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Social-cognitive brain function and connectivity during visual perspective-taking in autism and schizophrenia

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ABSTRACT

Background: Autism spectrum disorder (ASD) and schizophrenia are neurodevelopmental conditions that are characterized by significant social impairment. Emerging genomic and neurobiological evidence has increasingly pointed to shared pathophysiologic mechanisms in the two disorders. Overlap in social impairment may reflect similar underlying neural dysfunction in social-cognitive brain networks, yet few studies have directly compared brain function and communication between those with ASD and schizophrenia.
Methods: Outpatients with schizophrenia (n = 36), ASD (n = 33), and healthy volunteers (n = 37) completed a visual perspective-taking task during functional neuroimaging at 3T to assess similarities and differences in fronto-temporal brain function and connectivity during social-cognitive processing. Analyses employed general linear models to examine differences in amplitude of BOLD-signal response between disorder groups, and computed functional connectivity coefficients to investigate differences in the connectivity profiles of networks implicated in social cognition.
Results: Despite similar behavioral impairments, participants with ASD and schizophrenia evidenced distinct neural abnormalities during perspective-taking. Functional activation results indicated reduced temporo-parietal junction and medial prefrontal activity in ASD compared to schizophrenia (all $P_{uncor} < 0.002$). Functional connectivity analyses further revealed significantly greater local orbitofrontal connectivity in ASD than schizophrenia (all $P_{FDR} < 0.028$) during perspective-taking. Differences in brain activation and connectivity were unrelated to antipsychotic medication dose.
Conclusions: Autism and schizophrenia are characterized by similar social-cognitive impairments that may stem from different underlying abnormalities in the functional organization and communication of the social brain.

1. Introduction

Autism spectrum disorder (ASD) and schizophrenia are neurodevelopmental conditions that share similarities in some of their cognitive and behavioral manifestations (Kanner, 1965). Although the two disorders emerge at different developmental periods, both are characterized by significant impairments in social behavior and understanding (American Psychiatric Association, 2013). Individuals with these conditions often spend the majority of their adult lives socially isolated (Harrow et al., 2005; Howlin et al., 2013), have few to no significant friendships (Macdonald et al., 2000; Orsmond et al., 2013), and a poor quality of life (Mazurek, 2014; Eack et al., 2007). Brain-based impairments in social cognition, e.g., those abilities that support the processing and interpretation of socio-emotional information in oneself and others (Newman, 2001), have been shown to contribute to some of the interpersonal challenges that characterize ASD and schizophrenia (Wallace et al., 2011; Fett et al., 2011). Further, direct comparisons of social cognition deficits across the two disorders have yielded analogous profiles and impairments of similar magnitude in many (Couture et al., 2010; Eack et al., 2013a, 2013b; Sasson et al., 2016), but not all cases (Sasson et al., 2007), increasingly suggesting the possibility of common underlying mechanisms contributing to social disability in ASD and schizophrenia.

Emerging biological evidence has supported the notion of shared genetic and neural mechanisms across autism and schizophrenia spectra (Cheung et al., 2010; Guilmatre et al., 2009; Radeloff et al., 2014). With respect to studies of brain functions supporting social cognition, a recent meta-analysis of the separate social neuroscience literatures in ASD and schizophrenia indicated that both conditions were characterized by medial-temporal and ventrolateral prefrontal hypoactivity

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during social-cognitive processing (Sugranyes et al., 2011). Pinkham et al. (2007) found similarly reduced brain activity in the amygdala, fusiform gyrus and ventrolateral prefrontal cortex in 12 adults with ASD and 12 adults with paranoid schizophrenia during a trustworthiness task. Ciaramidaro et al. (2015) also found comparable reductions in superior temporal sulcus and ventromedial prefrontal cortex activity during a mentalizing task relative to healthy volunteers among 23 individuals with ASD and 18 patients with paranoid schizophrenia. Furthermore, they extended this work to examine functional connectivity, and found that both autism and schizophrenia were characterized by reduced fronto-temporal (superior temporal sulcus to ventromedial prefrontal cortex) connectivity.

This growing literature suggests that the behavioral overlap in social-cognitive deficits present in ASD and schizophrenia may be due to shared neural mechanisms reflecting reduced coordination and activation of fronto-temporal systems. However, few studies have directly compared social-cognitive brain function in the two disorders, particularly in adequately powered samples. This study sought to examine fronto-temporal brain function and connectivity during a visual perspective-taking task among individuals with ASD, schizophrenia, and healthy volunteers. It was hypothesized that relative to healthy individuals, participants with ASD and schizophrenia would evidence similar reductions in fronto-temporal activity in social-cognitive brain networks during perspective-taking. Further, it was hypothesized that both patient groups would demonstrate reduced functional connectivity between prefrontal and temporal networks previously shown to support perspective-taking in healthy individuals.

2. Method

2.1. Participants

Participants consisted of 36 individuals with schizophrenia or schizoaffective disorder, 33 individuals with ASD, and 37 healthy volunteers. Participants were recruited for brain imaging studies at the University of Pittsburgh and generally included if they were age 18 years or older, had an IQ ≥ 80, and were free from any MRI contraindications. Individuals with schizophrenia (n = 31) or schizoaffective disorder (n = 5) were required to be receiving antipsychotic medication and have their diagnosis verified by the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002). Individuals with ASD were required to meet criteria for autism (n = 17) or autism spectrum disorder (n = 15) based on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989). Healthy individuals were included if they were free from a current psychiatric diagnosis as evaluated using the SCID.

Table 1 provides an overview of demographic and clinical characteristics for the sample. Participants were mostly young adults and predominantly male. No significant differences were observed between study groups with regard to age, race, or IQ. However, fewer individuals with ASD were female, and healthy volunteers had attended more years of education than both patient groups (all $p < 0.001$), with no difference between patients ($p = 0.679$). All individuals with schizophrenia were receiving antipsychotic medication, by design, and 3 individuals with ASD were receiving antipsychotic treatment as part of their routine care. Psychiatric symptomatology was low for all groups, significantly lower for healthy individuals than patients (all $p < 0.001$), and not significantly different between ASD and schizophrenia ($p = 0.580$).

2.2. Visual perspective-taking task

Brain functions supporting visual perspective-taking ability were assessed using a novel paradigm based on a looking-time task developed by Epley et al. (2004) and previously described elsewhere (Eack et al., 2013b). The task requires participants to identify items in a 5 × 5 virtual grid array (see Fig. 1) from the perspective of a confederate (the research assistant). The virtual grid array contains two sides with four occludes, such that items visible from the participant's perspective are not always in view from the perspective of the assistant. Participants were instructed that the research assistant was going to play the game with them from the MRI control room and that because the assistant would only be able to see the back of the array, the participant had to be sure to only select objects that the assistant could see from her perspective. The target object and 8 distractor objects, randomly interspersed, then appeared in the array for each trial. Trials were 8000 ms in length and consisted of a 2500 ms instruction image (e.g., "hand me the bottle"), a 3500 ms task image displaying the grid array and selection options, and a 2000 ms fixed inter-trial interval during which a blank fixation screen was presented. A total of 63 trials were administered in blocks of 7 trials each, which consisted of either randomly interspersed control ($k = 27$) or perspective-taking trials ($k = 36$). Although the task was administered in blocks, it was modeled using an event-related design because of the random interspersion of control and perspective-taking trials within a single block. All conditions asked the participant to complete the same task: select an item in the grid array from the visual perspective of the assistant. During control trials, this

Table 1
Demographic and clinical characteristics of individuals with autism spectrum disorder, schizophrenia, and healthy volunteers.

Variable	HC (N = 37) M (SD)/N (%)	ASD (N = 33) M (SD)/N (%)	SZ (N = 36) M (SD)/N (%)	p[a]
Age	25.41 (4.71)	23.91 (6.05)	26.25 (6.83)	0.257
Female	8 (22%)	3 (9%)	14 (39%)	0.014
Non-white	7 (19%)	4 (12%)	10 (28%)	0.261
Years of education	16.16 (2.70)	14.06 (1.78)	13.83 (2.18)	< 0.001
IQ	106.70 (10.81)	108.36 (14.13)	107.25 (11.90)	0.849
BPRS Total	20.38 (2.45)	32.82 (10.41)	33.86 (8.80)	< 0.001
Anxiety/depression	1.30 (0.39)	2.45 (1.25)	2.53 (0.91)	< 0.001
Withdrawal/motor retardation	1.11 (0.24)	2.09 (0.70)	1.63 (0.88)	< 0.001
Thought disorder	1.17 (0.23)	1.71 (0.64)	2.05 (0.75)	< 0.001
Hostility	1.01 (0.06)	1.36 (0.52)	1.82 (0.74)	< 0.001
ADOS				
Communication	–	3.39 (1.17)	–	–
Reciprocal social interaction	–	7.21 (2.38)	–	–
Stereotyped behavior	–	2.36 (1.34)	–	–
Receiving antipsychotic medication	–	3 (9%)	36 (100%)	–
Receiving second-generation	–	3 (100%)	33 (92%)	–
Chlorpromazine equivalent dose	–	104.17 (83.23)	416.92 (295.26)	0.079

Note. BPRS = Brief Psychiatric Rating Scale (Overall and Gorham, 1962), HC = Healthy control, ASD = autism spectrum disorder, SZ = schizophrenia, ADOS = Autism Diagnostic Observation Schedule.
[a] χ^2 test or analysis of variance, two-tailed, for significant differences between study groups.

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