Differential sensory fMRI signatures in autism and schizophrenia: Analysis of amplitude and trial-to-trial variability

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1. Introduction

Autism and schizophrenia share multiple phenotypic and genotypic markers, and there is ongoing debate regarding the relationship of these two disorders. To examine whether cortical dynamics are similar across these disorders, we directly compared fMRI responses to visual, somatosensory and auditory stimuli in adults with autism (N = 15), with schizophrenia (N = 15), and matched controls (N = 15). All participants completed a one-back letter detection task presented at fixation (to control attention) while task-irrelevant sensory stimulation was delivered to the different modalities. We focused specifically on the response amplitudes and the variability in sensory fMRI responses of the two groups, given the evidence of greater trial-to-trial variability in adults with autism. Both autism and schizophrenia individuals showed weaker signal-to-noise ratios (SNR) in sensory-evoked responses compared to controls (d = 0.42), but for different reasons. For the autism group, the fMRI response amplitudes were indistinguishable from controls but were more variable trial-to-trial (d = 0.47). For the schizophrenia group, response amplitudes were smaller compared to autism (d = 0.44) and control groups (d = 0.74), but were not significantly more variable (d < 0.29). These differential group profiles suggest (1) that greater trial-to-trial variability in cortical responses may be specific to autism and is not a defining characteristic of schizophrenia, and (2) that blunted response amplitudes may be characteristic of schizophrenia. The relationship between the amplitude and the variability of cortical activity might serve as a specific signature differentiating these neurodevelopmental disorders. Identifying the neural basis of these responses and their relationship to the underlying genetic bases may substantially enlighten the understanding of both disorders.

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et al., 2000; Schneider et al., 1998) and in fusiform gyrus (autism: Hall et al., 2003; Pierce et al., 2001; Schultz et al., 2000; schizophrenia: Quintana et al., 2003; Streit et al., 2001).

Despite abnormal sensory behavior being a key commonality, there are differential cortical dynamics of sensory responses. The majority of sensory fMRI studies in schizophrenia have reported weaker activation (i.e. weaker signal-to-noise ratios, SNR) in sensory cortices (Silverstein et al., 2009; Gaebler et al., 2015; Kircher et al., 2004; Woodruff et al., 1997). Autism individuals show either greater (Green et al., 2015; Kaiser et al., 2015; Takarae et al., 2014; Green et al., 2013) or weaker fMRI activation compared to healthy controls (Dinstein et al., 2012; Haigh et al., 2014; Cascio et al., 2012). Very few studies have compared the two groups directly under identical conditions. Doing so is critical to reach definitive conclusions about transdiagnostic similarities between the groups.

We have shown perturbations in neural processing in autism in response to sensory stimuli (Dinstein et al., 2012; Haigh et al., 2014). Relative to matched controls, autism individuals evinced greater trial-to-trial variability in fMRI responses, despite responses being indistinguishable in amplitude, resulting in weaker SNRs. Greater variability has been reported in the amplitude and latency of P1 ERP responses to visual stimuli (Milne, 2011). There are similar reports in schizophrenia (Jordanov et al., 2011; Müller et al., 1986), which could potentially contribute to smaller average responses (Iyer et al., 2011). Greater trial-to-trial variability may be the result of an imbalance between neural excitation and inhibition, which is associated with autism (Jamain et al., 2002; Markram et al., 2007; Vattikuti and Chow, 2010; Rubenstien and Merzenich, 2003; Sigurdsson, 2015; Uhlhaas, 2013; Lisman, 2012), and with schizophrenia (Baron-Cohen et al., 2009; Gomot et al., 2002; Simmons et al., 2009). One hypothesis is that there is excess excitation due to either increased glutamatergic activity, or reduced GABAergic signaling. The neural variability may be correlated across time and clusters of neurons, thereby affecting the fMRI signal. Variability in sensory responses could impact more complex information processing: if the individual is unable to gain reliable information about their surroundings, then this might make complex environments like social situations confusing and potentially over-whelming, leading to social withdrawal (Dinstein et al., 2015).

Greater trial-to-trial variability offers a potential signature of the cortical response in autism and the key question is whether greater variability in sensory-evoked activity is specific to autism, or is apparent in schizophrenia as well. If the latter, this would offer a transdiagnostic endophenotype related to the sensory abnormalities seen in autism and schizophrenia, and may relate to their shared genetic markers. Differences in response variability across the two groups would alternatively indicate that the overt manifestation of the underlying neurobiology may differ or be differentially modulated by environmental or other genetic factors.

2. Methods and materials

2.1. Participants

Ten males and five females (mean age 26, range 19–34 years) with schizophrenia or schizoaffective disorder (diagnosed using the Structured Clinical Interview for DSM-IV (First et al., 2005) and the Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986)) by an expert diagnostician participated in a 90-minute study and were paid $75 for their time (see Table 1 for demographics). Fourteen of the individuals with schizophrenia were taking antipsychotics (average chlorpromazine equivalent was 255 mg, SD 306 mg) (see Supplementary Materials for more information on medication use).

Data from twelve male and three female age-matched individuals with autism (mean age 26, range 19–36 years), and eleven male and four female typical controls (mean age 27, range 20–40 years) were included in this study, and were previously reported (Dinstein et al., 2012; Haigh et al., 2014). Participants were chosen according to closest match to the schizophrenia group on age. All of the individuals with autism were Caucasian and met the DSM-IV criteria for autism based on the Autism Diagnostic Observation Schedule (ADOS-G) (Lord et al., 2000) and Autism Diagnostic Interview (ADI) (Le Couteur et al., 1989; Lord et al., 1994). These assessments were carried out at the Center For Excellence in Autism Research, at the University of Pittsburgh (see Table 2 for demographics) and confirmed by expert opinion (NJM). One individual with autism was taking antipsychotic medication, and six were taking antidepressants (see Supplementary Materials).

All autism and schizophrenia participants had an IQ above 88, had normal or corrected-to-normal vision, and gave their written consent to take part in the study. The Institutional Review Boards at Carnegie Mellon University (CMU) and the University of Pittsburgh approved the experimental procedures, which were in compliance with the safety guidelines for MRI research, and the individuals with autism consented to the use of their data in this study.

2.2. Experimental design

The design of the experiment was identical to that described previously (Dinstein et al., 2012; Haigh et al., 2014). Participants took part in a single fMRI session in which neural responses to visual, auditory and somatosensory stimuli were measured in separate runs following an event-related design (see Fig. 1 for example of visual display and the timing of a single trial). Participants were presented with 72 trials for each of three sensory modalities over two runs, which were blocked and the blocks were randomly interleaved across modality. For each modality, the trial began with an adapter followed by a test stimulus. Adapters were either 2 circular apertures containing 500 white dots each (visual), 11 air puffs directed to the back of the left hand (somatosensory), or eleven pure tone beeps (auditory). The test stimuli were either identical to the adapters (the adapted condition); different from the adapter (the unadapted condition) in motion direction (visual), body location (location on left hand, somatosensory); or tone frequency (auditory); or no test was presented (the no-test condition).

During the sensory stimulation, participants were asked to complete a one-back task which was orthogonal (and irrelevant) to the sensory stimuli. This ensured that any sensory differences between groups were not a function of differential attention. Participants were instructed to attend to a sequence of letters and identify immediate repetitions. The letters, shown in lower case, were presented at fixation throughout each block of trials, one at a time and changed every 500 ms. Participants used their right index finger to indicate when a repetition was noted. Participants had 1 s to respond and received...
feedback (correct response – fixation green; incorrect response – fixation red). Misses were not indicated.

2.3. Data Acquisition

All data were collected on the same 3T Siemens MRI scanner at CMU. Six functional (two per sensory modality) and one anatomical scan were acquired per participant. The scanner was equipped with a Siemens 12 channel birdcage head coil, which was used for RF transmit and receive. Functional images were acquired with a T2*-sensitive echo planar imaging pulse sequence (repetition time = 1500 ms, echo time = 30 ms, flip angle = 75°, 24 slices, 3 × 3 × 3 mm voxels, field of view = 192 mm). Anatomical volumes were acquired with a T1-weighted 3D-MPRAGE pulse sequence (1 × 1 × 1 mm).

2.4. Data analysis

fMRI data were preprocessed using Brain Voyager, in-house software written in Matlab (Mathworks, Natick, MA) and the NeuroElf toolbox (http://neuroelf.net/, JW). Preprocessing included 3D motion correction, temporal high-pass filtering with a cutoff frequency of 6 cycles per scan, spatial smoothing using a Gaussian kernel with 8 mm width at half height, alignment with the anatomical volume using trilinear interpolation, and transformation to the Talairach coordinate system (Talairach and Tournoux, 1988). Scans containing head movements in excess of 2 mm (approximately 7% of scan volumes) were excluded from data analysis. Voxel intensity was corrected for the residual motion, by regressing the head motion on the fMRI responses and then using the residuals to calculate the adjusted fMRI responses. There was no significant difference in the amount of head motion between the autism, schizophrenia and control groups (see Supplementary Materials, Fig. S1).

Individual regions of interest (ROIs) were created by identifying the 200 most significant voxels within the relevant sensory area of the cortex bilaterally for each participant. This ensured that ROI size was equivalent across participants and across modalities (see Fig. S2 for activation maps, which appeared to be similar across groups), and was consistent with previous studies (Dinstein et al., 2012; Haigh et al., 2014). The response from each hemisphere was analysed. The first functional scan from each sensory modality was used to define these
bilateral ROIs, unless the scan was removed from analysis due to excess motion artefact (see head motion section) in which case the remaining scan was used to define the ROIs. Responses from both runs were analysed.

An epoch of the fMRI time series, for each voxel in the ROI, was then extracted from adapter-onset to 12 s (8 time-points) after adapter-onset. Response amplitudes were calculated, separately for each trial, by averaging the responses at time-points 4 and 5, which corresponded to the peak of the haemodynamic response. Response standard deviations (SD) were calculated by averaging the response across time-points 3–6 (to capture the peak of the fMRI response, while retaining a more accurate measure of response variability), separately for each trial, and then computing the SD across trials. SNRs were calculated by dividing the response amplitudes by the response variances. We also performed complementary randomization tests to assess differences between groups without assuming normal distributions, and an additional regression analysis using a general linear model to utilize more of the data rather than just the peak of the fMRI response (see Supplementary Materials). The responses from the no-test condition (12 no-test presentations per scan) were used for the main analysis. The results were similar (see Supplementary Materials).

Effect sizes were calculated for group differences in fMRI response amplitude, SDs and SNR, using the following formula:

\[
d = \frac{\text{Mean}_1 - \text{Mean}_2}{SD_{\text{pooled}}} = \sqrt{\frac{(N_1 - 1)SD_{G1}^2 + (N_2 - 1)SD_{G2}^2}{N_1 + N_2}}
\]

Formula 1. Calculations for Cohen’s d effect size for each group comparison. \(N\) = number of observations; \(SD\) = standard deviation; \(G_1\) = group 1, \(G_2\) = group 2.

3. Results

Mixed analyses of variance were conducted separately for the fMRI response amplitudes, the SD in fMRI responses and the SNR, and separately for each pairwise group comparison. Sensory modality served as the within-subjects variable (responses from visual, somatosensory and auditory ROIs) and group served as the between-subjects variable (responses from visual, somatosensory and auditory ROIs) and group served as the between-subjects variable (responses from visual, somatosensory and auditory ROIs) and group served as the between-subjects variable (responses from visual, somatosensory and auditory ROIs). 

For all analyses, there was a significant main effect of sensory modality, due to the smaller fMRI responses, smaller variability, and weaker SNRs in the somatosensory modality. Significant interactions between modality and group are highlighted and are of key interest.

3.1. fMRI analyses

Individuals with autism produced statistically indistinguishable fMRI response amplitudes compared to controls (Fig. 2A; \(F(1,21) = 0.60, p = 0.446; d = 0.17\)). However, individuals with schizophrenia produced smaller fMRI amplitudes compared to controls (\(F(1,23) = 11.68, p = 0.002; d = 0.74\)), and marginally smaller amplitudes compared to autism (\(F(1,22) = 4.01, p = 0.058; d = 0.44\)).

The SD of the fMRI response were greater in autism compared to controls (Fig. 2B; \(F(1,21) = 4.58, p = 0.044; d = 0.47\)), but there was no significant difference between autism and schizophrenia on SD \((F(1,22) = 1.64, p = 0.213; d = 0.17)\), or between controls and schizophrenia \((F(1,23) = 0.59, p = 0.451; d = 0.28)\).

There was no significant difference between schizophrenia and autism in SNR (Fig. 2C; \(F(1,22) = 0.04, p = 0.842; d = 0.04\)). Both autism and schizophrenia exhibited smaller SNRs than controls (autism versus controls: \(F(1,21) = 4.20, p = 0.053; d = 0.45\); schizophrenia versus controls: \(F(1,23) = 4.35, p = 0.048; d = 0.45\)). The smaller SNR in autism was due to the greater variability in fMRI responses, whereas, the smaller SNR in schizophrenia was due to the smaller response amplitudes.

Analysis of the responses in the adapted and unadapted trials yielded qualitatively similar results (Supplementary Materials). Because the individuals with schizophrenia showed consistently smaller fMRI response amplitudes compared to controls, any differences in SD in fMRI responses between groups might be difficult to interpret. In particular, if the variance increases with the mean fMRI response (a Poisson distribution), then any difference in SD might be a direct consequence of the difference in response amplitudes. To circumvent this potential confound, fMRI response amplitudes were equated across groups by selecting individuals from the groups who were closely matched on overall amplitude \((N = 10\) in each group). Individuals with autism still exhibited greater SD in fMRI responses than controls \((F(1,18) = 8.05, p = 0.011)\), but there was still no significant difference between autism and schizophrenia on SD in fMRI responses \((F(1,18) = 0.76, p = 0.394)\), or schizophrenia and control groups \((F(1,18) = 2.74, p = 0.115)\; \text{see Supplementary Materials for further analyses}\).

The randomization test and the regression analysis showed similar results to the trial-triggered analyses, except that individuals with autism still exhibited greater SD in fMRI responses than controls \((F(1,18) = 8.05, p = 0.011)\). There was no significant difference between schizophrenia and autism in SNR (Fig. 2C; \(F(1,22) = 0.04, p = 0.842; d = 0.04\)). Both autism and schizophrenia exhibited smaller SNRs than controls (autism versus controls: \(F(1,21) = 4.20, p = 0.053; d = 0.45\); schizophrenia versus controls: \(F(1,23) = 4.35, p = 0.048; d = 0.45\)). The smaller SNR in autism was due to the greater variability in fMRI responses, whereas, the smaller SNR in schizophrenia was due to the smaller response amplitudes.

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schizophrenia did not exhibit significant differences in response amplitudes compared to controls ($F(1,15) = 0.10, p = 0.761$) or individuals with autism ($F(1,17) < 0.01, p = 0.993$; Supplementary Materials, Fig. S4). We discuss the apparent inconsistency in the outcome of these two analyses below.

There was no significant correlation dosage between antipsychotic medication and fMRI responses in the schizophrenia group, and no significant effect of antidepressants on responses in the autism group (see Supplementary Materials for details). There were also no significant correlations between IQ and amplitude, SD or SNR for the autism or the schizophrenia group ($p > 0.05$).

### 3.2. Behavioral responses

One possible explanation for the group differences in fMRI responses is that certain groups might have been more attentive/variable over time. If the former, then we would expect to see poorer response accuracy and/or slower reaction times (RT) in behavioral responses. If the latter, then we would expect to see more variable RT. We measured performance accuracy and RT on the letter repetition detection task at fixation, as a proxy for attention (Fig. 3).

There were no significant differences in accuracy (% correct), or in mean RT to the repeated letter between autism, schizophrenia and control groups (see Supplementary Materials for statistical comparisons). Individuals with schizophrenia, however, exhibited significantly greater trial-to-trial variability in RT compared to controls ($F(1,23) = 9.52, p = 0.005$), but not compared to autism ($F(1,24) = 2.14, p = 0.156$), and there was no significant difference between autism and controls ($F(1,23) = 2.68, p = 0.114$). There were also no significant correlations between SDs in RT and fMRI responses that were consistent across the sensory modalities (see Supplementary Materials).

The greater trial-to-trial variability in RT in the schizophrenia group might suggest that their attentional state may have been more variable. But there was no evidence for greater variability in the fMRI responses from the schizophrenia group. Hence, these findings do not indicate that the differences in fMRI responses between groups were due to differences in attention or performance per se.

### 4. Discussion

This investigation was designed to characterize sensory fMRI responses in autism and schizophrenia, which is critical given questions about their common pathophysiology. Compared to controls, both autism and schizophrenia produced weaker SNRs (somatosensory responses were weaker in amplitude across the board, potentially yielding a floor effect for somatosensory SNR). For autism, weaker SNR arose from greater trial-to-trial variability in fMRI responses (in particular, for visual and auditory responses) while the amplitude was indistinguishable from controls. For schizophrenia, weaker SNR arose from smaller fMRI amplitudes, while trial-to-trial variability was indistinguishable from autism and control groups. These results hold across a number of analytic approaches, and could not be attributed to differences in behavioral responses, motion artifacts during scanning, nor to medication. Together, these findings provide differential signatures of cortical activation in autism versus schizophrenia.

One potential concern about this study is the small sample size (15 participants per group), which may result in the analyses being under-powered or the findings difficult to replicate. First, the greater trial-to-trial variability in autism, originally reported by Dinstein et al. (2012), was subsequently replicated (Haigh et al., 2014), and the current study shows a medium effect size (Cohen, 1988). Second, the effect size for differences in trial-to-trial variability between schizophrenia and autism or control groups was small, so it is unlikely that increasing the sample size would yield different findings. A power analysis of the largest group effect size that was not significant ($d = 0.28$) would require at least 200 participants in each group to have 90% power in the results (Faul et al., 2007, 2009). Third, a number of analyses were conducted, including non-parametric randomization tests, to confirm that the findings were not an artefact of the analysis. Therefore, it is unlikely that these results were confounded by the small sample size. Finally, we note that the reduction in response amplitude in the schizophrenic participants was only evident in the trial-triggered analyses and not in the regression analysis. While this inconsistency suggests that the finding of a reduction in response amplitude in schizophrenia ought to be treated with caution, many existing studies have demonstrated such a result in sensory cortices spanning MRI and EEG/ERP methodologies (Silverstein et al., 2009; Gaebler et al., 2015; Kircher et al., 2004; Woodruff et al., 1997; Umbricht and Krljes, 2005; Salisbury et al., 2009). The robust evidence of hypo-activation in schizophrenia confirms that our observation of reduced amplitude in schizophrenia in this study is likely to be valid.

The finding of a differential signature across the two conditions suggests that a consideration of both the variability and the amplitude of sensory fMRI responses might be useful in differentiating the sensory

![Fig. 3. Behavioral performance from the autism, schizophrenia and control group. (A) Accuracy, the percent of letter repeats that were correctly identified. (B) Reaction time. (C) Standard deviation in reaction times. Error bars show one standard error.](http://dx.doi.org/10.1016/j.schres.2016.03.036)
cortical dynamics characteristic of autism and schizophrenia. The reduction in response amplitude in schizophrenic participants has been demonstrated in many studies, during visual (Silverstein et al., 2009) and auditory processing (Gaebler et al., 2015; Kircher et al., 2004), particularly in those with auditory hallucinations (Woodruff et al., 1997), and correlates with reduced performance at sensory tasks (Holcomb et al., 2000; Volz et al., 2001; Kim et al., 2011). This hypo-responsiveness has been linked to dendritic toxicity (shorter and fewer dendritic spines, especially in auditory cortex) (Sweet et al., 2008), and abnormalities in PING (Pyramidal Interneuron Network Gamma) circuits (Gonzalez-Burgos and Lewis, 2008; Lewis et al., 2012; Gonzalez-Burgos et al., 2011).

The greater variability may reflect the noise in the sensory systems. Approaches to noise reduction include the use of oxytocin (Owen et al., 2013); oxytocin is lower in autism (Modahl et al., 1998; Wu et al., 2005), and oxytocin-related treatments for autism are on the rise (Kuehn, 2011; Modi and Young, 2012; Gordon et al., 2013). As autism is a neurodevelopmental disorder, the greater variability may affect sensory input throughout development. Human sensory systems learn by detecting statistical regularities in the environment; unreliable sensory signals would make learning more difficult (perhaps leading to the repetitive behavior in autism), and make sensory environments unpredictable, leading to withdrawal from social situations.

In conclusion, both autism and schizophrenia evinced weaker SNRs in sensory fMRI responses compared to controls. However, the profile of the weaker SNRs appeared to differ between the two groups of individuals: autism was associated with greater trial-to-trial variability (perhaps leading to the repetitive behavior in autism), and make sensory environments unpredictable, leading to withdrawal from social situations.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

Sarah M Haigh – helped design and run the study, analysed and interpreted the data, and wrote the manuscript.
Akshat Gupta – recruited the participants, coordinated all involved with the scanning, and helped run the study.
Scott M Barb – recruited the individuals with schizophrenia, helped run the study, and helped with manuscript preparation.
Summer A F Glass – recruited the individuals with schizophrenia, provided demographic and symptom information, and helped with manuscript preparation.
Nancy J Minshew – recruited the individuals with autism, clinically assessed the participants, helped with manuscript preparation and provided comments on the final version.
Ilan Dinstein – helped with data analysis, helped with manuscript preparation and provided comments on the final version.
David J Heeger – helped with the design of the study, data analysis, manuscript preparation and provided final comments on the final version.
Shaun M Eack – recruited the individuals with autism, clinically assessed the participants, helped with manuscript preparation and provided comments on the final version.
Marlene Behrmann – helped with the design of the study, data analysis, manuscript preparation and provided final comments on the final version.

All authors reviewed the manuscript before submission.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2016.03.036.

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