Proactive response inhibition abnormalities in the sensorimotor cortex of patients with schizophrenia

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Background: Previous studies of response inhibition in patients with schizophrenia have focused on reactive inhibition tasks (e.g., stop-signal, go/no-go), primarily observing lateral prefrontal cortex abnormalities. However, recent studies suggest that purposeful and sustained (i.e., proactive) inhibition may also be affected in these patients. **Methods:** Patients with chronic schizophrenia and healthy controls underwent fMRI while inhibiting motor responses during multisensory (audiovisual) stimulation. Resting state data were also collected. **Results:** We included 37 patients with schizophrenia and 37 healthy controls in our study. Both controls and patients with schizophrenia successfully inhibited the majority of overt motor responses. Functional results indicated basic inhibitory failure in the lateral premotor and sensorimotor cortex, with opposing patterns of positive (schizophrenia) versus negative (control) activation. Abnormal activity was associated with independently assessed signs of psychomotor retardation. Patients with schizophrenia also exhibited unique activation of the pre-supplementary motor area (pre-SMA)/SMA and precuneus relative to baseline as well as a failure to deactivate anterior nodes of the default mode network. Independent resting-state connectivity analysis indicated reduced connectivity between anterior (task results) and posterior regions of the sensorimotor cortex for patients as well as abnormal connectivity between other regions (cerebellum, thalamus, posterior cingulate gyrus and visual cortex). **Limitations:** Aside from rates of false-positive responses, true proactive response inhibition tasks do not provide behavioural metrics that can be independently used to quantify task performance. **Conclusion:** Our results suggest that basic cortico-cortico and intracortical connections between the sensorimotor cortex and adjoining regions are impaired in patients with schizophrenia and that these impaired connections contribute to inhibitory failures (i.e., a positive rather than negative hemodynamic response).

Introduction

Efficient cognitive control is necessary for directing internal resources toward immediate cognitive or behavioural goals.¹ Poor cognitive control is associated with reduced clinical insight,² lower levels of remission,³ reduced daily living skills⁴ and greater suicide risk⁵ in patients with schizophrenia. Response inhibition, the ability to inhibit planned or ongoing motor actions, represents an important subcomponent of cognitive control.⁶ Previous research in patients with schizophrenia used tasks, such as the go/no-go and stop-signal tasks,^{7–10} which require the late-acting inhibition of prepotent motor responses on a trial-by-trial basis following stimulus presentation (hereafter referred to as reactive response inhibition). In contrast, the purposeful and sustained inhibition of motor responses in an anticipatory manner (hereafter referred to as proactive response inhibition) has been infrequently examined in patients with schizophrenia,¹¹ despite recent suggestions that proactive processes may represent a more sensitive marker of disease.^{11–13}

Simple reactive response inhibition tasks commonly activate the pre-supplementary motor area (pre-SMA), with individual task requirements and complexity driving activity in other regions.^{14–17} For example, the right middle frontal gyrus and inferior parietal lobule are typically activated during go/no-go tasks relative to the cingulo-opercular-thalamic network activated during stop-signal tasks.¹⁷ Previous studies^{15,18} and a recent meta-analysis¹⁴ have suggested that lateral prefrontal/posterior parietal activation are recruited by working memory/attentional task demands rather than by response inhibition per se. Thus, there are 2 potentially different paths (attention/working memory network v. response inhibition network) that could explain response inhibition deficits commonly reported in patients with schizophrenia.

Neuroimaging studies of reactive inhibitory control in patients with schizophrenia generally report reduced activation in lateral prefrontal cortices during the performance of go/no-go and stop-signal tasks.^{7–10} Similar findings emerge during more complex go/no-go tasks. For example, patients with schizophrenia fail to activate a dorsal prefrontal-parietal

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network while inhibiting responses for negative compared with neutral words.¹⁹ Patients also fail to deactivate the cingulate while inhibiting positive words, instead showing positive activation in the prefrontal cortex. Another study²⁰ reported both decreased dorsal anterior cingulate activity and increased functional connectivity between the dorsal anterior cingulate and lateral prefrontal cortex in patients with schizophrenia-spectrum disorders and unaffected siblings during a variant of the Flanker task. In contrast to these studies of reactive inhibition, proactive response inhibition likely involves unique cognitive and neuronal circuitry,^{6,14} which may reveal additional deficits in patients with schizophrenia owing to failures in planning.^{12,13} Deficits in proactive inhibitory control have been associated with striatal, inferior frontal and parietal abnormalities in patients with schizophrenia and their unaffected relatives during a stop-signal task that included an anticipatory component.^{11,21}

In the present study, we administered a simple inhibitory task during which participants were cued to withhold motor responses over an extended block of time during the passive viewing of multisensory stimuli. This task reduces the trial-by-trial response uncertainty associated with reactive tasks¹⁴ while maximizing power for detecting group differences.²² Importantly, the simplicity of the task should reduce behavioural performance confounds (i.e., reduced accuracy or slower responses) typically observed in patients with schizophrenia during more difficult reactive inhibitory control tasks.²³ We investigated abnormalities within networks responsible for both attention and working memory (i.e., inferior frontal gyrus, dorsolateral prefrontal cortex [DLPFC] and inferior parietal lobules) as well as response inhibition (i.e., premotor cortices) demands, predicting no group differences owing to the task simplicity. The integrity of these networks was also independently assessed using functional connectivity analyses.

Methods

Participants

We evaluated clinically stable patients with schizophrenia and a group of age- and sex-matched healthy controls. High-quality resting-state data were collected. All participants provided informed consent for the study, which was approved by the University of New Mexico Health Sciences Center Human Research Review Committee.

Diagnoses of schizophrenia were made by board-certified psychiatrists using the Structured Clinical Interview for DSM-IV-TR. Participants were required to be between 18 and 65 years old. Exclusion criteria were head trauma with loss of consciousness for more than 5 minutes; mental retardation or other severe developmental disorders; history of neurologic disorder; active substance (non-nicotine) dependence or abuse within the past year; and phencyclidine, amphetamine or cocaine dependence (lifetime) or use within the past year. Controls were also excluded if they had a history of a psychotic disorder in a first-degree relative or a current or past psychiatric disorder (with the exception of 1 lifetime depressive episode). Participants refrained from smoking for at least 1 hour before scanning.

Neuropsychological and clinical assessment

All participants completed the Wechsler Test of Adult Reading (WTAR). Patients with schizophrenia also completed urine drug screening and a comprehensive clinical battery, including the Measurement and Treatment Research to Improve Cognition in Schizophrenia battery (MATRICS), Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale, Clinical Global Impression Scale, Fagerstrom Test for Nicotine Dependence, Abnormal Involuntary Movements Scale (AIMS), Simpson–Angus Scale (SAS), Barnes Akathisia Scale (BAS) and the University of California, San Diego (UCSD) Performance Based Skills Assessment test (UPSA-2). Further details about the clinical assessments are provided in Appendix 1, available at jpn.ca. Medication load was calculated using olanzapine equivalents.²⁴

Tasks

Congruent or incongruent multisensory (auditory and visual) numeric stimuli were simultaneously presented at either low (0.33 Hz; 3 trials/block) or high (0.66 Hz; 6 trials/block) frequencies in 10-s blocks (Fig. 1). For each block, the stream of target numbers (“ONE”, “TWO” or “THREE”) was preceded by a cue word: “HEAR” (attend auditory condition), “LOOK” (attend visual condition) or “NONE” (response inhibition condition). In the attend auditory and attend visual conditions, participants responded via a right-hand button press to 1 of 3 target buttons corresponding to the target stimulus in the attended modality while ignoring simultaneously presented numbers in the opposite sensory modality. The results from the attend auditory and attend visual trial types from a similar cohort have been reported previously.²⁵ In contrast, during “NONE” trials (144 trials over 6 imaging runs), participants were instructed to inhibit a motor response. Interblock intervals were varied (8, 10 or 12 s) to decrease temporal expectations and improve the modelling of the hemodynamic response function (HRF). For the resting state scan, participants were instructed to stare at a fixation cross for approximately 5 min.

Imaging and statistical analysis

High-resolution (1 × 1 × 1 mm) T_1 -weighted and echo-planar images (repetition time [TR] 2000 ms, voxel size 3.75 × 3.75 × 4.55 mm) were collected on a Siemens 3 T Tim Trio scanner

Fig. 1: Proactive response inhibition during both (A) congruent and (B) incongruent trials. The right side of each panel indicates the inter-stimulus interval (ISI), determined by the frequency of stimulation, as well as the interblock interval (IBI).

using a 12-channel head coil (Appendix 1). Functional imaging maps were calculated with the Analysis of Functional NeuroImages (AFNI) software using standard preprocessing steps, including calculation of framewise displacement (FD).²⁶ Deconvolution was used to generate a single HRF for each trial type relative to baseline (visual fixation plus baseline gradient noise) for the first 22 s after stimulus onset. We calculated percent signal change (PSC) by summing β coefficients for images occurring 6–14 s after cue onset and dividing by the average model intercept. Error trials were modelled separately with event-related regressors to eliminate variance associated with false-positive responses.²⁷ Functional connectivity MRI maps were calculated by first regressing motion parameters, their first order derivatives, and estimates of physiologic noise (derived from white matter and cerebral spinal fluid) and applying a band-pass filter (0.01–0.1 Hz). Seeds were empirically derived from group comparisons of task data and used as an independent assessment of network integrity.

We conducted a whole-brain, voxel-wise $2 \times 2 \times 2$ (group [schizophrenia v. control] $\times$ congruency [congruent v. incongruent] $\times$ frequency [0.33 Hz v. 0.66 Hz]) mixed-measures analysis of covariance (ANCOVA) on PSC data from the NONE trials. An ANCOVA examined group differences in connectivity. We corrected all functional results for false positives at $p < 0.05$ ($p < 0.005$, minimum cluster size 2432 μL) based on 10 000 Monte-Carlo simulations. Multiple regres-

sion examined the association between activation abnormalities and either clinical symptoms (independent variables: PANSS positive symptoms score, PANSS motor retardation subscore, PANSS poor attention subscore, PANSS impulse control subscore, UPSA-2 total score) or neuropsychological performance (independent variables: CPT-II impulsivity summary score, MATRICS processing speed subscore) in patients with schizophrenia only.

Results

Demographics and behavioural data

We evaluated 37 patients with schizophrenia and 37 controls. Data from 1 patient were lost during acquisition, thus we discarded the data for that patient's matched control. Another patient was an outlier relative to the patient cohort for FD on several motion parameters. Finally, 1 control and 1 patient were eliminated for poor performance (failure to inhibit responses on more than 25% of trials), leaving a total of 34 patients (30 men, mean age 35.9 ± 13.8 yr) and 35 controls (30 men, mean age 34.6 ± 12.7 yr) available for analysis. We collected high-quality resting state data from 33 of 34 patients and from all controls. Twenty-eight of 33 patients reported atypical antipsychotic use. There were no significant age differences between the groups ($p = 0.68$; Table 1). Patients with schizophrenia obtained less education than controls ($t_{67} = 2.3$, $p = 0.024$) and exhibited a

Table 1: Demographic and clinical characteristics of the study sample

Characteristic	Group; mean ± SD*		<i>p</i> value	Cohen's <i>d</i>
	Schizophrenia	Control		
Demographics				
Sex, female:male	4:30	5:30		
Age, yr	35.94 ± 13.76	34.63 ± 12.72	0.68	0.10
Education, yr	12.53 ± 1.46	13.51 ± 2.03	0.024	−0.56
WTAR, <i>t</i> score†	50.73 ± 10.06	56.31 ± 6.27	0.008	−0.67
Clinical measures				
Age at illness onset, yr	21.61 ± 7.58	—	—	—
Illness duration, yr	13.58 ± 10.47	—	—	—
PANSS positive	15.68 ± 3.26	—	—	—
PANSS negative	15.94 ± 4.39	—	—	—
PANSS total	59.52 ± 9.93	—	—	—
UPSA total	100.71 ± 12.20	—	—	—
MATRICES total	34.06 v± 13.43	—	—	—
Clinical Global Impression	3.72 ± 0.73	—	—	—
Calgary Depression Scale	0.56 ± 0.67	—	—	—
FTND	0.79 ± 1.10	—	—	—
Olanzapine equivalent	12.87 ± 7.50	—	—	—
SAS	1.15 ± 1.35	—	—	—
AIMS	1.47 ± 2.43	—	—	—
BAS	0.26 ± 0.51	—	—	—

AIMS = Abnormal Involuntary Movements Scale; BAS = Barnes Akathisia Scale; FTND = Fagerstrom Test for Nicotine Dependence; MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia; PANSS = Positive and Negative Syndrome Scale; SAS = Simpson Angus Scale; SD = standard deviation; UPSA = University of California, San Diego Performance-Based Skills Assessment; WTAR = Wechsler Test of Adult Reading.

*Unless indicated otherwise.

†All clinical scores are raw data with the exception of the WTAR.

lower estimate of premorbid intelligence ($t_{33.3} = 2.7$, $p = 0.008$). False-positive responses on NONE trials were non-normally distributed and near floor levels (Fig. 2C), with 29 of 35 controls and 17 of 34 patients exhibiting no errors. There were no significant differences in error rate between patients and controls on congruent trials (1.51% v. 0.75%, $p = 0.14$), whereas we observed a trend-level difference between patients and controls during incongruent trials (1.23% v. 0.44%, $U_{67} = 490.5$, $z = -1.9$, $p = 0.06$).

Motion parameter analysis

We performed 2 multivariate analyses of variance (MANOVA) to examine group differences in FD over the 6 individual

motion parameters. A significant multivariate effect indicated greater rotational motion for patients with schizophrenia than controls ($F_{3,65} = 4.52$, $p = 0.006$), with univariate tests also reaching significance (pitch: $F_{1,67} = 10.70$, $p = 0.002$; yaw: $F_{1,67} = 9.52$, $p = 0.003$). The multivariate effect of translational motion was not significant ($p = 0.20$). Therefore, we included mean FD as a covariate in all functional analyses.

Between-group comparisons

Results from the group (patients v. controls) $\times$ congruency (congruent v. incongruent) $\times$ frequency (0.33 Hz v. 0.66 Hz) mixed-measures ANCOVA indicated significant group differences

Fig. 2: (A) Both the left (L) and right (R) sensorimotor cortex (SMC) exhibited a significant main effect of group during the current task. The magnitude of p values are denoted in red ($p < 0.005$) or yellow ($p < 0.001$), and activation was greater in patients with schizophrenia (SP) than healthy controls (HC). Sagittal (x) and axial slice locations (z) are given according to the Talairach atlas. (B) Percent signal change (PSC) data are presented for the entire hemodynamic response function (HRF; 22-s poststimulus interval) collapsed across frequency and congruency for patients (red) and controls (blue). Error bars are based on the standard error of the mean for each image time point. The grey drop lines indicate the images that were used to measure the peak hemodynamic response. (C) The scatterplot presents percentage of false-positive responses for low (L; 0.33 Hz) and high (H; 0.66 Hz) stimulus frequencies during congruent (CT) and incongruent (IT) trials. Scatterplot data are presented with a vertical jitter of 0.5% to better visualize overlapping data.

within the bilateral pre- and postcentral gyri extending into the lateral premotor cortex (Brodmann areas [BA] 1, 2, 3, 4, 6; Fig. 2A). Follow-up 1-sample t tests indicated that whereas patients with schizophrenia exhibited a positive blood-oxygen level-dependent (BOLD) response over baseline for both the left ($t_{33} = 4.1, p < 0.001$) and right ($t_{33} = 3.2, p = 0.003$) sensorimotor cortex (SMC), controls exhibited a statistically significant negative BOLD response from baseline (left: $t_{34} = -2.4, p = 0.020$; right: $t_{34} = -3.0, p = 0.005$). A binary logistic regression examined whether activation in the left or right SMC could successfully classify patients with schizophrenia and controls. The overall model was not significant (71.4% of controls and 70.6% of patients classified correctly, $p = 0.29$), although a trend for successful classification (Wald = 3.5, $p = 0.06$) existed for the left SMC.

We observed a significant effect of congruency in the bilateral cerebellar vermis, with increased activation observed in the congruent relative to the incongruent condition. The main effect of frequency and the frequency $\times$ congruency interaction are presented in Appendix 1 (Fig. S1 and Fig. S2, respectively).

Supplemental analyses using more stringent exclusion criteria for the percentage of false-positive errors (i.e., a 5% rather than 25% cutoff rate) were performed next to ensure that lateral premotor and SMC activity were not driven by errors. The stricter criteria led to the exclusion of 3 additional patients and 2 additional controls from our data analyses. Supplemental analyses resulted in similar group differences in activation both in terms of volume (left: 131.0% of original; right: 94.0% of original) and location. We used multiple regression to confirm that activation within the SMC was not related (all $p > 0.10$) to current medication load (olanzapine equivalent usage), smoking status (Fagerstrom score), duration of illness or medication-related motor side effects (independent variables: AIMS, SAS and BAS scores) in patients with schizophrenia. Finally, supplemental analyses also confirmed that group differences in SMC activity were not directly related to head motion (Appendix 1).

Within-group comparisons

Given significant differences in lateral premotor and SMC activation, data were collapsed across all of the NONE trials and contrasted against baseline separately for controls and patients with schizophrenia. Results from these analyses indicated largely overlapping activation within the bilateral auditory cortex, visual cortex, posterior superior temporal sulcus, lateral prefrontal cortex, posterior parietal cortex and cerebellum across both groups (Fig. 3). Patients with schizophrenia exhibited additional areas of unique activation within both the SMA complex (pre-SMA and SMA; BA 6, 32, right 8, 24) and the precuneus (BA 7, 19). Healthy controls uniquely exhibited task-induced deactivation within the bilateral rostral anterior cingulate gyrus (rACC; BA 10, 24, 32) and left superior frontal gyrus (BA 8, 9, 10).

We performed 2 multiple regressions to ascertain whether any of the regions of unique activation in patients with schizophrenia (pre-SMA/SMA and precuneus) or deactivation in healthy controls (rACC and superior frontal gyrus) were related to differing patterns of positive versus negative activity

in the lateral premotor cortex and SMC. The average grey matter PSC was used as a covariate to control for individual differences in global brain activity. Results indicated that the degree of pre-SMA/SMA activation across both groups was associated with SMC activity levels in the right (unstandardized $b = 0.736, t_{63} = 3.9, p < 0.001$) and left (unstandardized $b = 0.749, t_{63} = 3.5, p = 0.001$) hemispheres. Similarly, activation level in the rACC was also associated with SMC activity on a bilateral basis (right SMC: unstandardized $b = 0.567, t_{63} = 3.5, p = 0.001$; left SMC: unstandardized $b = 0.550, t_{63} = 3.0, p = 0.004$). There was no association between activity levels in the precuneus or the left superior frontal gyrus with either the right or left SMC (all $p > 0.10$).

Associations with clinical variables

Four multiple regression analyses examined the association between hemodynamic activity in the right and left lateral premotor and SMC (dependent variables) with either clinical symptoms (UPSA-2 total score and PANSS positive, motor retardation, poor attention and poor impulse control subscores) or cognitive performance (MATRICS processing speed, Continuous Performance Test impulsivity score) for patients with schizophrenia only. No models were significant for the overall variance explained (all $p > 0.10$). However, the PANSS motor retardation subscore accounted for a significant amount of variance in the left (unstandardized $b = 0.169, t_{29} = 2.7, p = 0.012$) and right (unstandardized $b = 0.112, t_{29} = 2.3, p = 0.033$) SMC.

Connectivity results

Group activation differences within the bilateral premotor cortex and SMC served as empirical seeds for connectivity analyses. Results (Fig. 4) indicated that healthy controls exhibited significantly increased connectivity relative to patients with schizophrenia in the right (BA 1, 2, 3, 4, 5, 6, 7, 40) and left (BA 1, 2, 3, 4, 5, 40) posterior SMC extending into the inferior parietal lobule; the right superior temporal gyrus (BA 21, 22, 38, 40, 41, 42); and the right (BA 7, 18, 19, 31, 37) and left (BA 18, 19, 36, 37) associative visual cortex. Controls also exhibited increased anticorrelation between the SMC seeds and bilateral lingual gyrus (BA 17, 18) and left cerebellar tonsil. There was no correlation between the SMC seeds and the bilateral posterior cingulate gyrus/precuneus (BA 23, 29, 30, 31) for healthy controls, whereas this region exhibited anticorrelation with the SMC for patients. Finally, connectivity between the SMC and the thalamus/subthalamic nuclei was reversed for patients with schizophrenia (positive correlation) relative to healthy controls (anticorrelation).

Discussion

The present study examined frontoparietal and premotor cortex abnormalities during a simple task that required proactive inhibitory control in a large cohort of patients with schizophrenia. Behavioural results indicated that the majority of patients and controls successfully inhibited overt-motor responses, with patients exhibiting a nonsignificant tendency for increased false-positive responses during

incongruent trials. In contrast to previous studies examining reactive response inhibition,^{7–11,19,21} there were no differences between groups within the lateral prefrontal cortex, subcortical regions or inferior parietal cortex. Instead, opposing patterns of activation (patients: positive BOLD; con-

trols: negative BOLD) were observed within the right and left lateral premotor cortex and SMC, with patients also exhibiting decreased connectivity between the anterior and posterior regions of the SMC. Finally, patients with schizophrenia exhibited unique activation of the pre-SMA/SMA

Fig. 3: Within-group contrasts comparing functional activation during proactive response inhibition relative to baseline separately for both healthy controls (HC) and patients with schizophrenia (SP). **(A)** Regions in Talairach space that were commonly activated across both groups (yellow), as well as regions that were uniquely activated for controls (purple) or patients (red). **(B)** Regions of unique deactivation in controls (striped bars = not applicable). **(A, B)** Clusters derived from the significant main effect of group within the premotor and sensorimotor cortices (SMC) are presented in green. **(C)** Hemodynamic response function (HRF) within selected common areas of activation including the right inferior parietal lobe (R IPL) and left lateral prefrontal cortex (L LPFC). **(D)** Areas of unique activation for patients within the pre-supplementary motor area (pre-SMA)/SMA and precuneus (PCUN). **(E)** Regions of unique deactivation within the rostral anterior cingulate (rACC) and left superior frontal gyrus (L SFG) for controls. For all tracings (patients = red; controls = blue), percent signal change (PSC) is graphed along the Y axis, error bars represent the standard error of the mean and the grey drop lines indicate the images that were used to measure the peak hemodynamic response.

and precuneus in contrast to baseline while subsequently failing to deactivate the anterior nodes of the default mode network (DMN).

Invasive recordings suggest that a negative BOLD response results from neuronal suppression in deep cortical layers, leading to arteriolar vasoconstriction, decreases in cerebral blood flow and volume, and a subsequent increase in local deoxyhemoglobin.^{28–30} The magnitude of the negative BOLD response has also been linked with γ -aminobutyric acid (GABA) levels in the anterior cingulate gyrus during noninvasive human studies,³¹ providing additional support as a surrogate marker of neuronal suppression. In healthy controls, negative BOLD responses have been observed during transcallosal motor inhibition,³² when information from a single sensory modality is actively suppressed^{33,34} and when participants switch from passive to attentionally demanding states.³⁵ Thus, the present findings of a positive rather than negative BOLD response in patients with schizo-

phrenia suggest an inhibitory failure. Importantly, the magnitude of activation in the lateral premotor/SMC was positively associated with greater motor retardation, providing a potential physiological basis for independently documented clinical motor deficits.

Of all the nodes in the upper motor network (i.e., primary motor cortex, medial/lateral premotor cortex, lateral prefrontal cortex, basal ganglia, thalamus, subthalamic nuclei and cerebellum), our results indicate the lateral premotor cortex or the SMC itself (i.e., within inhibitory interneurons) as the loci of inhibitory failure. Dense excitatory and inhibitory cortico-cortico connections exist between the premotor and the primary motor cortex,³⁶ with inferior premotor cortex neurons firing in a predictive manner during both observed and performed no-go trials in primates.³⁷ Similar to the pattern of BOLD abnormalities observed in the present experiment, previous studies using repetitive transcranial magnetic stimulation of the premotor cortex have reported increased

Fig. 4: Connectivity analysis performed with seeds obtained from the main effect of group within the bilateral premotor and sensorimotor cortex (SMC; green) during the task. **(A)** Regions of the brain showing significant functional connectivity MRI differences between patients with schizophrenia (SP; warm colours) and healthy controls (HC; cool colours). Locations of the sagittal (x) and axial (z) slices are given according to the Talairach atlas for the left (L) and right (R) hemispheres. **(B)** Fisher z-transformed correlation values within selected regions of interest including the right and left posterior SMC (pSMC), the bilateral posterior cingulate gyrus (PCC), the left cerebellum (Cbm) and the bilateral thalamus/subthalamic nuclei (Thal).

motor evoked potentials in patients with schizophrenia and reduced potentials in healthy controls.³⁸

Intracortical inhibition driven by both GABA_A and GABA_B activity also occurs within the primary motor cortex itself^{39,40} and has been shown to be impaired in both medicated and unmedicated patients with schizophrenia.^{38,41–43} BOLD abnormalities in the SMC (e.g., reduced activation) have been previously observed in fMRI studies involving motor tasks in patients with schizophrenia,^{44,45} suggesting that neural abnormalities are not strictly inhibitory in nature. Finally, further evidence of SMC dysfunction was independently observed during a resting state scan, with reduced connectivity for patients between more anterior (abnormally activated by task) and posterior regions of the SMC itself. Similar to the premotor cortex,³⁶ strong reciprocal cortico–cortico connections exist between the primary motor and primary somatosensory cortices in animal models.⁴⁶ Collectively, present and previous results suggest that basic cortico–cortico and intracortical connections between the SMC and adjoining regions may be impaired as part of the disease course itself.

However, the motor network is complex, connected through both direct and indirect inhibitory and excitatory pathways, all of which phasically and tonically affect motor readiness and could have contributed to our findings.⁴⁷ There was only limited evidence suggesting that other nodes of the motor network, including the lateral prefrontal cortex, contributed to the inhibitory BOLD abnormalities observed in the present study. The lateral prefrontal cortex has both direct and indirect projections to the SMC⁴⁷ and plays a critical role in reactive response inhibition.⁴⁸ Postmortem studies suggest reduced dendritic GABAergic interneuron projections in the lateral prefrontal cortex of patients with schizophrenia,^{49,50} and previous neuroimaging studies have consistently observed BOLD abnormalities in the dorsolateral, ventrolateral and inferior frontal cortices in patients with schizophrenia during inhibitory control.^{7–11,19}

The null findings observed in the lateral prefrontal cortex in the present study relative to previous studies in patients with schizophrenia therefore likely resulted from differences in task demands. Specifically, the use of a cue (i.e., proactive inhibition) precluded participants from making decisions following stimulus presentation (i.e., reactive inhibition), eliminating the response uncertainty that may trigger inhibitory mechanisms during both go and no-go trials and engaging tonic rather than phasic response inhibition.^{6,14,51} Additionally, the task used in the present study required the inhibition of a typical rather than prepotent motor response and did not require halting a motor program following initiation,^{11,21} both of which may place additional demands on the lateral prefrontal cortex.⁶ Finally, the present task involved minimal attention/working memory demands, which have been shown to drive activation in the dorsolateral and inferior frontal cortices during response inhibition¹⁴ and are differentially affected by load in patients with schizophrenia.^{52,53} As such, the present task was also less affected by the behavioural confounds (i.e., greatly reduced accuracy and response time slowing) that characterize most studies of reactive response inhibition in patients with schizophrenia.

Unlike previous studies using proactive cognitive control,^{11,21} there was no evidence of functional abnormalities within the basal ganglia, with differences in thalamic activity observed only during connectivity analyses. Results were also largely negative for the cerebellum, with observed connectivity differences falling outside traditional cerebellar motor areas.⁵⁴ Patients with schizophrenia exhibited unique activation of the medial premotor cortex (pre-SMA/SMA) relative to baseline, and medial premotor activity was positively correlated with the degree of activation within the lateral premotor cortex/SMC across both patients and controls, even when controlling for global neuronal activity. The pre-SMA/SMA is commonly activated across multiple reactive response inhibition¹⁷ and cognitive control^{27,55,56} tasks, and shows strong functional connectivity with the SMC.⁵⁷ The absence of pre-SMA/SMA activation in healthy controls was therefore surprising, although further examination indicated that the activation levels (Fig. 3D) were likely just below threshold levels. As discussed previously, the lack of robust pre-SMA/SMA activation in the present study versus previous response inhibition tasks¹⁷ is likely a result of different task demands.

Finally, patients with schizophrenia exhibit inhibitory deficits across a variety (e.g., antisaccade, auditory gating, sensorimotor gating) of tasks^{58,59} as well as reduced GABA levels across multiple cortical regions.⁶⁰ Thus, inhibitory deficits in the SMC could also be reflective of a more global phenomenon. Consistent with this suggestion, patients with schizophrenia also failed to deactivate (i.e., show a negative BOLD response) the anterior nodes of the DMN, with DMN task-induced deactivations also correlating with lateral premotor/SMC abnormalities across both groups of participants. A failure to disengage the DMN contributes to errors during cognitive control,⁶¹ and there is considerable literature suggesting both connectivity deficits and task-induced deactivation abnormalities within the DMN for patients with schizophrenia.^{62,63} These abnormalities could ultimately impair patients' ability to switch from passive to more attentionally demanding tasks, directly leading to task-related BOLD abnormalities due to the inherent reliance on contrasting cognitive states.

It is unlikely that the observed positive BOLD response was driven by false-positive or subthreshold motor responses for several reasons. First, minimal behavioural performance differences were observed between groups,²³ with abnormalities persisting even after we adopted a more stringent false-positive threshold. Second, false-positive responses were modelled with a separate regressor, which is effective for removing variance associated with infrequent trial types.²⁷ Finally, BOLD abnormalities were observed bilaterally rather than in left SMC, as would be expected if positive BOLD response was driven solely by subthreshold right-hand responses. It is also unlikely that our results were secondary to global hemodynamic differences, as many other regions (e.g., auditory and visual cortex, frontal and parietal heteromodal cortex) showed a statistically similar response across groups. Finally, there was no association between positive BOLD response in the SMC and medication levels, illness duration or

treatment-induced motor symptoms, which are common confounds in schizophrenia research.

Limitations

Several limitations of our experiment should be noted. First, proactive response inhibition tasks by definition do not provide behavioural metrics that can be independently used to quantify task performance (other than false-positive rate). Thus, while it is impossible to confirm that participants were actively inhibiting motor responses (e.g., versus passive viewing of stimuli), the overall task demands (i.e., required motor responses in other conditions) and observed patterns of activity (negative BOLD) suggest that was true for healthy controls. Second, significant differences in head motion existed between patients and controls. However, both principle (FD as covariate) and supplemental analyses suggested that head motion did not significantly contribute to the observed group differences. Third, the dopaminergic properties of antipsychotic medications have deleterious side effects on motor functioning. However, previous work suggests that inhibitory motor deficits are present in both medicated and unmedicated patients with schizophrenia.⁴¹ Finally, and potentially most importantly, BOLD is a proxy measure of neuronal activity, and our utilization of a single imaging modality does not permit the disambiguation of the inhibition of neurons versus differences in cerebral blood flow or vascular reactivity.

Conclusion

The present study provides evidence of proactive response inhibition deficits in the bilateral premotor and SMC rather than the lateral prefrontal cortex in patients with schizophrenia. Connectivity results provide independent evidence suggesting deficits in basic cortico-cortico and intracortical connections in the premotor cortex and SMC itself. Thus, our results confirm that inhibitory failure represents a core deficit in patients with schizophrenia, and one that can be measured with a basic task that does not severely confound differences in behavioural performance that are frequently observed during reactive inhibitory control.

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