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Neural Circuit Disruptions of Eye Gaze Processing in Autism Spectrum Disorder and Schizophrenia: An Activation Likelihood Estimation Meta-Analysis

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Abstract

Impairment in social cognition, particularly eye gaze processing, is a shared feature common to autism spectrum disorder (ASD) and schizophrenia. However, it is unclear if a convergent neural mechanism also underlies gaze dysfunction across these conditions. The present study examined whether this shared eye gaze phenotype is reflected in a profile of convergent neurobiological dysfunction in ASD and schizophrenia. All fMRI experiments were published between January 1990 and December 2021. Experiments were selected comparing brain responses across domains of gaze processing for ASD or schizophrenia vs healthy controls and reporting whole-brain findings. Fifty-nine experiments from 36 articles met inclusion criteria. Activation likelihood estimation (ALE) meta-analyses were conducted on peak voxel coordinates to identify spatial convergence across disorders. Functional coactivation was conducted with regions emerging as significant using meta-analytic connectivity modeling. Functional decoding was also conducted. The 59 experiments from 36 articles included 629 patients (ASD, schizophrenia) and 613 healthy controls (1242 participants). Across disorders, aberrant activation was found in the right inferior frontal gyrus and right fusiform gyrus during gaze processing. Functional decoding mapped the right inferior frontal gyrus to domains related to cognition and perception, and the right fusiform gyrus to visual perception, spatial cognition, and emotion perception. These regions also showed meta-analytic connectivity to frontoparietal circuitry. Aberrant activation in frontotemporal and frontoparietal circuitry emerged as convergent neural markers in ASD and schizophrenia across domains of gaze processing. These findings have implications for advancing transdiagnostic brain biomarkers to inform diagnosis and targeted treatments for ASD and schizophrenia.

Introduction

Autism spectrum disorder (ASD) and schizophrenia share overlapping clinical symptoms of impairments in social cognitive functioning[1–5], despite broad differences in symptom presentations, ages of onset, and developmental courses. There is also emerging evidence to suggest that social cognitive impairment, such as face and eye gaze perception, is a potential marker for ASD and schizophrenia[1]. For instance, a recent meta-analysis showed similar levels of social cognitive impairment during emotion and eye gaze processing tasks in individuals with ASD and schizophrenia[6]. Given the interest in cross-disorder or transdiagnostic research on social cognition that is consistent with the NIMH Research Domain Criteria framework—which prioritizes circuits and systems for improving functional outcome—examination of social cognitive functioning across ASD and schizophrenia can advance understanding of convergent neural disruptions in social cognitive circuitry that may lead to related but distinct diagnostic presentations[7–9]. Thus, identification of shared neural disruptions across ASD and schizophrenia has potential to contribute to development of brain-based biomarkers to inform screening/early detection, diagnosis, and targeted-treatments support[9, 10]. Here, the current study investigates underlying, convergent neural markers of social cognitive functioning in ASD and schizophrenia across domains of eye gaze processing.

Eye Gaze Processing Impairments Common To Asd And Schizophrenia

Individuals with ASD and schizophrenia both exhibit social cognitive deficits. ASD is a developmental disorder characterized by impairment in social communication and interaction[2] including emotion recognition[11], reduced eye contact, and eye gaze abnormalities[12]. Impairments in higher level social cognitive skills are also common in ASD, such as the ability to represent the mental states of others or mentalizing (i.e., 'theory of mind')[13, 14]. Similarly, impairments in social communication, interaction, and cognition are also prominent features of schizophrenia[15, 16], including abnormalities in emotion perception[9, 17–19], mentalizing[17, 20, 21], making complex social judgments[22, 23], and emotional expression such as reduced eye gaze[2, 24]. Studies directly comparing ASD and schizophrenia suggest convergent abnormalities in social cognitive processes[3, 9, 17, 25, 26] including emotion recognition and solving emotion-based problems[27], and mentalizing or theory of mind[25]. For instance, studies that have directly compared individuals with ASD and schizophrenia report similar levels of impairments in lower- and higher-order social cognitive tasks (e.g., emotion recognition, mentalizing, eye gaze processing) relative to unaffected controls[1, 5]. In support of this, a recent meta-analysis comparing ASD and schizophrenia reported similar deficits across subdomains of social cognition including emotion processing, theory of mind, and eye gaze processing[6]. In particular, there is evidence to suggest similar impairment levels in those with ASD and schizophrenia vs typically developing individuals on tasks that span across domains of eye gaze processing[6, 28–30]. For example, studies directly comparing ASD and schizophrenia during eye gaze processing tasks reported less time fixating on face stimuli than controls as well as reduced accuracy and visual attention during congruent emotional contexts[31, 32]. However, it is unclear if a convergent neural mechanism also underlies this gaze dysfunction across these conditions. Thus, the current study investigated whether shared or differentiated neural correlates underpin eye gaze impairments across ASD and schizophrenia using an activation likelihood estimation (ALE) meta-analysis.

Impairments have also been observed in ASD and schizophrenia across different gaze processing paradigms[8, 33, 34]. Imaging studies have consistently shown functional abnormalities during gaze and eye movement paradigms within regions of frontotemporal and frontoparietal circuitry, implicated in social cognition and cognitive control, in ASD[30, 35] and schizophrenia[18, 34]. For instance, hypoactivation in the superior temporal sulcus[36, 37], temporoparietal junction[38], and lateral prefrontal cortex[35, 39] has been shown in ASD during gaze perception. Amygdala[38, 40, 41] and fusiform gyrus[30, 42–45] hypoactivation are also implicated in ASD during the perception of gaze[26, 46]. In schizophrenia, disruptions in frontoparietal circuitry have been shown during eye movement paradigms, such as smooth eye pursuit and antisaccades[47–50]. Similar to ASD, perturbations in lateral prefrontal cortex, fusiform gyrus and amygdala are also shown in schizophrenia during gaze processing tasks[18, 34]. Additionally, disruptions in frontolimbic and frontoparietal circuits during social cognition tasks, such as face and eye gaze

processing, has been shown in ASD and schizophrenia[51–53]. However, no imaging meta-analysis to date has examined if a convergent neural mechanism also underlies gaze dysfunction across these disorders.

A range of eye gaze processing paradigms have been used to understand gaze and cognitive control deficits in ASD and schizophrenia [54, 55]. Imaging studies of gaze in ASD have employed paradigms including eye gaze fixations, face processing, and viewing faces with direct or averted gaze. Similarly, imaging studies of gaze in schizophrenia have employed paradigms including eye gaze fixations, face processing, smooth pursuit movements (i.e., gaze fixation while tracking slowly moving objects), and saccades/antisaccades (i.e., gaze fixation on a central stimulus followed by a shift of gaze in the opposite direction towards a peripheral target). Gaze fixation, smooth pursuit, and saccadic paradigms are conceptually similar to gaze shift/congruency paradigms in functional MRI (fMRI) studies of ASD, where attention is directed towards the eye region and/or averted vs direct gaze patterns are compared. While paradigm variability may hinder understanding of how gaze dysfunction may differ between ASD and schizophrenia, examining dysfunction across domains of eye gaze paradigms has potential to reveal underlying, shared neural correlates among these conditions. For instance, in schizophrenia studies, saccadic fMRI paradigms can be interpreted together with other gaze paradigms in ASD since broader, rather than specific, eye gaze deficits may be involved in context processing and executive functioning, which can mediate social cognitive impairments across both disorders (e.g., difficulty in actively representing situation-relevant or socially salient information from gaze in working memory to guide social responses).

Evaluating A Convergent Neurobiological Mechanism Of Gaze Processing Impairments In Asd And Schizophrenia

We focused the meta-analysis on ASD and schizophrenia for the following reasons. First, while aberrant eye gaze and gaze perception are symptoms common in multiple psychiatric disorders, there is a relatively vast imaging literature in ASD and schizophrenia examining gaze deficits relative to other mental health disorders, providing a sufficient number of experiments necessary for meta-analytic methods pooled across disorders. Second, there is emerging evidence that social cognitive deficits, particularly eye gaze impairments, are common to both ASD and schizophrenia[1, 3, 4, 17, 25, 26, 56]. For instance, while prior direct comparisons between ASD and schizophrenia indicate shared general impairments in social cognitive processes including eye gaze[1, 4, 5, 27, 57], the underlying neural mechanisms of these convergent impairments remain unclear. Additionally, prior meta-analytic work has focused exclusively on ASD and schizophrenia to identify common underlying frontoparietal control and default mode network dysfunction during heterogenous tasks of social perception[56]. Thus, we focused the meta-analysis on these conditions given evidence that they share clinical and neurobiological features, and to build on prior imaging studies directly comparing ASD and schizophrenia. Third, while prior meta-analyses that directly compared ASD and schizophrenia examined broader deficits in social cognition[3, 25, 56], such as perception of emotional facial expressions and mentalizing, no meta-analytic

study to date has examined the neural mechanisms of aberrant gaze processing as a specific social cognitive domain common to both disorders. However, prior meta-analytic work has commonly pooled heterogenous social cognitive tasks within and across ASD and schizophrenia, suggesting convergent abnormalities across a range of social processes[1, 3, 9, 17, 25, 26]. It is also important to note that social cognitive deficits in ASD and schizophrenia have been observed across a range of gaze processing paradigms[8, 33, 34]. Therefore, given that the primary aim of the study is to examine deficits across domains of gaze processing as a potential transdiagnostic neural marker, we used a similar approach and pooled different gaze paradigms to maximize statistical power and.

Here, we examined fMRI studies across domains of gaze processing in ASD and schizophrenia. The primary aim was to quantitatively summarize the existing imaging literature to identify convergent patterns of neural disruptions associated with gaze processing across ASD and schizophrenia. Thus, we pooled coordinates for hypo- and hyperactivation across both disorders compared to controls—using methodology consistent with recent meta-analyses across psychiatric disorders[58, 59]—in order to assess aberrant activation in hubs associated with gaze processing. Sub-analyses were then conducted to test for the contribution of gaze processing domains, participant characteristics (child vs adult), and patterns of hyper- vs hypoactivation. Exploratory sub-analyses also assessed regions associated with aberrant activation within each disorder relative to controls. Based on prior studies[60, 61], we hypothesized that ASD and schizophrenia would have convergent deficits in frontotemporal and frontoparietal circuitry implicated in social perception and cognitive control—particularly the lateral prefrontal cortex—consistent with convergent deficits in social cognition.

The second aim was to investigate coactivation with regions emerging as significant in the primary ALE analysis across ASD and schizophrenia. Here, meta-analytic connectivity modeling (MACM) was used to identify patterns of coactivation with clusters resulting from the primary meta-analysis, which can then be described in terms of behavior constructs and linked to functional properties. The third aim was to functionally decode the identified regions across ASD and schizophrenia using meta-data of the BrainMap database or behavioral decoder, which is ideal for data-mining and meta-analysis of brain mapping literature. Consistent with recent meta-analytic approaches[62–66], we used MACM and functional decoding to infer interaction patterns to gain insight into the pathophysiology of gaze abnormalities in ASD and schizophrenia. MACM[67] is a data-driven approach used to examine the functional coactivation between a region of interest and all other voxels across the brain. Functional decoding is also a data-driven method that provides quantitative inference on the psychological constructs associated with a particular neural region[68]. Specifically, functional decoding assesses the association between activation in a region and cognitive processes in a large number of fMRI studies of healthy subjects, which is stored in large-scale databases. We reasoned that MACM and decoding may provide novel insights into the contribution of convergent brain networks implicated in gaze processing impairments in ASD and schizophrenia. Additionally, these approaches allow mapping brain regions to functions not necessarily tested in individual studies, thus suggesting possible novel functions for those regions. Given that our

second and third aims served to interrogate regions emerging as significant from the primary ALE analysis, we did not have a priori hypotheses.

Methods And Materials

Study Selection

The literature review and selection of manuscripts was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[69, 70]. Functional MRI studies investigating the neural correlates of gaze processing in subjects with ASD or schizophrenia were identified through a literature search for functional neuroimaging (fMRI or Positron Emission Tomography) experiments examining eye gaze, eye movement, and gaze cueing conducted in ASD and/or schizophrenia samples (exact terms and detailed search strategy are provided in the **Supplemental Methods**). The search was conducted using the Cochrane, PubMed, Ovid MEDLINE, Embase, CINAHL, PsycINFO, Web of Science, ERIC, and Sociological Abstracts databases as well as additional searches through reference lists of included studies. The web-based software platform Covidence (https://www.covidence.org) was used for independent title and abstract screening, full text review and data extraction. See **Figure S1** for the PRISMA flow chart outlining the number of studies screened and excluded.

The inclusion criteria for studies were as follows: 1) full text was written in English and published between January 1990 and December 2021 in a peer-reviewed journal; 2) measured brain function using task-based fMRI or blood flow positron emission tomography across domains of gaze processing; 3) examined ASD or schizophrenia vs healthy control contrasts; and 4) foci of significant activations were reported in standardized stereotaxic space (Talairach or Montreal Neurological Institute [MNI] atlases). Exclusion criteria were as follows: 1) studies that used a region-of-interest (ROI) approach with a priori hypotheses related to a subset of regions or a specific region, or 2) was a review or meta-analysis of other literature. All coordinates of included studies were converted to MNI space. Group-x-Condition interactions were included if studies provided relevant contrasts for sub-analyses to clarify neural patterns of ASD or schizophrenia hyper- versus hypoactivation during gaze processing.

After abstract screening, all papers were reviewed (full text) by the same two reviewers for inclusion (I.I.-S., M.V.). Disagreements were resolved through discussion with a third reviewer (K.I.). For all studies meeting inclusion criteria, data was extracted regarding sample characteristics, fMRI task design, statistical analyses, stereotaxic coordinates and statistical values of BOLD responses, and a summary of brain regions showing significant activation.

Statistical Analysis

Activation Likelihood Estimation. A quantitative synthesis was conducted using Activation Likelihood Estimation (ALE)[71]. The revised ALE algorithm, implicated in MATLAB, was used to identify regions of spatial convergence of reported coordinates for ASD and schizophrenia vs healthy controls for gaze

processing tasks that were higher than expected under a random spatial association[71–73]. The ALE algorithm treats the reported foci as centers for 3D Gaussian probability distributions (and not as single points) in order to capture the spatial uncertainty associated with each focus. The width of these uncertainty functions was determined based on empirical data on the between-subject variance (i.e., uncertainty of spatial localizations between different subjects) and the between-template variance (i.e., uncertainty of spatial localizations between different spatial normalization strategies). The between-subject and between-template variance represent the main components of this uncertainty. Importantly, the between-subject variance is weighted by the number of examined subjects per study, accommodating the notion that larger sample sizes should provide greater reliability and approximations of the true activation effect (i.e., higher uncertainty of findings from smaller samples), which should be modeled by smaller Gaussian distributions. It is also important to note that the modeled uncertainty is scaled by the number of subjects to accommodate higher un-certainty of findings from smaller samples. The probabilities of all foci reported in each experiment were then aggregated for each voxel to create a modelled activation map for each experiment[73]. The union across modelled activation maps yields voxel-wise ALE scores describing the convergence of results at each location of the brain. ALE scores were then compared to an analytically derived null-distribution reflecting a random spatial association between experiments to establish true convergence vs random overlap across experiments. Thus, a random-effects inference was implemented. The resulting non-parametric p values were thresholded using a cluster-level family-wise-error-corrected $p < 0.05$ and a cluster-forming threshold of $p < 0.001$, which were then transformed into Z scores for visualization.

To investigate shared, convergent neural markers of gaze impairment in ASD and schizophrenia, we pooled across coordinates for hypo- and hyperactivation for ASD/schizophrenia vs controls to identify Group-x-Condition interactions representing potential hubs of aberrant activation. We modelled these analyses based on a recent fMRI meta-analysis of transdiagnostic neural markers of emotion processing in psychopathology[58]. ALE sub-analyses were then conducted across disorders for activation coordinates to identify patterns of hyperactivation (ASD/schizophrenia > controls) and hypoactivation (controls > ASD/schizophrenia). Sub-analyses were also performed to test for the contribution of gaze processing subdomains or paradigms (e.g., gaze cueing, gaze direction, face perception, saccades), diagnostic group (ASD, schizophrenia), and age (children vs adults). To further characterize findings, exploratory sub-analyses were also performed within each diagnostic group to identify disorder-specific patterns.

Given that fMRI results tend to represent Group-x-Condition interactions, often with heterogeneous effects of the baseline condition, we reasoned that pooling hyper-/hypoactivation across domains of gaze processing would also circumvent concerns due to directionality of activation patterns masked by decreased activation of healthy controls in the paradigm control condition (i.e., increased activation in patients vs controls driven by decreased activation in controls at baseline). Sub-analyses were then conducted to further characterize directionality of activations by examining contributions of individual experiments or gaze domains and study characteristics to the observed clusters of convergence emerging as significant from the primary, pooled transdiagnostic ALE analyses. We modeled these analyses based

on recent ALE meta-analytic studies for consistency in methodology and to facilitate comparison of findings[58, 62, 64].

Meta-analytic Connectivity Modeling

Meta-analytic connectivity modeling (MACM) consists of testing whole-brain coactivation patterns of a seed region across large imaging datasets[67, 74]. We conducted MACM to examine whether clusters emerging as significant in the primary transdiagnostic ALE analyses of aberrant activation and hyper-/hypoactivation—representing shared gaze processing deficits in ASD and schizophrenia—were functionally associated with other neural regions across fMRI studies. This approach identifies brain areas of coactivation above chance with a particular seed region (i.e., here, each region emerging from the primary ALE meta-analyses) across imaging experiments in the BrainMap database. Consistent with prior work[62, 66], we constrained MACM analyses to experiments from normal mapping imaging studies (no interventions or group comparisons) in healthy participants.

Functional Decoding

To further unpack findings, functional decoding was performed on regions emerging as significant in the primary ALE analyses. Functional characterization of gaze processing derived clusters from the ALE analyses was based on 'Behavioral Domain' and 'Paradigm Class' meta-data categories available in the BrainMap database[75]. We reasoned that leveraging the BrainMap database for functional decoding would allow comparison to other transdiagnostic studies of cognitive control networks based on the same database[62, 76]. Consistent with prior work[62, 66], studies from BrainMap were included that reported experiments (i.e., within-group contrasts between two experimental conditions) in healthy participants. See the **Supplemental Methods** for more details.

Results

Characteristics of Included Studies

The final set of experiments consisted of 59 experiments from 36 articles (see **Figure S1** and **Tables S1** and **S2** in the Supplemental Methods). This included 27 experiments with ASD patients and 32 experiments with schizophrenia patients. For ASD, this represented a total of 354 individuals with ASD (Mean age = 19.6 years; 86.4% males) and 348 healthy controls (Mean age = 19.5 years; 82.2% males). For schizophrenia, this represented a total of 275 individuals with schizophrenia (Mean age = 30.0 years, 70.6% males) and 265 healthy controls (Mean age = 29 years; 65.4% males). On the task level, experiments represented 5 broad types of domains across gaze processing: gaze direction (n = 12), gaze cueing (n = 18), saccades/antisaccades (n = 10), smooth pursuit (n = 13), and face perception (n = 3). See **Tables S1-S3** for a summary of medication status for participants.

Aberrant Activation Across Disorders

First, we examined transdiagnostic neural correlates of gaze processing pooling across disorders. Aberrant patterns of activation were observed in two clusters in the right inferior frontal gyrus and right fusiform gyrus (Fig. 1). The corresponding clusters and Z values are shown in Table 1. Gaze cueing, gaze direction, saccadic and face perception tasks contributed to convergence (**Supplemental Table S1**). However, important for understanding transdiagnostic neural markers, data from both ASD and schizophrenia studies contributed to these clusters across domains of gaze processing.

Table 1
Peak Coordinates of Clusters for Activation Pooled Across Disorders versus Healthy Controls

				MNI Coordinates			
Region	**BA**	**H**	**Cluster Size (mm^3)**	**x**	**y**	**z**	**Z value**
Aberrant activation across ASD and schizophrenia vs healthy controls							
Inferior frontal gyrus	45	R	1144	48	20	4	5.5
Fusiform gyrus	37	R	744	30	-52	-14	4.5
Hypoactivation across ASD and schizophrenia vs healthy controls							
Inferior frontal gyrus	45	R	1144	48	20	4	5.8
Supplementary motor area	6	R	880	2	10	54	5.0

Note. ASD = Autism Spectrum Disorder; BA = probable Brodmann area; H = hemisphere; L and R = left and right hemispheres, respectively; x, y, and z = the Montreal Neurological Institute (MNI) coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively. Clusters denote the maximum peak value.

Hyper- Vs Hypoactivation Across Disorders

Next, sub-analyses tested for convergent patterns of hyper- vs hypoactivation in ASD and schizophrenia (pooled across disorders) vs controls. Hypoactivation in ASD and schizophrenia was observed in the right inferior frontal gyrus and right supplementary motor area (Fig. 2). A similar inferior frontal gyrus cluster as that reported above for aberrant activation emerged as significant here for patient hypoactivation. The corresponding clusters and Z values are shown in Table 1. For the inferior frontal gyrus cluster, experiments with gaze cueing and direction, saccades, and face perception tasks (with attention cued to the eye region) contributed to convergence (**Supplemental Table S4**). Additionally, results from ASD and schizophrenia contributed to the inferior frontal gyrus cluster. For the supplementary motor area cluster, saccades tasks and schizophrenia samples contributed the most to convergence relative to other gaze

tasks and ASD samples, respectively (**Supplemental Table S4**). No regions emerged as significant for convergent patterns of hyperactivation across disorders.

Exploratory Sub-analyses Based On Disorder

We then conducted exploratory sub-analyses within each disorder to identify disorder-specific patterns of aberrant activation during gaze processing. Within ASD results, aberrant activation was observed in the left amygdala (Table 2 and Fig. 3). Experiments with gaze cueing and direction contributed to convergence as well as both child and adult samples. Aberrant amygdala activation was characterized by patterns of hypo- and hyperactivation in ASD during gaze processing (**Supplemental Table S5**).

Table 2
Peak Coordinates of Clusters for Activation Within ASD and Schizophrenia versus Healthy Controls

				MNI Coordinates			
Region	**BA**	**H**	**Cluster Size (mm^3)**	**x**	**y**	**z**	**Z value**
Aberrant activation in ASD vs healthy controls							
Amygdala		L	720	-24	-6	-20	4.2
Aberrant activation in schizophrenia vs healthy controls							
Inferior frontal gyrus	44/45	R	944	46	20	4	5.5
Supplementary motor area	6	R	1368	2	8	54	5.7

Note. ASD = Autism Spectrum Disorder; BA = probable Brodmann area; H = hemisphere; L and R = left and right hemispheres, respectively; x, y, and z = the Montreal Neurological Institute (MNI) coordinates corresponding to the left-right, anterior-posterior, and inferior-superior axes, respectively. Clusters denote the maximum peak value.

Within schizophrenia results, aberrant activation was observed in the right inferior frontal gyrus and right supplementary motor area (Table 2 and Fig. 4). Saccade and face perception tasks contributed to convergence for the inferior frontal gyrus cluster, while predominately saccades tasks contributed to convergence for the supplementary motor area cluster. Both clusters were characterized by hypoactivation in schizophrenia vs controls (**Supplemental Table S5**).

Meta-analytic Connectivity Modeling (Macm)

To further explore the findings of the primary ALE analyses across disorders (Table 1, Figs. 1–2)—which includes volumes of interest for the right inferior frontal gyrus (MNI peak coordinates: 48, 20, 4), right fusiform gyrus (MNI peak coordinates: 30, -52, -14), and supplementary motor area (MNI peak coordinates: 2, 10, 54)—we conducted MACM to identify coactivation with other regions. The functional

coactivation patterns of each volume of interest are displayed in Fig. 5. The inferior frontal gyrus showed convergent coactivation with the lateral prefrontal cortex, frontal eye fields, superior temporal gyrus, and parietal regions including the supramarginal gyrus (**Supplemental Table S6**). The fusiform gyrus showed convergent coactivation with the visual cortex, lateral prefrontal cortex including the inferior frontal gyrus, supplementary motor area, and parietal cortex including the angular gyrus (**Supplemental Table S7**). The supplementary motor area showed convergent coactivation with the lateral prefrontal cortex, frontal eye fields, fusiform gyrus, cerebellum, and parietal cortex (**Supplemental Table S8**). Full details including the corresponding clusters and Z values are shown in **Supplemental Tables S6-S8**.

Functional Decoding

The inferior frontal gyrus volume of interest was associated with domains related to cognition including music and language (e.g., music comprehension and production, speech and language, attention), emotion processing, perception and somesthesis, and audition (**Supplemental Figures S2-S3**). The fusiform gyrus volume of interest was associated with domains related to action (e.g., motor learning, speech), visual perception, emotion processing, cognition (e.g., spatial perception, and executive function including memory) (**Supplemental Figures S4-S5**). The supplementary motor area volume of interest was associated with domains related to visual perception, action (e.g., speech, motor, inhibition), and cognition (e.g., language and speech, music, spatial processing) (**Supplemental Figures S6-S7**).

Discussion

The primary aim of this meta-analysis was to examine convergent neural correlates of gaze processing impairments in ASD and schizophrenia. Three key findings were observed. First, across disorders, aberrant activation during the processing of gaze was found in the inferior frontal gyrus and fusiform gyrus—regions implicated in cognitive control and social perception, respectively. Importantly, both ASD and schizophrenia results contributed to the convergence in these regions. Second, hypoactivation across disorders was identified in the inferior frontal gyrus and supplementary motor area during gaze processing. Third, exploratory sub-analyses within each disorder identified convergence of disorder-specific patterns of aberrant activation in the amygdala for ASD and in the inferior frontal gyrus and supplementary motor area for schizophrenia (see **Supplemental Discussion** regarding disorder-specific findings). Thus, as hypothesized, a convergent pattern of aberrant activation in frontoparietal and frontotemporal circuitry was observed in ASD and schizophrenia across domains of gaze processing. Our findings also suggest a shared underlying deficit in the functional brain organization associated with gaze processing that spans cognitive control and sensorimotor processes.

ALE analyses identified common neural dysfunction in the right inferior frontal gyrus across ASD and schizophrenia. The inferior frontal gyrus is involved in cognitive control processes including emotion regulation[66] and response inhibition[77]. For example, the inferior frontal gyrus plays a salient role in the inhibition of the prepotent prosaccade response in gaze tasks including saccades/antisaccades[78].

Additionally, saccades/antisaccades tasks tap interference resolution processes and engage frontoparietal networks involved in selecting information based on the relevance to an ongoing task while suppressing irrelevant information[78–80]. Recent meta-analytic work also implicates a role of the lateral prefrontal cortex, including the inferior frontal gyrus, in emotional inhibition (i.e., cognitive tasks involving task-irrelevant emotional elements or emotion-related distractors)[79], which is relevant to the current work given that several studies utilized gaze tasks involving fixation on a target in the presence of distractor stimuli.

The inferior frontal gyrus is also implicated in social perception including the processing of emotion and social cognitive processes[81, 82]. For instance, the inferior frontal gyrus is involved in a broad array of domains related to social perception including processing negative affect[83, 84], empathy[85], emotion regulation[63, 86], mentalization[82], biological motion[87], evaluation of trustworthiness[26], and gaze perception[88]. In line with these prior findings emphasizing the involvement of the inferior frontal gyrus in broader social perception processes, functional decoding suggested that this region may also be linked to domains of cognition and sensory perception. Findings from MACM analyses indicated that activation of this inferior frontal gyrus cluster converges with activation across cognitive control circuitry in the general population, which spans the lateral prefrontal cortex, sensorimotor regions including the supplementary motor area, insula, and the parietal cortex. Such a distributed network has also been described in a transdiagnostic sample of individuals with schizophrenia, bipolar disorder and ADHD, with connectivity in the default mode, limbic, subcortical, and cerebellar networks predicting overall memory performance[89]. Thus, these findings reflect the vast cortico-cortical connections of the inferior frontal gyrus and aligns with prior studies emphasizing the rich interconnectedness of this region[77].

In addition to a broader role in social perception and emotion processing[81, 82], the inferior frontal gyrus—particularly the right hemisphere—is thought to act as a ‘brake’ over response tendencies and other forms of inhibition involving limbic or memory representation[77]. Here, it is possible that disruption of the inferior frontal gyrus in ASD and schizophrenia could indicate a deficit-specific neural marker of impairment in broader cognitive control domains, which could hinder processing of salient cues (e.g., social and/or emotional stimuli) with downstream effects on the lack of modulation on attentional control for competing stimuli (e.g., distractors). Future longitudinal imaging studies will be important to assess the timing effects associated with inferior frontal gyrus pathophysiology in ASD and schizophrenia, and whether aberrant function in this region could serve as a potential transdiagnostic biomarker of psychiatric risk (e.g., intermediate phenotype)—which can help inform diagnosis and/or development of interventions targeting engagement of the lateral prefrontal cortex in treatment trials.

Aberrant activation was also observed in the right fusiform gyrus across disorders relative to controls, with both ASD and schizophrenia results contributing to the convergence of fusiform gyrus dysfunction. The fusiform gyrus is associated with face processing[90] and activation of this region has been reported during the perception of gaze[39, 91–94]. It is also thought that involvement of the fusiform gyrus during face perception may reflect enhanced attention to gaze[95]. However, while fusiform gyrus activity is

associated with face processing[90], particularly the right hemisphere, studies have suggested a broader role of the fusiform gyrus beyond the perception of faces. For instance, activation of the fusiform gyrus has been implicated in expertise for distinguishing objects[96–98], mental state attribution tasks[99], and visuo-attentional and perceptual processes[100]. In ASD, a vast neuroimaging literature implicates fusiform gyrus dysfunction with social impairment[30, 60, 61, 94]. Additionally, studies of ASD also suggest a broader network dysfunction of social cognitive circuitry during gaze that includes the fusiform gyrus[30, 42–45]. Similarly, in schizophrenia, studies report aberrant activation of the fusiform gyrus during social cognitive[26] and face emotion processing[101] tasks, as well as during eye movement/saccades tasks[102] and attentional control that requires the filtering of relevant vs distractor stimuli[103, 104]. In support of this, functional decoding suggested that this fusiform gyrus region may be linked to domains of spatial cognition, sensorimotor learning, emotion perception, and visual processing in the general population. Additionally, in line with recent work suggesting a role of the fusiform gyrus beyond face processing, findings from MACM analyses indicated that activation of this region converges with activation across the visual cortex, lateral prefrontal cortex, sensorimotor cortex, and parietal regions in the general population. Here, it is possible that our findings of fusiform gyrus dysfunction could reflect a disorder-general, transdiagnostic marker of impaired attentional control aspects of gaze processing (e.g., impaired attentional filtering leading to hypo- or hyperfocusing on stimuli), which may hinder social functioning and cognitive control processes (e.g., decreased sensitivity to attend to salient social cues such as faces or gaze). Alternatively, this pattern of neural dysfunction could also reflect a disorder-general marker in which individuals with social cognitive impairments show a similar pattern of neural dysfunction in the fusiform gyrus regardless of clinical diagnosis.

Hypoactivation of the supplementary motor area also emerged in analyses across disorders. Contribution sub-analyses indicated that hypoactivation in the supplementary motor area was largely driven by schizophrenia results. In line with this, we also observed hypoactivation of the supplementary motor area as a disorder-specific pattern in schizophrenia. In addition to controlling volitional aspects of motor movements[105], sensorimotor regions, including the supplementary motor area, are also implicated in the affective aspect of social cognition[106]. Additionally, more recent work implicates the integration of a distributed neural system including sensorimotor regions with lateral and medial prefrontal cortices, temporal, and parietal regions necessary for successful cognitive control such as emotion regulation and response inhibition[107]. In support of this, functional decoding indicated a broad domain of function associated with the supplementary motor area including aspects of cognition (i.e., language and spatial processing), cognitive control including inhibitory control, and visual perception. Additionally, findings from MACM analyses indicated that activation of this region converges in the general population with activation across frontoparietal circuitry that encompasses the lateral prefrontal cortex and parietal regions implicated in cognitive control—such as the dorsolateral prefrontal cortex, inferior frontal gyrus, and supramarginal gyrus. Impairment of the supplementary motor area has also been identified as a hub of cortico-basal ganglia network dysfunction related to disturbances in volitional motor control in schizophrenia[108]. Further, perturbations in supplementary motor area volume are associated with

impaired executive functioning in schizophrenia[109, 110]. Here, it is possible that aberrant activation of the supplementary motor area during gaze processing may reflect broader cognitive control dysfunction in schizophrenia. In support of this, a meta-analysis found that hypoactivation of the supplementary motor area was associated with executive function impairments in schizophrenia[111]. Given that recent work implicates associations between cognitive dysfunction and sensorimotor dysconnectivity and structure across mental disorders, particularly schizophrenia[112, 113], our results also converge on the idea that disruptions in lower-order brain systems could be disorder-general biomarkers linked to cognitive control deficits.

Study Limitations

Some limitations should be considered. First, inherent to all meta-analyses, there is the potential role of publication bias because we could include only published studies. Second, our data do not provide information on the causal relationship between social cognitive and cognitive control networks, and gaze impairments in ASD and schizophrenia. Third, there were relatively fewer studies in schizophrenia across eye gaze processing paradigm domains (e.g., facial emotions, gaze direction, gaze cueing), emphasizing the need for future studies in schizophrenia that leverage a range of eye gaze tasks[8]. Additionally, sub-analyses could not be conducted within experiments using the same paradigms due to limited sample size. As mentioned above, paradigm variability can hinder understanding how eye gaze dysfunction may differ between ASD and schizophrenia. While it would have been ideal to be able to perform analyses in a fully homogeneous set of experiments with regards to paradigms and/or age group, this was not possible given the current studies that met inclusion criteria. Nonetheless, we conducted post-hoc sub-analyses restricted to adult samples across ASD and schizophrenia, which showed a highly similar pattern of convergence, as the main findings, in the right lateral prefrontal cortex (inferior frontal gyrus) (see **Supplemental Results Figure S8** and **Table S9**). Thus, we were able to replicate findings in a relatively homogeneous sample of adults. Even so, the primary aim of this meta-analysis was to leverage a transdiagnostic approach to examine convergent neural correlates across domains of eye gaze processing in ASD and schizophrenia, rather than within or between each condition. Prior meta-analyses have also combined across broader social perception tasks encompassing both lower- and higher-order social cognitive processes. While future studies directly comparing the neural correlates of eye gaze dysfunction in ASD and schizophrenia using homogenous paradigms can be helpful, meta-analyses integrating a range of paradigms—reflecting task heterogeneity common across imaging research groups as well as samples—can also help advance development of biomarkers with potential generalization to heterogenous ASD and schizophrenia samples (e.g., in terms of complex neurocognitive traits and social cognitive performance) and/or identification of distinct subgroups[114]. It is important to note that the few number of eye gaze processing fMRI studies beyond ASD and schizophrenia also hindered inclusion of other disorders in this meta-analysis. Additionally, given the increasing shift toward transdiagnostic research related to social cognition leveraging the NIMH Research Domain Criteria framework[7, 8, 51], future work is needed to examine social cognitive impairments across a range of disorders. Because

impaired social cognitive functioning, including aberrant eye gaze perception, are symptoms common in multiple psychiatric conditions[115], task-based imaging studies are needed that explicitly test social cognitive networks in other disorders such as disruptive behavior disorders and anxiety disorders. Fourth, ASD studies included children and adults (vs adults only in schizophrenia studies), which may impact findings in terms of developmental aspects of brain neurophysiology. However, we relied on the contrast of ASD vs controls and imaging data from age-matched controls. Nonetheless, developmental aspects may affect activation patterns reported here and future longitudinal work will be necessary to understand how age-related differences map onto neural deviations and symptom trajectories. Fifth, most participants with schizophrenia were taking psychotropic medications, while the majority of ASD studies did not report psychotropic medication status. Because there is evidence that psychotropic medications may have long-term effects on brain function and structure in ASD and schizophrenia[116–118], it is not possible to establish the extent to which our results were influenced by medication effects. Additionally, potentially influential factors beyond medication types, such as illness duration and/or severity and comorbidities, could not be assessed because of inconsistent reporting across studies. Future longitudinal work will be important to unravel to what extent convergent gaze-related neural abnormalities across these disorders are driven by psychotropic medication effects and psychiatric comorbidity. Sixth, while there are other statistical packages for conducting coordinate-based meta-analyses (e.g., MKDA), we selected ALE for comparison to recent meta-analyses in ASD[60, 61] and schizophrenia[56]. Future studies may also consider conducting mega-analyses in which raw functional and/or structural MRI data are pooled across studies and sites. Nevertheless, our meta-analysis can provide a reliable map of anatomical regions (e.g., a priori regions-of-interest) for testing causal implications in such mega-analyses. Lastly, we acknowledge that findings from MACM and functional decoding analyses refer to general population functionality. However, MACM and functional decoding are commonly used approaches in imaging meta-analyses for further exploring and contextualizing regions emerging as significant and associated cognitive processes[62, 66].

Conclusion

The current ALE meta-analysis examined convergent patterns of underlying neural mechanisms associated with gaze processing in ASD and schizophrenia. Aberrant activation in the right inferior frontal gyrus and fusiform gyrus emerged as transdiagnostic neural markers in ASD and schizophrenia across domains of gaze processing. Frontotemporal and frontoparietal coactivation was found to be associated with these inferior frontal gyrus and fusiform gyrus regions. Shared features of neural dysfunction may be related to abnormal gaze processing, particularly in large-scale networks involved in social cognition and cognitive control.

Declarations

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Conflict of Interest

The authors have no competing interests or potential conflicts of interest to declare related to this study.

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Figures

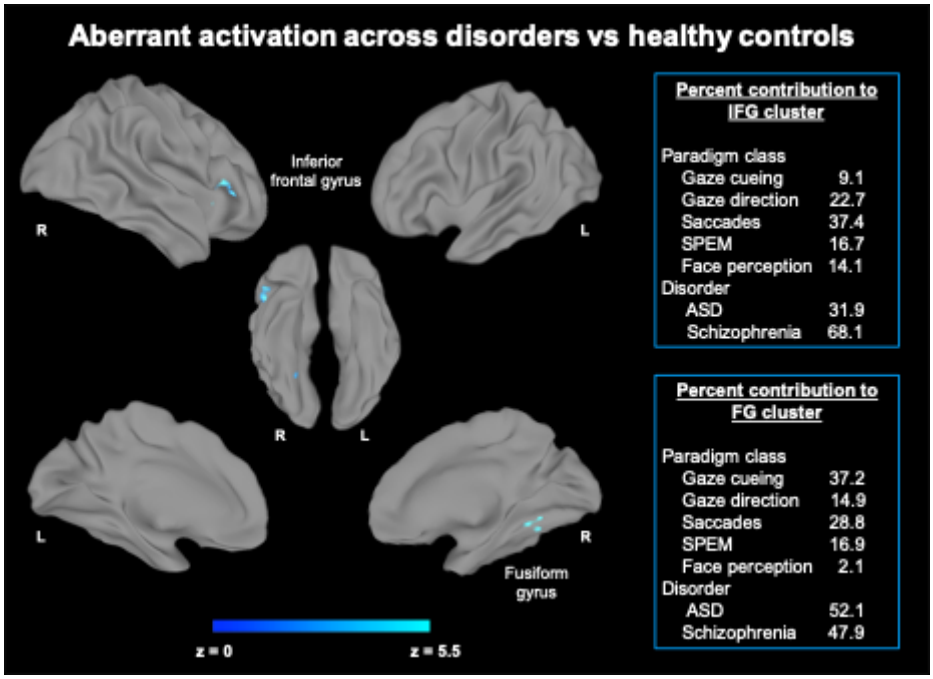

Figure 1

Regions of aberrant activation across ASD and schizophrenia during gaze processing. Aberrant activation in the right inferior frontal gyrus and right fusiform gyrus emerged as a shared dysfunction across ASD and schizophrenia. Primary ALE analyses pooled coordinates across hyper- and hypoactivation in ASD and schizophrenia vs healthy controls. The right panel indicates the contribution of gaze subdomains and disorder subgroups to the convergence on these regions.

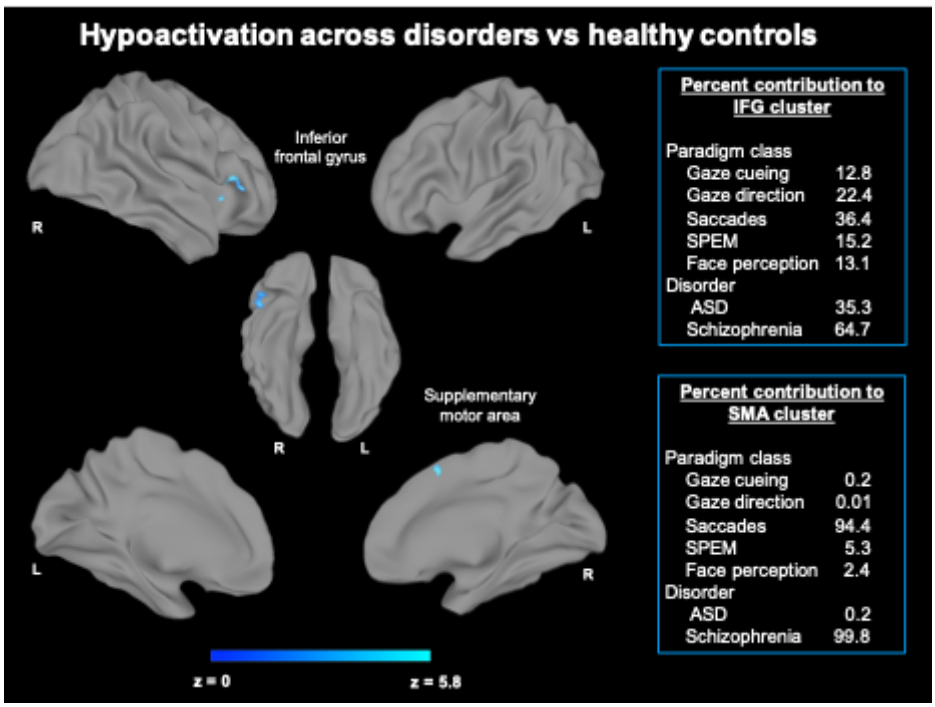

Figure 2

Regions of disruption based on hypoactivation across ASD and schizophrenia during gaze processing. Hypoactivation in the right inferior frontal gyrus and right supplementary motor area emerged as a shared dysfunction in ASD and schizophrenia. Sub-analyses pooled coordinates across gaze processing tasks and across ASD and schizophrenia vs healthy controls. The right panel indicates the contribution of gaze subdomains and disorder subgroups to the convergence on these regions.

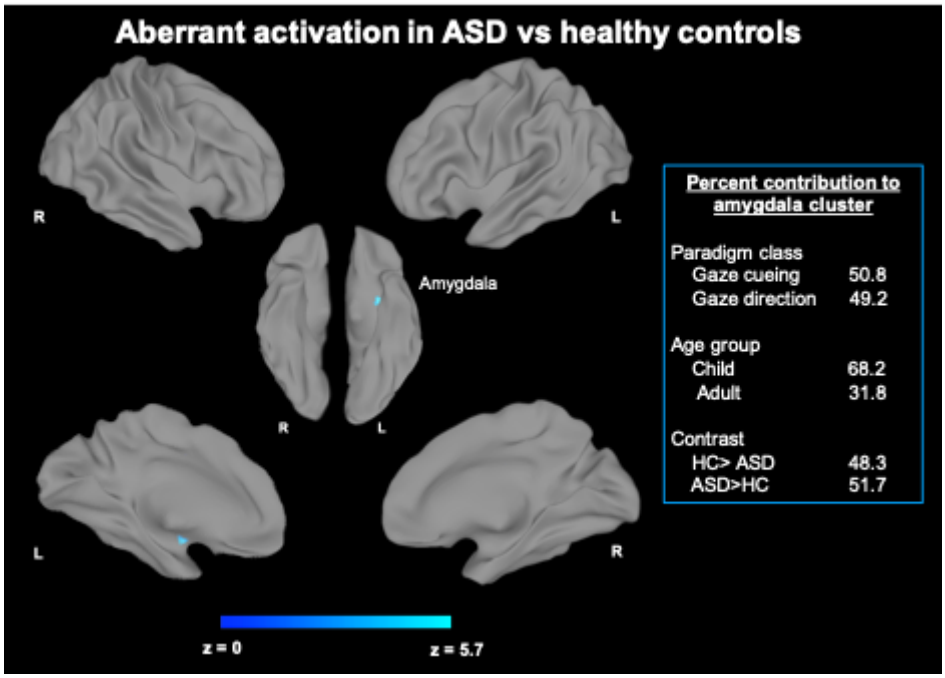

Figure 3

Regions of aberrant activation within ASD during gaze processing. Aberrant activation in the left amygdala emerged as a disorder-specific dysfunction in ASD. Disorder-specific sub-analyses pooled coordinates across hyper- and hypoactivation in ASD vs healthy controls. The right panel indicates the contribution of paradigm type or gaze subdomains, age group, and contrast (indicating hyper- vs hypoactivation in ASD) to the convergence on this region.

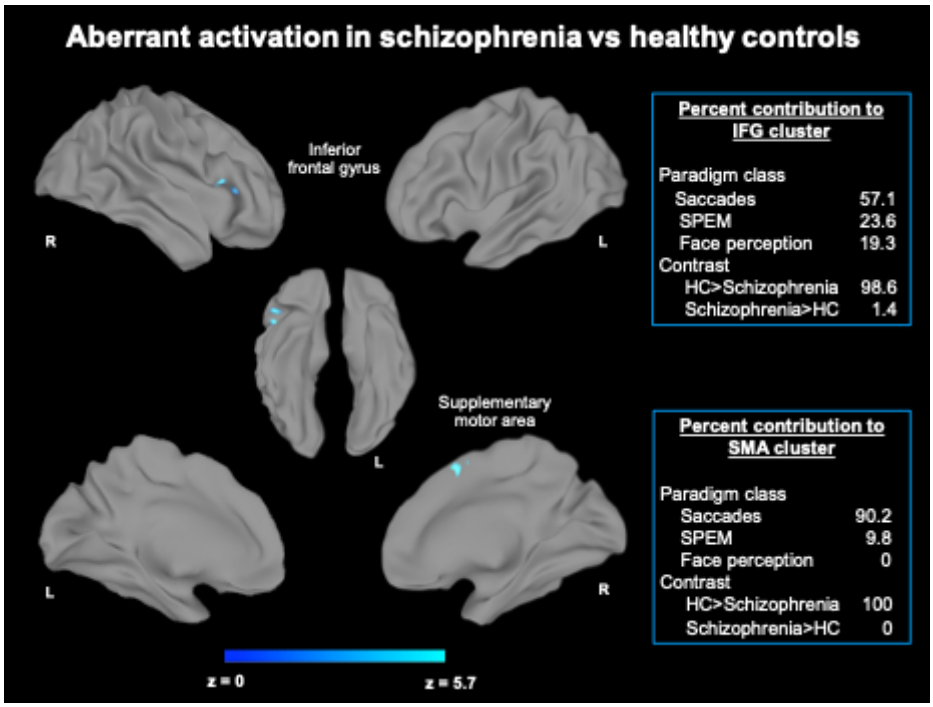

Figure 4

Regions of aberrant activation within schizophrenia during gaze processing. Aberrant activation in the right inferior frontal gyrus and supplementary motor area emerged as a disorder-specific dysfunction in schizophrenia. Disorder-specific sub-analyses pooled coordinates across hyper- and hypoactivation in schizophrenia vs healthy controls. The right panel indicates the contribution of paradigm type or gaze subdomains and contrast (indicating hyper- vs hypoactivation in schizophrenia) to the convergence on these regions.

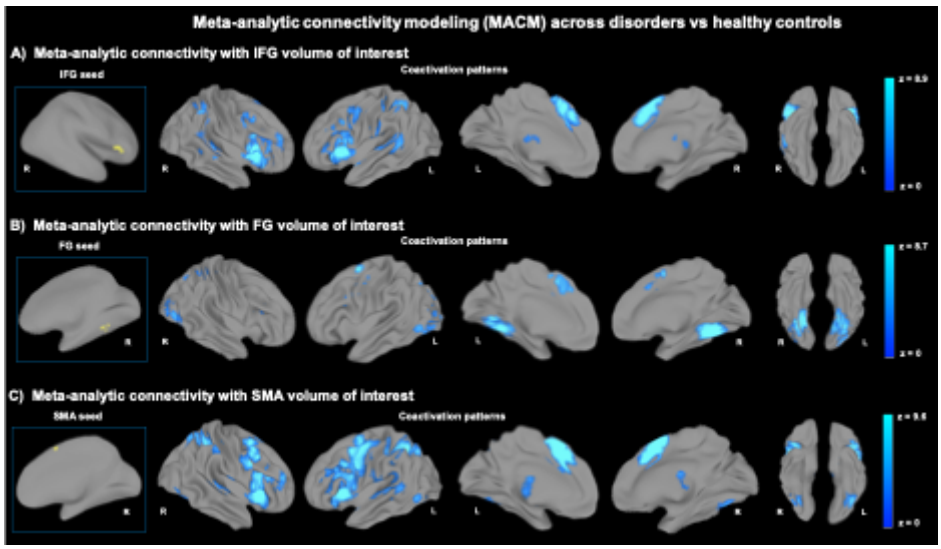

Figure 5

Connectivity maps for the volumes of interest in relation to regions of convergent aberrant activation in ASD and schizophrenia. Depicted are coactivation maps for the right inferior frontal gyrus (IFG) (**A**), the

right fusiform gyrus (FG) (**B**), and the supplementary motor area (SMA) (**C**). Coactivation patterns are labeled in blue and seed volumes of interest are labeled in yellow.

Supplementary Files

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- GazemetaanalysisSupplement20221119.docx