2.** Voxels showing a significant negative correlation with total negative symptoms (a), anhedonia/asociality (b), alolia (c) and avolition/apathy (d) ( $p < 0.05$ , Bonferroni-corrected).

**Table 1.** Comparison of negative symptom scores by showing means  $\pm$  standard deviations and correlation values

Symptom	Flat affect (1.73 $\pm$ 1.49)	Alogia (1.12 $\pm$ 1.24)	Avolition/apathy (2.29 $\pm$ 1.33)	Anhedonia/asociality (2.48 $\pm$ 1.44)	Attention (1.44 $\pm$ .31)
Total negative (9.07 $\pm$ 4.46)	0.77*	0.72*	0.67*	0.66*	0.44*
Flat affect		0.60*	0.40*	0.29*	0.19
Alogia			0.29*	0.26*	0.23*
Avolition/apathy				0.50*	-0.00
Anhedonia/asociality					0.06

d.f. = 87. \* $p < 0.05$ .

## Results

### Behavior

We found no difference between patients with schizophrenia and healthy controls in  $d'$  ( $t(198) = 1.185$ ,  $p = 0.2375$ ) or in response time ( $t(174) = -1.840$ ,  $p = 0.0674$ ) for target stimuli. Furthermore, we found no relationship between total negative symptom severity and  $d'$  ( $F(24, 66) = 1.391$ ,  $p = 0.1468$ ) or response time ( $F(5, 74) = 0.0551$ ,  $p = 0.998$ ) within the patient group.

### Clinical Symptoms

The total negative symptom score was highly correlated with the scores for each individual item, which were

all highly correlated with each other (table 1). The distribution of clinical symptoms is shown in supplementary figure 1.

### Schizophrenia Patients versus Healthy Controls

We found that the schizophrenia group showed decreased activation in response to targets in several brain regions compared with healthy controls in a whole-brain voxel-wise analysis (fig. 1, table 2). These regions included bilateral orbitofrontal cortex, inferior frontal gyrus, middle frontal gyrus, frontal pole, frontal operculum, insula, anterior cingulate, paracingulate, posterior cingulate, pallidum, putamen, thalamus, angular gyrus, supra-marginal gyrus, precuneus, intracalcarine cortex, lingual

**Table 2.** Statistically significant cluster locations and their respective local maxima compared between patients and healthy controls

Cluster (voxels)	Z-stat.	X	Y	Z	Cluster (voxels)	Z-stat.	X	Y	Z
HC vs. SCZ 1 (2,141)	4.74	60	-46	24	HC vs. SCZ 5 (836)	4.08	-6	-8	-4
Supramarginal	4.74	60	-46	24	R. thalamus	4.08	-6	-8	-4
Precentral	4.65	56	-2	34	R. thalamus	3.78	-6	-2	-2
Supramarginal	4.10	60	-24	24	Brainstem	3.69	2	-26	-16
Postcentral	4.08	48	-14	28	L. thalamus	3.54	0	-28	2
Insula	3.89	42	-8	4	R. VL thalamus <sup>a</sup>	3.24	-12	-12	8
Postcentral	3.82	54	-12	24	R. DM thalamus <sup>a</sup>	3.21	-4	-22	6
HC vs. SCZ 2 (4,708)	6.15	-66	-26	6	HC vs. SCZ 6 (3,670)	4.98	-36	18	-4
Superior temporal	6.14	-66	-26	6	Insula	4.98	-36	18	-4
Precentral	5.45	-56	2	30	Frontal pole	4.58	-30	56	22
Supramarginal	5.34	-48	-36	36	Frontal orbital	4.49	-38	30	2
Planum temporale	5.27	-56	-28	12	Insula	4.19	-30	20	2
Planum temporale	5.23	-56	-28	16	Frontal pole	3.94	-28	62	12
Heschl's gyrus	4.86	-50	-18	6	Inferior frontal	3.90	-52	14	2
HC vs. SCZ 3 (1,678)	4.68	56	-2	34	HC vs. SCZ 7 (7,854)	5.70	36	22	-4
Precentral gyrus	4.68	56	-2	34	Insula	5.70	36	22	-4
Supramarginal	4.45	62	-44	24	Insula	5.28	34	22	2
Supramarginal	4.05	60	-24	24	Insular cortex	5.27	34	18	0
Postcentral	3.91	48	-14	28	Paracingulate	4.87	8	28	30
Postcentral	3.77	64	-18	34	Middle frontal	4.60	40	34	24
Postcentral	3.75	54	-12	24	Inferior frontal	4.49	50	16	0
HC vs. SCZ 4 (4,117)	6.09	-66	-26	6	HC vs. SCZ 8 (11,198)	4.73	-44	-60	46
Superior temporal	6.09	-66	-26	6	Lateral occipital	4.73	-44	-60	46
Precentral	5.45	-56	2	30	Supramarginal	4.62	58	-52	34
Supramarginal	5.39	-48	-36	36	Posterior cingulate	4.59	6	-34	28
Planum temporale	5.27	-56	-28	12	Posterior cingulate	4.58	4	-30	40
Parietal operculum	5.16	-56	-28	18	Supramarginal	4.54	56	-50	30
Postcentral	4.89	-42	-30	48	Cuneal cortex	4.46	-10	-76	32

Regions identified using the Harvard-Oxford cortical/subcortical atlas. <sup>a</sup>Subthalamic nuclei identified using the TD Brodmann atlas. HC = Healthy controls; SCZ = schizophrenia.

gyrus and lateral occipital cortex as well as right hippocampus and left cuneal cortex. There were no regions where activity in response to the target tone was greater in the schizophrenia group than in controls.

#### Whole-Brain Correlation with Clinical Symptoms

Whole-brain voxel-wise correlation was performed between the BOLD response to targets and negative symptom scores within the schizophrenia group. This analysis was carried out for total negative symptom severity and for each of five negative symptoms: flat affect, alogia, anhedonia/asociality, avolition/apathy and attention. This allowed us to characterize symptoms correlations throughout the brain.

The total severity of negative symptoms was negatively correlated with target-related BOLD activity in several

clusters. These clusters (fig. 2a, table 3) are located in the right hippocampus, amygdala, superior temporal cortex, fusiform, and thalamus; left middle frontal gyrus and lateral parietal cortex; and bilateral insula, cuneus, and posterior cingulate.

Flat affect did not correlate with any voxels in the analysis; however, voxels in several brain regions were negatively correlated with severity of anhedonia/asociality, alogia and/or avolition/apathy. Regions showing a negative correlation with the severity of anhedonia/asociality (fig. 2b) are similar to those seen for total negative symptoms and include the right amygdala, hippocampus, and superior temporal gyrus; left post-central gyrus and middle frontal gyrus; and bilateral thalamus, including the dorsal medial and ventral lateral nuclei, insula, fusiform gyrus, cuneus, precuneus and lateral occipital cortex. Re-

**Table 3.** Statistically significant cluster locations and their respective local maxima in correlation with clinical symptoms

Cluster (voxels)	Z-stat.	-X	Y	Z	Cluster (voxels)	Z-stat.	X	Y	-Z	Cluster (voxels)	Z-stat.	X	Y	Z
T. Neg. 1 (700)	3.67	62	-6	2	T. Neg. 5 (6,656)	5.04	-36	-8	-4	AnAs 3 (1,122)	4.49	-36	-4	-2
Sup. temporal	3.67	62	-6	2	Insular cortex	5.04	-36	-8	-4	Insula	4.49	-36	-4	-2
Mid. temporal	3.65	60	-4	-12	-	4.67	-26	-24	4	-	4.19	-24	-28	6
Mid. temporal	3.63	66	-24	-16	L. DM thalamus <sup>b</sup>	4.53	6	-14	2	-	4.18	-26	-24	4
Mid. temporal	3.44	60	-10	-22	L. thalamus	4.29	10	-12	0	Insula	4.14	-38	-20	-2
Sup. temporal	3.34	50	-26	0	P. cingulate	4.16	2	-28	28	Insula	4.00	-36	-2	-12
Sup. temporal	3.18	54	-20	-4	L. thalamus	4.07	22	-32	0	Central opercular	3.71	-40	10	4
T. Neg. 2 (828)	3.95	32	-56	-16	AL 1 (2,280)	4.25	-24	-22	6	AnAs 4 (17,540)	5.10	36	-4	10
T-O fusiform	3.95	32	-56	-16	-	4.25	-24	-22	6	Insula	5.10	36	-4	10
Temp. fusiform	3.75	22	-46	-22	R. thalamus	4.12	-4	-16	16	Temp. fusiform	5.04	24	-48	-22
T-O fusiform	3.54	20	-50	-16	L. caudate <sup>a</sup>	3.99	16	14	18	Occ. fusiform	4.88	28	-70	-16
T-O fusiform	3.44	22	-58	-12	L. putamen <sup>a</sup>	3.94	22	12	12	Cuneus	4.82	6	-82	36
Lat. occipital	3.05	38	-76	-12	Brainstem	3.85	-14	-40	-40	Insula	4.61	36	20	0
Occ. fusiform	2.99	30	-64	-14	R. caudate <sup>a</sup>	3.83	-14	0	12	T-O fusiform	4.55	-34	-50	-22
T. Neg. 3 (853)	3.88	-38	50	10	AnAs 1 (753)	3.95	-60	-12	28	AvAp 1 (708)	3.80	2	-36	36
Frontal pole	3.88	-38	50	10	Postcentral	3.95	-60	-12	28	P. cingulate	3.80	2	-36	36
Frontal pole	3.87	-40	44	12	Heschl's gyrus	3.71	-56	-10	4	P. cingulate	3.40	8	-20	26
Frontal pole	3.33	-24	44	22	C. opercular	3.41	-56	-10	10	-	3.21	14	-42	22
Frontal pole	3.27	-34	38	38	Supramarginal	3.28	-58	-42	24	Precuneus	3.17	-16	-36	42
Frontal pole	3.21	-38	48	28	C. opercular	3.25	-52	-12	16	-	3.08	16	-26	30
Frontal pole	3.12	-32	60	-4	Supramarginal	3.21	-66	-38	34	Middle cingulate <sup>a</sup>	3.03	8	-18	32
T. Neg. 4 (1,625)	3.93	4	-82	34	AnAs 2 (1,118)	4.51	-38	44	12	AvAp 2 (991)	3.66	16	-78	22
Cuneus	3.93	4	-82	34	Frontal pole	4.51	-38	44	12	Cuneus	3.66	16	-78	22
Precuneus	3.68	-2	-68	64	Frontal pole	4.03	-36	50	8	Precuneus	3.34	14	-52	12
Cuneus	3.42	-2	-86	18	Frontal pole	3.84	-34	40	36	Occipital fusiform	3.33	28	-68	-4
Precuneus	3.35	2	-84	46	Frontal pole	3.42	-44	36	14	-	3.27	30	-46	10
Cuneal cortex	3.21	16	-78	22	Frontal pole	3.33	-40	40	26	Intracalcarine	3.14	26	-74	8
Lat. occipital	3.13	-10	-64	70	Frontal pole	3.32	-32	56	4	Occipital fusiform	3.11	30	-78	-6

Regions identified using the Harvard-Oxford cortical/subcortical atlas. <sup>a</sup> Regions identified using the Automated Anatomical Labeling atlas. <sup>b</sup> Subthalamic nuclei identified using the TD Brodmann atlas. - = Atlases gave no clear identification.

gions showing a negative correlation with the severity of alogia (fig. 2c) include right caudate, left pallidum, bilateral thalamus and posterior cingulate. Regions showing a negative correlation with the severity of avolition/apathy symptoms (fig. 2d) include right fusiform gyrus, right precuneus, bilateral cuneus and posterior cingulate.

## Discussion

Consistent with previous auditory oddball findings, we found that participants with schizophrenia had decreased functional activation throughout the brain in response to the target tone [28, 41]. These decreases were found in the frontal, insular, cingulate and parietal cortex as well as several subcortical structures including the thal-

amus, caudate and hippocampus. As the frontoparietal, frontolimbic and frontostriatal networks are important in executive functions, this diminished activation is consistent with known impairments in schizophrenia [21, 28]. These findings were similar to those of Kim et al. [21], who found significant between-group differences in components that included dorsolateral prefrontal cortex, anterior cingulate, thalamus, insula, inferior and superior parietal lobules, medial occipital visual regions, middle and superior temporal auditory regions, posterior cingulate and precuneus.

In contrast, there was no significant difference in behavioral performance between groups on this task. The auditory oddball literature is mixed, with some studies reporting behavioral differences between groups [22, 42] and others finding no difference [28, 41]. The absence of



group differences in behavior suggests that the observed differences in functional activation are not a consequence of performance, but instead may reflect underlying pathology of schizophrenia, such as a compensatory mechanism or altered baseline function.

Group differences in functional activation during auditory oddball tasks are well established [21, 30, 43], but little is known about the relationships between auditory oddball task activation and symptom severity. Our results revealed a significant relationship between BOLD activity in response to the target tone and the severity of total negative symptoms, alogia, avolition/apathy and anhedonia/asociality. Overall, increasing symptom severity corresponded with decreased BOLD activation. These findings contrast with some previous studies [30] that reported the absence of a relationship between BOLD response to targets and negative symptom severity as measured by total SANS. This discrepancy may be attributed to that study's smaller sample size. On the other hand, the authors did find a relationship between symptom severity and BOLD activation to novel stimuli, which were not included in our oddball task.

Total negative symptoms were correlated with activity in subcortical regions, including bilateral thalamus and limbic regions such as the right hippocampus and right amygdala. Cortical regions that were correlated included bilateral insula, left middle frontal gyrus, left lateral parietal cortex, right superior temporal cortex, right fusiform, bilateral cuneus and posterior cingulate. These regions suggest the involvement of several networks, including the limbic system and frontoparietal attention networks, but also possibly implicating early sensory networks as well.

The severity of anhedonia/asociality was correlated with activity in a qualitatively similar set of regions as total negative symptoms. Higher symptom severity was associated with lower BOLD response to the target tone in limbic areas such as the right amygdala, right hippocampus, bilateral thalamus and bilateral insula; in higher-order cognitive regions such as the left middle frontal gyrus; in DMN regions such as the bilateral precuneus; and in early sensory regions including bilateral fusiform gyrus, bilateral cuneus, bilateral lateral occipital cortex, left post-central gyrus and right superior temporal gyrus. Rather than being an inability to experience pleasure, anhedonia in schizophrenia seems to be related to decreased prediction of pleasure [44, 45]. While this study did not use a reward paradigm, decreased BOLD activity in ventromedial prefrontal cortex and ventral striatum have been observed in people with schizophrenia during the perfor-

mance of reward tasks [44]. In the context of our study, decreased activity in brain regions involved in the formation of hedonic memories, such as the hippocampus and other limbic areas such as the amygdala and insula, may underlie a general inability to predict pleasure. We also found a negative correlation between anhedonia/asociality and activity in the posterior cingulate and precuneus, which are typically considered to be part of the DMN. The DMN is thought to be a task-negative network that is reciprocally connected to a variety of other 'task-positive' networks such as those involved in executive and sensory processing [46]. Several studies have shown that patients with schizophrenia have increased DMN activity during the completion of neurocognitive tasks, which may reflect an inability to turn the DMN 'off' [47, 48]. Our findings seemingly contradict the expectation that symptom severity would be positively correlated with DMN activity during task performance. This may be because most previous studies compared task activation with non-task activation, whereas our data result from contrasts between standard and target tones (task vs. task).

Unfortunately, patient medication data were not available in the FBIRN dataset and so were not included in these analyses. This makes it difficult to discern whether the negative symptoms experienced by the patient group were primary or secondary in nature. However, the participants were all clinically stable, so we can expect that secondary negative symptoms due to acute psychosis were minimal.

Importantly, the activity patterns for alogia and avolition/apathy differed from those that correlated with total negative symptom severity. Severity of alogia was associated with decreased activity in the bilateral thalamus, right caudate and left pallidum. These regions are key components of the basal ganglia and their involvement here suggests that alogia symptom severity may reflect deficits in the ability to engage in voluntary motor behavior. We might, however, expect that avolition/apathy would be related to this circuitry as well, but instead it was associated with activity in the right precuneus and bilateral posterior cingulate, which are thought to be involved in the DMN, as well as regions typically thought to be involved in visual processing, including the bilateral cuneus and the right fusiform gyrus. While it is difficult to explain the involvement of the cuneus and the fusiform gyrus, the involvement of the posterior cingulate may be similar to its involvement in anhedonia/asociality symptoms.

Most importantly, we found that some individual negative symptoms were associated with a different pattern of functional activity than total negative symptoms. The

severities of alogia and avolition/apathy were both associated with patterns of activation that were qualitatively different from each other and from total negative symptoms. Anhedonia/asociality, on the other hand, was associated with a pattern that was nearly identical to total negative symptoms, suggesting that this symptom domain may have dominated our sample. However, severity of anhedonia/asociality was not greater than other symptom categories in our sample, nor was it more strongly associated with the severity of total negative symptoms. It may also be the case that these individual negative symptoms are not truly equal in terms of how closely related they are to the core etiology of schizophrenia. In the context of the two-factor model of negative symptoms [11–14], our results suggest a relationship between elements of the ‘avolition’ factor and functional activation during the oddball task. Alogia was the only component symptom of the ‘emotional expressiveness’ factor to be found to be correlated with functional activation in this study. This may be expected given the lack of emotional content in the auditory oddball task. Furthermore, alogia may load onto both factors [11], and in this context, we may be seeing neural activity related to the ‘avolition’ aspects of alogia rather than problems with emotional ‘expressiveness’. Interestingly, our findings suggest distinct correlations between functional activation and avolition/apathy and anhedonia/asociality. This, along with our failure to identify any voxels that were significantly correlated with the

combined anhedonia factors, underscores the notion that even though symptoms may be highly interrelated clinically, that they do not necessarily share the same neurobiological underpinnings.

In either case, our findings suggest that the use of broad global symptom dimensions may be counterproductive when seeking to characterize higher-order functions. Instead, the use of subdimensions may be a more appropriate target for research. However, it is likely that global domains such as total negative symptom severity will remain useful for clinical and phenomenological purposes, as these negative symptoms tend to co-occur. Our clinical findings certainly echo previous findings by demonstrating that the severities of these clinical symptoms are highly correlated. All five individual symptom categories exhibited a robust correlation with total severity, as one might expect. Attention deficits were less strongly associated with total negative symptoms and with the other five categories, suggesting, as some do [49], that attention deficits may be categorized separately from negative symptoms. Finally, as most individuals lacked any given individual symptom domain from the SANS, the distribution of symptom severity ratings was not normally distributed. From a research perspective, this suggests that targeted enrollment or large samples may be needed in order to carry out research on these individual symptom categories, as a large fraction of patients will be asymptomatic for any given domain.

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