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Altered Neural Activation in First Episode Psychosis Patients With Comorbid Conduct Disorder: A Pilot Investigation

Nathan J. Kolla, MD, PhD, FRCPC, Ryan Aloysius, BSc, George Gainham, BSc, Colin Hawco, PhD

Nathan J. Kolla and Ryan Aloysius contributed equally to this work.

Objective: Most individuals with psychosis do not perpetrate violence. However, conduct disorder (CD) increases the risk of violence in psychotic conditions. Because it is currently unknown whether the neural correlates of first-episode psychosis (FEP) differ when CD is present, we used functional magnetic resonance imaging (fMRI) during a Go/No-Go impulsivity paradigm to investigate. Based on previous research, we hypothesized that activation differences between FEP and FEP+CD would be found in the prefrontal cortex, cingulate cortex, and inferior parietal lobule.

Method: We scanned 51 male participants: 17 FEP, 16 FEP+CD, and 18 healthy controls with an average age of 24.2 years (range, 17-34 years). Whole-brain images were analyzed via a general linear model, and first-level contrast images were created comparing successful No-Go > Go trials. Paired *t* tests were conducted at the group level and included confound regressors for age, IQ, antipsychotic dose, psychotic symptoms, and framewise displacement. A voxel-based *Z*-score threshold of $Z > 3.1$ ($p < 0.001$, uncorrected) and a cluster-level extent threshold of $p < 0.01$, corrected, was considered significant.

Results: Successful response inhibition elicited hyperactivation in FEP+CD vs FEP in the cingulate gyrus; regions of the PFC, including right middle frontal gyrus (RMFG); bilateral inferior parietal lobule; temporal gyrus; and cerebellum (*p* values ranged from 1.11E-08 to 0.0031). There was no region in which activation was greater in FEP > FEP+CD.

Conclusion: These preliminary results tentatively suggest that brain regions subserving response inhibition may be altered when CD is comorbid with FEP.

Plain language summary: Conduct disorder increases the risk of aggression among individuals with psychosis. This study used fMRI during a task measuring impulsivity to determine whether individuals with first episode psychosis and comorbid conduct disorder have different brain responses than individuals with first episode psychosis alone and healthy controls. Increased activation of the prefrontal cortex, cingulate gyrus, bilateral inferior parietal lobule, temporal gyrus and cerebellum was found in first episode psychosis with conduct disorder versus first episode psychosis alone. These preliminary results suggest that brain regions subserving response inhibition may be altered when conduct disorder is comorbid with first episode psychosis.

Key words: First episode psychosis; conduct disorder; imaging; response inhibition; impulsivity

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Although the vast majority of individuals with psychotic disorders do not perpetrate violence, the risk of violence is still elevated in this population. The neurobiological basis of violence in psychotic disorders has not been fully elucidated. Gray matter volume reductions have been documented within several regions in relation to violence in schizophrenia (SCZ), including the fusiform gyrus,[1] inferior parietal lobe,[2] hippocampus and putamen,[3] as well as disrupted functioning in the inferior parietal lobe and superior frontal gyrus.[4]

A potential pathway to violence in SCZ is impulsivity,[5] which has been shown to be greater in first-episode-psychosis (FEP) patients than in healthy controls.[6] This is relevant, because one longitudinal study of FEP patients enrolled in a specialized clinical first-episode psychosis program found that impulsivity was a predictor of violent behavior in FEP and that impulsivity could differentiate FEP patients who were violent from those who were not at the end of the program.[7] Greater trait impulsivity has also been associated with a lower hemodynamic response in the prefrontal cortex (PFC) in other psychotic disorders[8] and includes failure of response inhibition.[8]

Response inhibition, or the voluntary "top-down" suppression of motor activity, forms part of the cognitive control system that permits efficient and flexible behavior.[9] Response inhibition can be assessed by Go/No-Go tasks that require participants to respond to specific targets and to refrain from reacting to distractor targets. At the neural level, cognitive control can be largely localized to the PFC,[10] although input from dorsolateral PFC (DLPFC), anterior cingulate cortex (ACC), and posterior parietal cortex likely results from supplementary task demands on working memory, protracted attention, and response selection.[11–13] Functional aberrations in these frontal and

parietal areas are found in studies of response inhibition in individuals with psychotic disorders, disruptive behavior disorders,[14] and those with high self-reported psychopathic traits.[13]

There are few Go/No-Go studies of response inhibition using functional magnetic resonance imaging (fMRI) in adolescents and younger youth who are in the early phase of their psychotic illness or are at high risk for developing a psychotic disorder. Relative to healthy controls, individuals at clinical high risk for developing psychosis and early-illness SCZ patients demonstrated significantly less No-Go/Go activation in the bilateral dorsal ACC and right inferior frontal cortex during an fMRI Go/No-Go task.[15] However, this study did not parse out potential comorbid conduct disorder (CD) in the study participants.

CD is a risk factor for violence[16] and is present in approximately 40% of individuals with schizophreniform disorders.[17] CD that is present before the age of 15 years has been linked to antisocial and violent behavior during adult life in individuals with SCZ, even after controlling for current and past substance misuse.[18] Brain alterations are present in SCZ with CD compared to SCZ without this comorbidity.[19] However, it is currently unknown whether the neural correlates of first-episode psychosis (FEP) patients with CD differ from FEP patients without CD. Few studies have investigated response inhibition in youth and adolescents who perpetrate violence. One study evaluated response inhibition using a stop task in boys with CD, and reported that they had reduced activation in bilateral temporal parietal regions.[14] A Go/No-Go study comparing violent adolescents with healthy controls found that the former group's activation was more extensive in bilateral PFC than in the control group when comparing the No-Go condition to the Go condition.[20] Nevertheless, our understanding of response inhibition in young aggressive populations is limited, particularly in relation to comorbid psychosis.[16]

To overcome the limitations of previous studies, we sampled 3 groups of male participants in an fMRI Go/No-Go task: individuals with FEP and comorbid CD; individuals with FEP without comorbid CD; and healthy controls. We examined male participants in particular because of noted differences in neurostructural sex differences across both CD[21] and SCZ[22] as well as a higher proportion of research available in violent male individuals[23] largely because of the greater proportion of male individuals who are incarcerated for violent crimes.[24,25] We hypothesized that differences in performance as well as differences in neural activation would be found among all 3 groups, and that these activation differences would be found within the PFC, inferior parietal lobe, and cingulate cortex. We expected that PFC activation could differentiate groups within the precentral gyrus, postcentral gyrus,[26] right inferior frontal gyrus,[11] bilateral middle frontal gyrus,[14,27] and dlPFC[11] in particular, but did not constrain our search to these subregions in particular because of the novelty of the population, which is relatively understudied. The identification of regions of functional difference among these groups could be the first step in treating symptoms of impulsivity and aggression at the neural level in FEP populations.

METHOD

Participants

A total of 51 participants completed the Go/No-Go task under fMRI. General inclusion criteria included male sex and age between 16 and 35 years. General exclusion criteria included a current alcohol or drug use disorder, determined by Alcohol Use Disorders Identification Test (AUDIT)[28] and Drug Use Disorders Identification Test (DUDIT)[29] scores, respectively; an estimated IQ below 70, determined by the Wechsler Test of Adult Reading[30]; presence of claustrophobia; neurological illness; and history of a head injury rendering the person unconscious.

All participants provided written informed consent prior to study involvement. All study components were approved by the institutional review board at the Centre for Addiction and Mental Health, Toronto, Ontario, Canada.

FEP Group

FEP participants (n = 17) were recruited through an early psychosis outpatient service as well as through the community, and had already received a diagnosis of a primary psychotic disorder (eg, SCZ, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder) or a mood disorder with psychotic features (eg, bipolar disorder I, bipolar disorder II, major depressive disorder) from a psychiatrist. Participants were required to be within 3 years of their first treatment with an anti-psychotic medication. Diagnoses were confirmed by a trained rater using the Structured Clinical Interview for *DSM-5* Research Version (SCID-5-RV).[31] Participants were also assessed using the CD module of the Structured Clinical Interview for *DSM-5* Personality Disorders Version (SCID-5-PD)[32] to rule out a diagnosis of CD. To further corroborate the lack of a CD diagnosis, participants' medical charts were inspected and collateral information was obtained from an informant who knew the participant well, for example, a parent or sibling.

FEP+CD Group

FEP+CD participants (n = 16) were recruited through an early psychosis outpatient service, as well as through the

community, and had already received a diagnosis of a primary psychotic disorder (eg, SCZ, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder) or a mood disorder with psychotic features (eg, bipolar disorder I, bipolar disorder II, major depressive disorder) from a psychiatrist. Participants were required to be within 3 years of their first treatment with an anti-psychotic medication. Diagnoses were confirmed by a trained rater using the SCID-5-RV. Participants were also assessed using the CD module of the SCID-5-PD to capture a diagnosis of CD. This interview confirms that participants engaged in behaviors before the age of 15 years, which meets criteria for CD symptoms. As these behaviors must be present before the age of 15 years, their onset was prior to the onset of their psychosis. In addition, participants' medical charts were inspected, and collateral information was also obtained from an informant who knew the participant well, for example, a parent or sibling, to corroborate or supplement the information obtained via the SCID-5-PD.

Healthy Control Group

Healthy controls (HCs; n = 18) were assessed using the SCID-5-RV to rule out any psychiatric illness and also the SCID-5-PD to rule out CD or personality disorder. HC participants could endorse no more than one CD symptom, and it could not involve aggression toward people or animals. HC participants were recruited from the community.

Additional Measures

All participants completed the Buss–Perry Aggression Questionnaire (BPAQ),[33] which measures current aggressive behavior along 4 axes: physical aggression, verbal aggression, hostility, and anger. Participants also completed the Positive and Negative Syndrome Scale (PANSS)[34] to assess for the severity of psychotic symptoms at time of scanning. For the FEP and FEP+CD participants, their antipsychotic medication intake was recorded, and medication dosages were converted into olanzapine equivalents.[35] No participant was taking clozapine.

Go/No-Go Task

Participants completed a Go/No-Go task under fMRI (Figure 1). Participants were given instructions on how to complete the task prior to entering the MRI scanner. This task consisted of 208 trials, of which 183 trials were Go trials and 25 were No-Go trials. These trials were randomly ordered. During Go trials, participants were presented with the letter "X" during which they were to respond as quickly as possible when encountering a Go trial on a button box placed in their dominant hand. During No-Go trials, participants were presented with the letter "K" and were required to inhibit any response on the button box. Go trials in which participants failed to make any response and No-Go trials in which participants did make a response were both error trials. Each trial lasted 500 milliseconds, with an interstimulus interval ranging from 1,000 milliseconds to 1,500 milliseconds between trials.

Behavioral Data Analysis

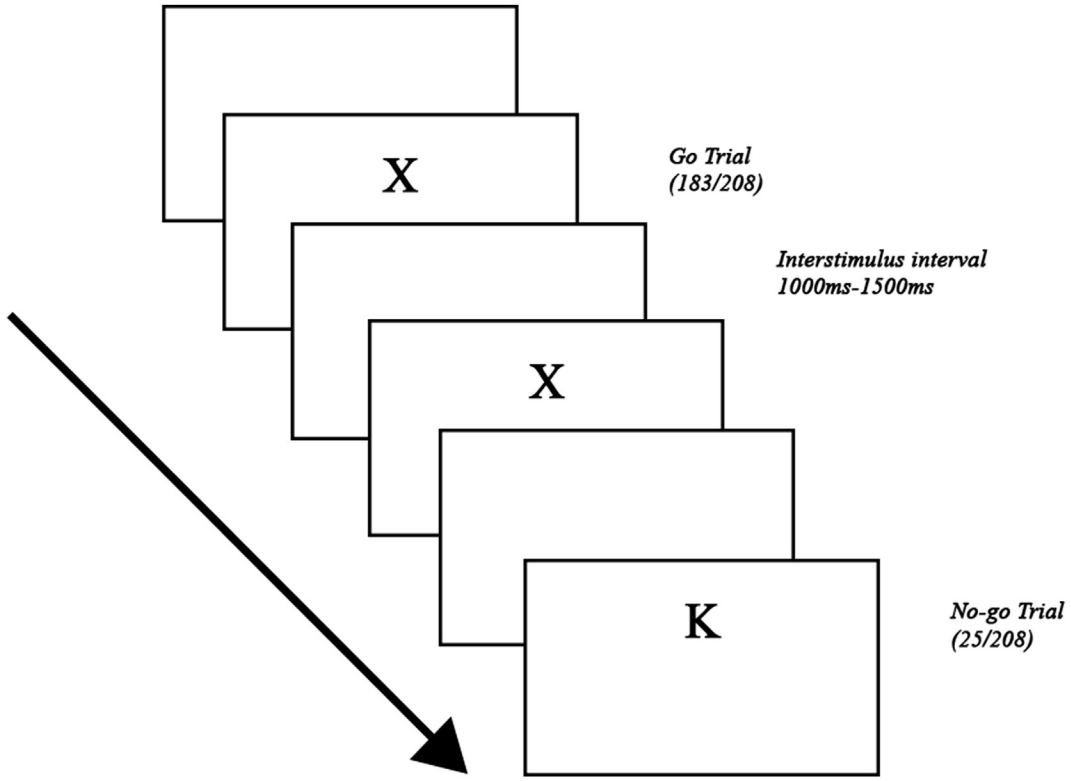
Performance on the Go/No-Go task was assessed via accuracy on Go trials and No-Go trials, both expressed as percentages, as well as reaction time for Go trials. Participants who were deemed as outliers on any of these metrics (eg, >2.5 SDs away from the sample mean) were removed from the full dataset. Two participants were removed as a result of outlier performance on Go trials (1 HC, 1 FEP; 23% accuracy and 2% accuracy, respectively). Analysis of variance was conducted on these scores. Clinical measure scores, age, and handedness were also compared between groups.

Imaging Data Acquisition and Processing

Images were acquired on a 3T MRI scanner (GE Discovery 3T 750W, General Electric). Functional images were obtained using an echo-planar imaging sequence (time-to-repetition [TR] 850 milliseconds; time-to-echo [TE] 30 milliseconds; flip angle [FA] 52°; field of view [FOV] 216 × 216 × 156 mm; voxel size 2.4 × 2.4 × 2.4 mm; slice thickness 2.4 mm; 60 slices per volume; 470 volumes). A high-resolution T1-weighted image was collected for each participant for within-subject registration (TR 6.8 milliseconds; TE 3.0 milliseconds; FA 8°; FOV 230 × 230 × 200 mm; voxel size 0.9 × 0.9 × 0.9 mm). Field map images were also acquired for b0 unwarping (TR 8000 milliseconds; TE 80 milliseconds; FOV 216 × 216 × 156 mm; voxel size 2.4 × 2.4 × 2.4; 66 slices; 2 volumes).

Images were preprocessed and analyzed with FSL.[36] The first 4 volumes were removed. Images were re-aligned within subject to account for head motion throughout the scan.[37] Alignment parameters for each subject were used to calculate framewise displacement at each volume. Participants who exhibited an average framewise displacement over 0.4 mm were excluded from the data set. No participants were removed based on this criterion. Data were unwarped to remove distortions with FSL's topup tool[38] using a method similar to one previously described.[39] Images were smoothed with a Gaussian kernel with a full width half maximum (FWHM) of 7 mm, and a generalized linear model (GLM) was applied to estimate activation between

FIGURE 1 Go/No-Go Task Layout



Note: *Participants were presented with a series of Go trials in which they were to respond with a button press. Between these Go trials, participants were randomly presented with the letter "K," during which they were to inhibit their response (eg, No-Go trial).*

conditions at the subject level. These first-level models are described below. All subjects' models were registered to an anatomical T1 image using a mutual information-based method with FSL's FLIRT tool[40] and then normalized to MNI space before higher-level analyses were conducted.

Neuroimaging Analysis

GLMs were constructed with FSL's FEAT tool.[41,42] Trial condition (Go vs No-Go) as well as participant accuracy (Correct vs Incorrect) on any trial were used to create 4 regressors for first-level GLMs along with their temporal derivatives: correct Go, correct No-Go, incorrect Go, incorrect No-Go. Although failed trials have previously been examined in fMRI studies using the Go/No-Go paradigm,[43,44] our dataset contained an inconsistent number of incorrect No-Go trials across subjects (minimum = 0, maximum = 18). Therefore, we examined only correct trials, as has also previously been done.[15,45] First-level contrast images were created comparing successful No-Go > Go.[43] These first-level contrast images were input into a whole-brain analysis at the group level via paired t tests, including confound regressors for age, IQ, antipsychotic olanzapine equivalents, total PANSS scores, and framewise displacement. Statistical significance required a voxel-based Z-score threshold of $Z > 3.1$ (corresponding to $p < .001$, uncorrected) and a cluster-level extent threshold of $p < .01$ corrected for familywise error. This cluster-level correction ensures that for groups of voxels found to activate above the Z threshold of 3.1, the spatial extent of the cluster is larger than one would expect by chance with a random Gaussian field.[46,47] The locations of clusters were determined via visual inspection alongside the Talairach atlas within FSL, a digitized form of the original Talairach atlas registered into MNI152 space.[48,49]

To capture the nature of differences found between groups within the No-Go > Go contrast, activation within significant clusters for No-Go trials were extracted and plotted between groups. For all clusters within these regions that showed significantly different activity between FEP and FEP+CD groups, we created 5-mm orbital ROIs around the voxel of peak activation. Each participant's activity estimate for successful No-Go trials within these spherical ROIs was extracted from their subject-level models, which had been normalized to MNI space. Spherical ROIs were used rather than atlas-based ones to minimize the effects of

between-subject structural variance and to account for activation occurring between distinct regions. Plots of these parameter estimates were used to determine whether differences found in the prior No-Go > Go contrast were due to alterations in inhibition during No-Go trials or baseline responding during Go trials.

RESULTS

Sample Characteristics

Descriptive statistics as well as comparisons between groups can be found in Table 1. Age differed significantly between groups, with HC participants being older than the clinical groups. As such, age was included as a covariate in GLMs of fMRI data. No significant differences were found between groups in terms of handedness or IQ. As expected, analyses of variance revealed a difference between groups in PANSS scores and olanzapine equivalent antipsychotic usage, but results of *t* tests between FEP and FEP+CD groups were non-significant. As expected, the FEP+CD group endorsed more CD symptoms than the FEP group. Among the 16 CD+FEP participants, 15 endorsed a CD symptom of aggression to people and animals. Mean framewise displacement did not differ between groups.

Lifetime psychiatric diagnoses obtained from the SCID-5-RV are presented in Table S1, available online. There was no difference in frequency for any category of diagnoses between FEP+CP and FEP groups.

Task Performance

There were no group differences for reaction time for Correct Go-trials ($F_{2,46} = 1.41$, $p = .254$) or Incorrect No-Go trials ($F_{2,46} = 1.07$ $p = .352$). When comparing trial accuracy, there was no group difference for Go trials ($F_{2,46} = 0.94$, $p = .398$). However, a group difference was found for No-Go trial accuracy ($F_{2,46} = 3.67$, $p = .033$). Follow-up *t* tests revealed that the FEP group (mean = 0.80, SD = 0.12) was more accurate for No-Go trials than both the HC group (mean = 0.66, SD = 0.16; $t[29.74] = 2.84$, $p = .008$) and the FEP+CD group (mean = 0.66, SD = 0.21; $t[23.64] = 2.27$, $p = .032$). No difference was found between the HC and FEP+CD groups ($t[27.57] = 0.02$, $p = .988$).

Whole-Brain Analysis: fMRI results

Whole-brain analyses revealed 4 clusters of increased activation in the FEP+CD group compared to the FEP group (Figure 2). These clusters were located in the cingulate gyrus, bilateral middle frontal gyri, medial frontal gyrus, bilateral interior parietal lobule, right superior temporal gyrus, right inferior temporal gyrus, and cerebellum (Table 2). The FEP+CD group also showed higher activation than the HC group in bilateral inferior parietal lobules (Figure 2; Table 2). No areas of reduced activation for the FEP+CD group were detected compared with the FEP or HC groups. No areas of altered activation were found between the FEP and HC groups. No significant activation patterns were associated with any of the included covariates (olanzapine-equivalent antipsychotic medication use, PANSS general score, age, IQ, or framewise displacement).

Post Hoc Comparisons

To clarify the nature of activation differences for clusters between groups (eg, whether observed increases in contrast differences were due to increased No-Go activity vs reduced Go activity), subject-level activation within each cluster for successful No-Go trials (without contrast to successful Go trials) was extracted for visual comparison between groups. To account for subject differences in neural structure and activation spread as well as to increase parameter estimates for all participants, we extracted activation for each subject from a 5-mm sphere around the peak voxel of activation for each cluster. Because of the distance of the medial frontal gyrus cluster to the surface of the brain, a large portion of the spherical ROI for this cluster was situated outside the brain and did not yield accurate activation estimates. Thus, this ROI was removed from further analysis. These activation parameters are depicted in Figure 3. Mean activation was highest in the FEP+CD group in all regions (Table S2, available online).

Sensitivity Analysis

The current dataset included 16 to 18 participants per group, 2 of whom were removed because of exceptionally poor performance of the task. In the final dataset, participant accuracy on the 25 No-Go trials ranged from 7 (or 28%) to 25 (100%), a large range of accuracy, with 7 participants completing less than 50% of No-Go trials correctly (Figure 4). To assess the volatility of our results, all 7 participants with No-Go accuracy under 50% (3 HC and 4 FEP+CD) were removed from the dataset. Estimates from the No-Go > Go contrast within the spherical ROIs created for assessment of No-Go trials only was plotted against No-Go > Go estimates in these ROIs from the original dataset of 49 participants (Figure 5). Despite removal of these subjects, quartiles between the reduced dataset were similar for the HC group (reduced Q1 = –24.05, Q2 = 35.55, Q3 = 105.99, Q4 = 360.34; original Q1 = –23.79, Q2 = 41.42, Q3 = 116.62, Q4 = 360.34) and the FEP+CD group (reduced Q1 = 25.31, Q2 = 95.06, Q3 = 171.79, Q4 = 437.26; original Q1 = 38.48, Q2 = 110.09, Q3 = 187.93, Q4 = 458.38). As no participants were removed from the FEP group, quartiles were

TABLE 1 Demographic and Behavioral Characteristics of Subjects

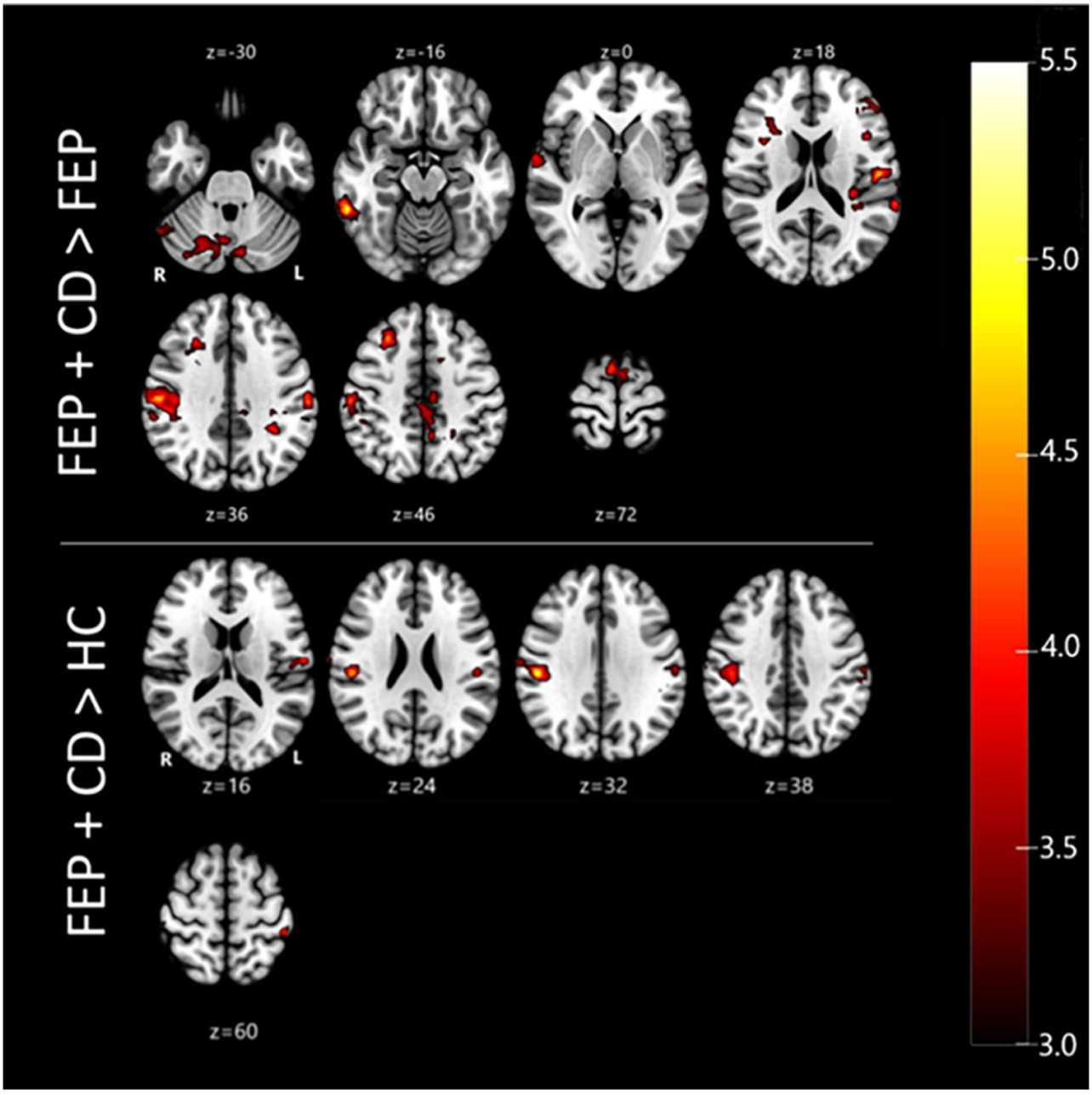
	HC	FEP	FEP+CD			*t* Test (*p*)		
	n = 17	n = 16	n = 16	Statistic	*p*	HC vs FEP	HC vs FEP +CD	FEP vs FEP+CD
Age, y	26.65 ± 4.97	22.38 ± 3.12	23.94 ± 4.39	$F_{2,46} = 4.29$	.02[a]	.006	.107	.256
Right-handed participants	N = 15	N = 16	N = 15	$\chi_{2,49} = 1.96$	.37[b]			
WTAR IQ	114.06 ± 8.4	115.63 ± 10.48	109.2 ± 13.76	$F_{2,46} = 1.43$	.249[a]			
PANSS								
General symptom severity	16.06 ± 0.25	19 ± 3.66	19.2 ± 5.36	$F_{2,42} = 3.48$	.04[a]	.01	.04	.907
Negative symptom severity	7 ± 0	7.5 ± 0.94	8.13 ± 2.42	$F_{2,42} = 2.25$	.119[a]			
Positive symptom severity	7.19 ± 0.4	10.29 ± 3.6	10.13 ± 4.37	$F_{2,42} = 4.51$	.017[a]	.007	.021	.919
Total symptom severity	30.25 ± 0.45	36.79 ± 6.47	37.47 ± 11.08	$F_{2,42} = 4.57$	.016[a]	.002	0.024	.84
AP medication use (olanzapine equivalent)	0 ± 0	8.42 ± 9.13	9.57 ± 9.07	$F_{2,46} = 8.39$	.0008[a]	.002	.001	.726
No. of diagnosed CD symptoms	0.12 ± 0.33	0.56 ± 0.81	4.13 ± 1.59	$F_{2,30} = 63.87$	<.001[a]	<.001	<.001	<.001
Participants diagnosed with a CD symptom of aggression toward people and animals	n = 0	n = 0	n = 15					
Buss–Perry Aggression Questionnaire								
Physical	15.29 ± 15.29	20.6 ± 20.6	18.53 ± 18.53	$F_{2,44} = 4.51$	.029	.018	.076	.307
Verbal	12.53 ± 12.53	13.33 ± 13.33	13.07 ± 13.07	$F_{2,44} = 2.25$	.857			
Anger	11.76 ± 11.76	13.73 ± 13.73	14.93 ± 14.93	$F_{2,44} = 3.48$	.209			
Hostility	15.59 ± 15.59	22.36 ± 22.36	19.8 ± 19.8	$F_{2,44} = 4.57$	.032	**.007**	.112	.364
Total	55.18 ± 55.18	68.53 ± 68.53	66.33 ± 66.33	$F_{2,44} = 1.24$	.108			
Framewise displacement	0.11 ± 0.06	0.11 ± 0.04	0.12 ± 0.04	$F_{2,46} = 0.21$	.811[a]			

Note: *AP = antipsychotic; CD = conduct disorder; FEP = first-episode psychosis; FEP+CD = first-episode psychosis with conduct disorder; HC = healthy control; PANSS = Positive and Negative Syndrome Scale; WTAR = Weschler Test of Adult Reading.*

[a]*t Test.*

[b]χ^2 *Test.*

FIGURE 2 Z-Thresholded Maps of No-Go > Go Activity Differences



Note: *Brain regions showing greater activity for the No-Go > Go contrast in the FEP+CD group compared with the FEP group, as well as the FEP+CD group compared with the HC group (Z threshold 3.1, p < 0.01 cluster corrected for multiple comparisons). HC = healthy control; FEP = first-episode psychosis; FEP+CD = first-episode psychosis with conduct disorder.*

identical between datasets (Q1 = –72.66, Q2 = –11.09, Q3 = 171.79, Q4 = 276.12).

DISCUSSION

To the best of our knowledge, these preliminary results are the first to identify neural alterations in response inhibition among FEP+CD patients. In this pilot investigation, successful response inhibition elicited hyperactivation in FEP+CD vs FEP in the cingulate gyrus; regions of the PFC, including the middle frontal gyrus and medium frontal gyrus; bilateral inferior parietal lobules; postcentral gyri; temporal gyrus; and cerebellum. The FEP+CD group also displayed higher activation than the HCs in bilateral

TABLE 2 Location, Size, *Z* statistics, and *p* Values of Brain Regions Showing Group Differences in No-Go > Go Contrast

Group	x	y	z	Side	Cluster size	*Z* score	*p*	Location
FEP+CD > FEP	−50	−22	26	L	1,440	5.02	1.11E-08	Inferior parietal lobe/postcentral gyrus
	56	−20	32	R	1,259	5.33	5.96E-08	Inferior parietal lobe/postcentral gyrus
	−4	−36	44	L/R	919	4.68	2.32E-06	Cingulate gyrus/precuneus
	4	−66	−26	L/R	749	4.4	1.66E-05	Cerebellum
	60	−44	−18	R	692	5.35	3.30E-05	Inferior temporal gyrus/fusiform gyrus
	28	26	46	R	651	4.96	5.47E-05	Middle frontal gyrus/superior frontal gyrus
	54	0	−6	R	396	4.12	1.70E-03	Superior temporal gyrus
	6	4	74	L/R	385	4.49	2.00E-03	Superior frontal gyrus/medial frontal gyrus
	−46	40	24	L	308	4.61	0.00654	Middle frontal gyrus/inferior frontal gyrus
FEP+CD > HC	52	−24	30	R	698	5.43	0.0000306	Inferior parietal lobe/postcentral gyrus
	−48	−34	60	L	356	4.27	0.0031	Inferior parietal lobe/postcentral gyrus
FEP > FEP+CD	No clusters identified							
FEP > HC	No clusters identified							
HC > FEP+CD	No clusters identified							
HC > FEP	No clusters identified							

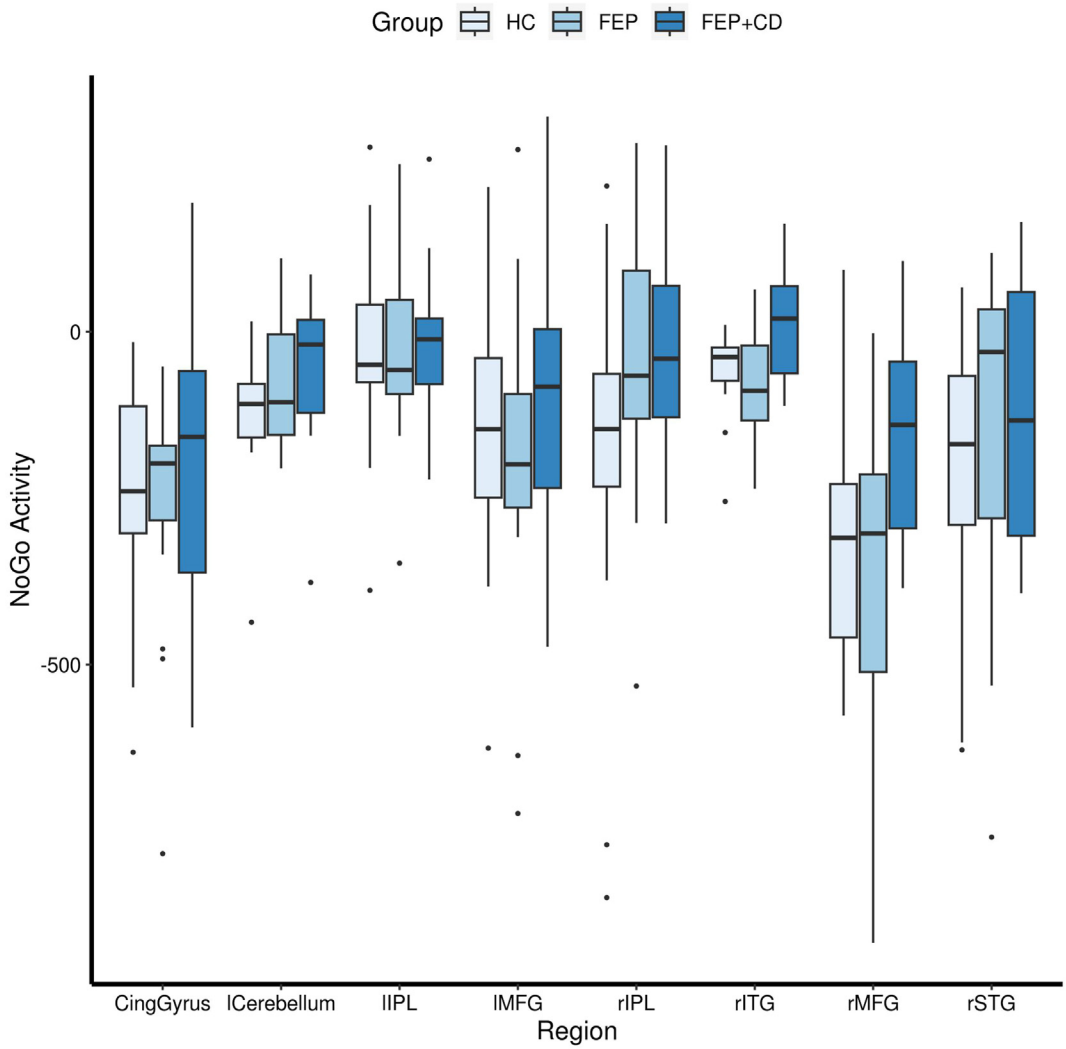
Note: *FEP = first-episode psychosis; FEP+CD = first-episode psychosis with conduct disorder; HC = healthy control.*

inferior parietal lobules. Despite these differences in neural activity during response inhibition, task performance did not differ between groups.

One of our main findings was that FEP+CD exhibited greater neural activation in the PFC, particularly the bilateral middle frontal gyrus and medial frontal gyrus vs the FEP participants. The right middle frontal gyrus (rMFG) has been described as a key locus for executing response inhibition in the inhibitory neural network system.[27] The left middle frontal gyrus (lMFG) has displayed altered activation in youth with oppositional defiant disorder.[14] The involvement of the medial frontal gyrus is unclear during response inhibition. Welender *et al.* did not find altered activity in this region during a Go/No-Go task in bipolar I disorder, but it is thought to be involved in cognitive control. Cortical thinning has been found in antisocial personality disorder patients in this region, among other prefrontal areas.[50] Nonetheless, the fact that these PFC regions showed greater activation during successful inhibition in FEP+CD relative to FEP tentatively suggests that this region may be altered during response inhibition among individuals with CD or when CD is comorbid with psychotic conditions.

We note the direction of this activity difference and its effect on task performance. We found greater PFC activation in FEP+CD patients, which has been found in one study of conduct-disordered youth,[14] whereas reduced frontal activation during the same task has been observed in offending adolescents,[20] individuals with antisocial personality disorder,[51] and SCZ patients with a history of violence.[4] We also found that task performance for response inhibition was equivalent between the FEP+CD and HC groups. This result was surprising, as we expected the FEP+CD group to perform poorly in comparison to both the FEP group and the HC group. This lack of a behavioral difference does simplify our neural findings, however, as we can more confidently attribute group differences to true neural variance rather than to task performance difficulties. Together, this may suggest a compensatory mechanism in FEP+CD patients in order to maintain task demands in a manner not observable in the previously mentioned populations. Increased activation of the PFC, particularly the right dlPFC, may reflect difficulty in maintaining task demands and selection of appropriate behaviors in FEP+CD.[11]

FIGURE 3 No-Go Activation for All Groups Across Regions of Interest

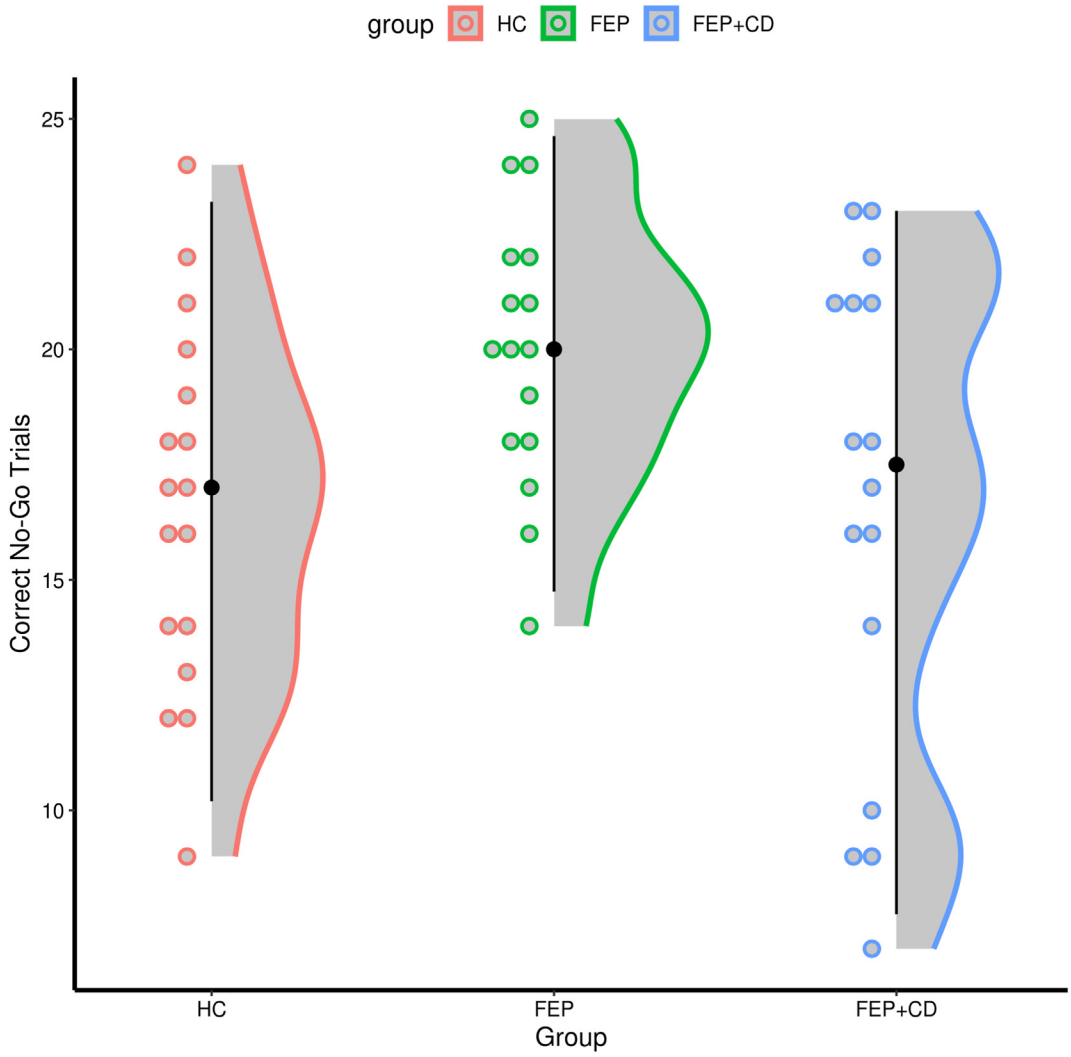


Note: *Activation during No-Go trials was significantly higher for the FEP+CD group than both FEP and HC within the rIPL and rMFG. CingGyrus = cingulate gyrus; lCerebellum = left cerebellum; lIPL = left inferior parietal lobule; lMFG = left middle frontal gyrus; rIPL = right inferior parietal lobule; rITG = right inferior temporal gyrus; rMFG = right middle frontal gyrus; rSTG = right superior temporal gyrus. HC = healthy control; FEP = first-episode psychosis; FEP+CD = first-episode psychosis with conduct disorder. *Analysis of variance, $p < .05$.*

We also found increased activation of the cingulate gyrus, postcentral gyrus, and inferior parietal lobules in FEP+CD compared to FEP. This increased inferior parietal lobule activity was also exhibited in comparison to the HC group. The anterior cingulate cortex has been implicated in response inhibition; however, the region that we noted was more posterior, closer to the precuneus. This region has been associated with many functions, including memory retrieval, attention, and error processing.[52,53] Alterations in inferior parietal lobule activity have been documented, such as reductions in activity for SCZ patients during a working memory task[4] and reduced spontaneous brain activity in CD youth.[54] Compensatory activation of the postcentral gyrus has been found in children with attention-deficit/hyperactivity disorder during a Go/No-Go task.[26]

Several limitations of this preliminary investigation should be noted. First, our sample size was relatively modest. Given our small sample size, we consider this to be a pilot investigation to inform future studies. Second, we did not perform urine drug testing on the day of scanning. It is therefore possible that some of the participants were using cannabis or illicit substances that could have affected the results obtained. However, our assessment protocol ensured that none of the participants had active substance use disorders. Hence, we have some confidence that our results were not affected by heavy use of cannabis or illicit

FIGURE 4 Number of Correct No-Go Trials Completed per Participant Within Groups

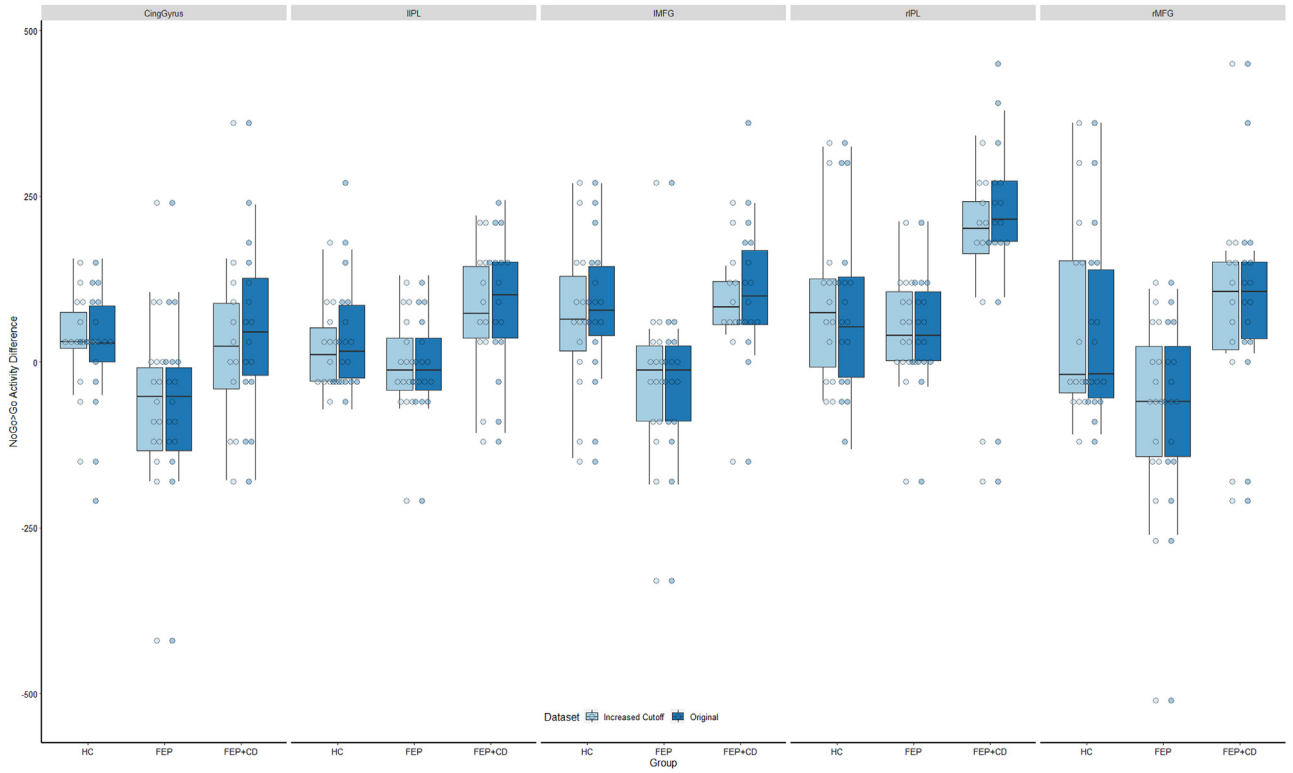


Note: *The maximum possible number of correct No-Go trials to complete was 25. HC = healthy control; FEP = first-episode psychosis; FEP+CD = first-episode psychosis with conduct disorder.*

substances. Third, all FEP and FEP+CD participants were taking antipsychotic medication, which could have confounded the results. However, there was no difference in olanzapine-equivalent doses between groups. We also included this variable as a regressor in the GLMs, and olanzapine equivalents were not independently associated with any neural activity. Fourth, our sample was heterogeneous in both diagnosis and age. Both primary and affective psychoses were captured by our FEP diagnoses, and comorbid diagnoses were acceptable as long as they did not conflict with other inclusion/exclusion criteria (eg, substance use).[21–23] Age did vary between groups, such that HCs were older than other participants. We therefore controlled for age by including it as a covariate in our analyses. Fifth, task performance differed between groups in an unexpected direction, whereby FEP patients performed better in response inhibition than HC participants, although we expected FEP patients to perform more poorly than HC participants.[55] Sixth, we lacked data on potential callous unemotional (CU) traits and proactive vs reactive aggression. More detailed measures could be used to stratify groups. Finally, we did not test a group of participants who had CD without a psychotic disorder. Therefore, we are unable to determine whether the results obtained for the FEP+CD group are due to the presence of CD alone or are the result of the combination of disorders.

In summary, this preliminary study reports altered neural activation during response inhibition in FEP+CD vs

FIGURE 5 Parameter Estimate Changes After Removing Low-Accuracy Participants



Note: *Difference between No-Go and Go activity for all groups across regions of interest before and after removing subjects with a trial accuracy under 50%. Group-level activation parameters were nearly equivalent between datasets after removal of poor performers. CingGyrus = cingulate gyrus; lIPL = left inferior parietal lobule; lMFG = left middle frontal gyrus; rIPL = right inferior parietal lobule; rMFG = right middle frontal gyrus. HC = healthy control; FEP = first-episode psychosis; FEP+CD = first-episode psychosis with conduct disorder*

FEP in the prefrontal cortex, cingulate gyrus, temporal gyrus, inferior bilateral lobules, and cerebellum.

CRediT authorship contribution statement

Nathan J. Kolla: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Ryan Aloysius:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **George Gainham:** Writing – review & editing, Project administration, Data curation. **Colin Hawco:** Writing – review & editing, Methodology, Formal analysis.

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Nathan J. Kolla, Ryan Aloysius, and Colin Hawco are with Centre for Addiction and Mental Health, Toronto, Ontario, Canada. Nathan J. Kolla is also with the University of Saskatchewan, Saskatoon, Saskatchewan, Canada. Nathan J. Kolla and Colin Hawco are also with the University of Toronto, Toronto, Ontario, Canada. George Gainham is with Western University, London, Ontario, Canada.

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Correspondence to Nathan J. Kolla, MD, PhD, FRCPC, University of Saskatchewan, Department of Psychiatry, Royal University Hospital, 103 Hospital Drive, Room 109 Ellis Hall, Saskatoon, Saskatchewan, S7N 0W8 Canada; e-mail: nathan.kolla@camh.ca

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