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Relationship Between Cortical Excitation and Inhibition and Task-Induced Activation and Deactivation: A Combined Magnetic Resonance Spectroscopy and Functional Magnetic Resonance Imaging Study at 7T in First-Episode Psychosis

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ABSTRACT

BACKGROUND: Schizophrenia is thought to be a disorder of brain dysconnectivity. An imbalance between cortical excitation/inhibition is also implicated, but the link between these abnormalities remains unclear. The present study used magnetic resonance spectroscopy and functional magnetic resonance imaging at 7T to investigate how measurements of glutamate and gamma-aminobutyric acid (GABA) relate to the blood oxygen level–dependent (BOLD) response during a cognitive task, and how these relationships are altered in schizophrenia.

METHODS: Usable functional magnetic resonance imaging data from 17 first-episode psychosis (FEP) patients (4 women, 13 men) and 21 matched healthy control subjects (HCs) (5 women, 16 men) were acquired during a Stroop task. Within- and between-group comparisons of the BOLD response were performed. Neurometabolite levels were measured in the dorsal anterior cingulate cortex. Two multiple regressions investigated how glutamate, glutamine, and GABA related to the BOLD response in HCs and FEP patients separately. A third investigated between-group differences in the relationships between the BOLD response and each of these neurometabolites.

RESULTS: Compared with HCs, FEP patients showed an increased BOLD response within regions of the executive and default mode networks. In FEP patients, the relationship between anterior cingulate cortex glutamate levels and the BOLD response in regions of the posterior default mode network was opposite to that of HCs. In FEP patients but not HCs, anterior cingulate cortex GABA levels correlated with the local BOLD response and with the Stroop reaction time.

CONCLUSION: These results suggest a mechanism whereby alterations in the relationship between cortical glutamate/GABA and BOLD response is disrupting the dynamic of major neural networks, possibly affecting cognition.

Keywords: 7T, Functional magnetic resonance imaging, GABA, Glutamate, Magnetic resonance spectroscopy, Schizophrenia

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Schizophrenia is a brain connectivity disorder that is characterized by faulty interactions between spatially distinct brain regions (1,2). Response to antipsychotic drugs is highly variable, and medications do not improve negative or cognitive symptoms. A better understanding of the pathophysiology of dysconnectivity could lead to identification of new drug discovery targets.

Abnormalities in the excitation/inhibition balance as a result of *N*-methyl-D-aspartate receptor hypofunction on gamma-aminobutyric acidergic (GABAergic) interneurons are implicated in the pathophysiology of schizophrenia (3–6). Postmortem studies reported glutamatergic and GABAergic abnormalities in schizophrenia (7). In humans, *N*-methyl-D-aspartate receptor antagonists induce a behavioral phenotype that mirrors the symptoms of schizophrenia (8), including cognitive impairments (9–11). Glutamate and GABA can be measured in vivo using magnetic resonance spectroscopy (MRS). Studies in schizophrenia have reported abnormal glutamatergic measurements (12–18) that may depend on voxel location, illness stage, and medication status. Measurements of GABA have been less frequent, but abnormalities have been identified as well (19–22).

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Together, the excitatory glutamatergic neuron and the inhibitory GABAergic interneuron represent the basic processing unit throughout the cerebral cortex (23). More than 75% of the brain's energy consumption is coupled to cycling of these neurotransmitters (24). Glutamate mediates fast synaptic transmission and plays a key role in long-term potentiation. GABA is involved in regulating synaptic transmission and the probability and timing of action potential generation. In addition, fast-spiking GABA interneurons are thought to facilitate the rhythmic entrainment (i.e., synchrony) of cortical pyramidal neurons (25). In contrast to glutamatergic neurons, cortical GABA neurons synapse locally and do not project to other regions. After release from presynaptic terminals, glutamate and GABA are taken up by glial cells and converted to glutamine that is then returned to neurons and converted back to the original neurotransmitters.

Using functional magnetic resonance imaging (fMRI), several large-scale neural networks were identified, including task-positive (executive control, salience) and task-negative (default mode) networks (26,27). In contrast to task-positive networks, the default mode network (DMN) comprises a set of regions that are active during rest and that deactivate during task. A balance between the activation of task-positive networks and deactivation of the DMN appears to be necessary for cognitive functioning (28). Alterations in the blood oxygen level–dependent (BOLD) signal at rest and during tasks, alterations in DMN deactivation, and alterations in the relationships between the DMN and other networks have been reported in schizophrenia (29,30), suggesting that the dynamic of activation/deactivation in task-positive/DMNs is altered.

As addressed in a comprehensive review, different neuroimaging methods, such as magnetoencephalography and fMRI, measure different physiological aspects of neural activity (31); because of their role in neuroenergetics, glutamate and GABA have been found to be related to the fMRI BOLD response (31,32). Combined MRS/fMRI studies reported evidence for a negative correlation between GABA and stimulus-induced BOLD responses within the measured region, while glutamate was positively correlated with the stimulus-induced response within the measured regions as well as within spatially distant regions. This suggests that glutamate is related to long-range connections (33). While many studies have evaluated connectivity by measuring the relationships between BOLD signals across brain regions, evaluations of glutamate/GABA and BOLD signal relationships may yield additional insights. It is important to note that studies examining functional networks and neurometabolites in schizophrenia do not give a unanimous view on the illness. Combining MRS with fMRI in the same subjects allows us to concurrently investigate several (possibly connected) mechanisms involved in schizophrenia that may contribute to a better understanding of the disease mechanisms. However, only a few studies, including our own (34–36), have evaluated the relationships between glutamate and the BOLD response, and none have investigated the effect of GABA or glutamine. In healthy control subjects (HCs) we reported a robust positive correlation between hippocampal glutamate + glutamine/creatine and inferior frontal activation during a memory task; this association was not present in schizophrenia (35). Likewise, others reported an altered relationship between anterior cingulate cortex (ACC) glutamate and the BOLD response in the inferior parietal cortex during a cognitive control task in schizophrenia (37).

We combined fMRI and MRS to evaluate the relationship between neurometabolites and the BOLD signal in a group of first-episode psychosis (FEP) patients and matched HCs. Our patient population allows us to study the neural correlates of psychosis without confounds of illness chronicity and long-term antipsychotic medication exposure. Because higher-field-strength magnets provide a better signal-to-noise ratio and spectral resolution, we used a 7T magnet to measure glutamate, glutamine, and GABA from a dorsal ACC voxel, as well as the BOLD response during a cognitive control task known to activate the dorsal ACC. In the same participants, we have previously reported that glutamate, but not glutamine or GABA, was significantly lower in FEP patients versus HCs (38).

We hypothesized that FEP patients demonstrate altered patterns of BOLD activation and deactivation during cognitive control performance. We hypothesized that in HCs we would replicate findings of negative correlation between ACC GABA and ACC BOLD and of positive correlation between ACC glutamate and BOLD in the ACC as well as in regions distant from the measured region (33). Given the role of GABA in the regulation of local transmission, we expected to observe local rather than long range relationships with the BOLD signal (25). Based on previous studies (35,37,39) we further hypothesized that in FEP patients we would observe an aberrant relationship between ACC glutamate and the BOLD response in regions distant from the voxel, and more specifically in regions of the posterior DMN. Finally, we explored the relationship between ACC GABA and glutamine and the BOLD response in FEP patients and compared it with that of HCs. Glutamine and especially the glutamine/glutamate ratio are of interest because they are thought to index the rate of glutamatergic synaptic activity (40,41). We thus expected the glutamine/glutamate ratio to provide additional insights in understanding of group differences in BOLD response as a consequence of impaired glutamatergic transmission in FEP patients.

METHODS AND MATERIALS

Twenty-three FEP patients determined by a clinician to be clinically stable were recruited from the University of Alabama at Birmingham's emergency room and outpatient psychiatric clinics (38). Twenty-six HCs were recruited using flyers matched on age, sex, and parental socioeconomic status. Exclusion criteria were major medical/neurological conditions, substance abuse within 6 months of imaging, previous head injury with loss of consciousness, and pregnancy. Two FEP patients (claustrophobia, weight exceeding scanner limit) and five HCs (failed drug screen, magnetic resonance contraindication, and lost to follow-up) did not complete the imaging portion of the study. fMRI data were excluded for four FEP patients because of poor data quality (study withdrawal, corrupted images, and button confusion). Data from one of the two fMRI sessions were not used for two HCs (button confusion, response data lost). Therefore, 19 FEP patients and 21 HCs were included in the behavioral analyses, and 17 FEP patients and 21 HCs were included in the imaging analyses.

Diagnoses were established by a psychiatrist and confirmed through medical record review. Positive and negative symptom severity was assessed using the Brief Psychiatric Rating Scale. Cognitive function was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (42).The University of Alabama at Birmingham and Auburn University Institutional Review Boards approved this study. All participants gave written informed consent.

Functional Task

Participants completed a computerized version of the Stroop color-naming task during the scan (43). An Integrated Functional Imaging System-SA system using E-Prime software (Psychology Software Tools, Sharpsburg, PA) was used to present task stimuli to participants and record their response and response time. For each trial, participants were presented one of three words ("red," "green," or "blue"), and the color of the font was one of these same three colors. Participants were instructed to ignore the lexical meaning of the word and instead indicate the color of the font by pressing one of three buttons. Congruent trials were trials where the lexical meaning matched the font color, and incongruent trials were trials where it did not. Participants completed two sessions consisting of 64 trials each (30% incongruent).

Image Acquisition/Preprocessing

Imaging was performed on a whole-body Magnetom 7T MRI scanner (Siemens Healthineers, Erlangen, Germany) equipped with a 32-channel head coil (Nova Medical, Wilmington, MA) at the Auburn University MRI Research Center. A structural scan was acquired for anatomical reference (magnetization prepared rapid acquisition gradient-echo, repetition time = 2200 ms, echo time = 2.96 ms, inversion time = 1050 ms, 7° flip angle, generalized autocalibrating partial parallel acquisition acceleration factor = 2; field of view = 224 × 224 mm, 0.7-mm isotropic voxels).

The anatomical scan was used to guide spectroscopy voxel placement in the bilateral dorsal ACC (2.7 × 2 × 1 cm^3) (Supplemental Figure S7). After shimming with FASTESTMAP and optimization of the radiofrequency power, spectra were acquired using a ultrashort echo time stimulated echo acquisition mode sequence (repetition time = 10,000 ms, echo time = 5 ms, mixing time = 45 ms, 32 averages, 4-kHz bandwidth, 2048 points), outer volume suppression, and variable power radiofrequency pulses and optimized relaxation delays water suppression. Two averages of unsuppressed water scans were obtained as references. During the MRS scan, participants were instructed to keep their eyes open. Spectra were processed in LCModel software (version 6.3-1) using a simulated basis set and default processing parameters [see Reid *et al.* (38)]. Metabolite levels were corrected for partial volume using the method described by Gasparovic *et al.* (44).

fMRI data were acquired using the gradient recalled echo-planar sequence (repetition time = 3000 ms, echo time = 28 ms, 70° flip angle, field of view = 200 × 200 mm, voxel size = 0.85 × 0.85 × 1.8 mm, 1-mm gap, 37 axial slices, 120 acquisitions per session). A second anatomical scan was acquired for coregistration of the functional images (repetition time = 2000 ms, echo time = 2.89 ms, inversion time = 1050 ms, 7° flip angle, generalized autocalibrating partial parallel acquisition acceleration factor = 2, field of view = 190 × 190 mm, 0.7-mm isotropic voxels). Data analyses were performed in SPM12. Preprocessing included realigning, unwarping, coregistering to the magnetization prepared rapid acquisition gradient-echo, normalizing to Montreal Neurological Institute space, and smoothing with a 5-mm full width at half maximum Gaussian kernel. A single-subject voxel-by-voxel whole-brain general linear model was calculated for each individual. Five conditions were included in the event-related model: correct nonrepeat incongruent trials, correct nonrepeat congruent trials, error trials, no response trials, and repeat trials [also see Reid *et al.* (34)]. Repeat trials were trials where both the lexical meaning and font color of the word were identical to the previous trial. Motion parameters were used as nuisance regressors.

Statistical Analyses

Behavioral Data and MRS. Analyses were performed using SPSS software (version 22; IBM Corp., Armonk, NY) using a threshold of $p < .05$. Mean incongruent and congruent reaction times (RTs), and the Stroop effect RT (incongruent − congruent RT) were compared across groups using *t* tests. Mean framewise displacement was calculated and compared across groups (Table 1). Mean BOLD Stroop effect extractions were taken from seven peak regions found in an across-groups analysis. These values did not correlate with framewise displacement in within- or across-groups analyses (all $p > .05$).

fMRI. The BOLD Stroop effect (incongruent > congruent trials) was used to measure task-related activation in the whole brain, in an effort to examine the neural underpinnings of the cognitive process of inhibitory control. Similar analyses of the reverse (congruent > incongruent) contrast were used to measure relative deactivation. Between-group analyses tested for regions where the BOLD Stroop effect was different between groups. We performed whole-brain multiple regression analysis to evaluate group differences in the relationship between BOLD and the Stroop RT (Supplemental Methods; Supplemental Figure S5).

fMRI and MRS Multiple Regression Analyses. For each group, whole-brain multiple regression analysis was used to test for voxels with a significant relationship between the BOLD Stroop effect and glutamate, GABA, and glutamine according to the following equation:

$$\text{BOLD Stroop effect} = \beta_1 \times \text{Glu} + \beta_2 \times \text{GABA} + \beta_3 \times \text{Gln} + \beta_4 \times \text{WM\_fraction} + \text{Error} \quad (1)$$

In SPM12, this equation was used for the HCs and FEP patients within-group neurometabolite/fMRI analyses. The BOLD Stroop effects, neurometabolite levels, and white matter fraction were entered for each individual, and the combination of beta weights that resulted in the smallest standard error were determined. *t* tests were used to determine if the magnitude of the beta weight for a voxel was significant, and the voxel-by-voxel whole-brain analyses of these relationships are reported at *p* familywise error (FWE) < .05. A positive beta

Table 1. Demographics, Behavior, and Magnetic Resonance Spectroscopy Metabolites

Measure	HCs (n = 21)	FEP Patients (n = 21)	Statistic	p
Age, Years	23.5 (4.5)	23.2 (4.4)	t_{40} = 0.21	.84
Sex, Female/Male	5/16	5/16	χ^2_1 = 0	1
Smoker, Yes/No	0/21	6/15	χ^2_1 = 7.0	.01
Parental SES[a]	3.4 (3.3)	4.3 (4.4)	t_{39} = 0.72	.48
RBANS Score[b]	94.8 (8.6)	74.0 (15.0)	t_{34} = 5.11	<.001
Treatment Duration, Weeks	—	55.3 (65.0)	—	—
BPRS Rating[c]				
Total	—	32.3 (9.8)	—	—
Positive	—	5.5 (3.3)	—	—
Negative	—	5.9 (2.4)	—	—
Incongruent Reaction Time,[d] Seconds	1.00 (0.18)	1.23 (0.22)	t_{38} = 3.57	.001
Congruent Reaction Time, Seconds	0.88 (0.19)	1.02 (0.21)	t_{38} = 2.20	.034
Stroop Effect Reaction Time, Seconds	0.11 (0.10)	0.20 (0.11)	t_{38} = 2.64	.012
Mean Framewise Displacement,[e] mm	0.14 (0.06)	0.17 (0.12)	$t_{21.69}$ = 1.04	.311
Glutamate, IU	6.87 (0.47)	6.52 (0.49)	$F_{1,37}$ = 4.63	.04
CRLB	2.0%	2.1%		
Glutamine, IU	1.90 (0.22)	1.81 (0.32)	$F_{1,37}$ = 1.09	.30
CRLB	5.8%	6.7%		
GABA, IU	0.92 (0.18)	0.90 (0.18)	$F_{1,37}$ = 0.02	.89
CRLB	11.0%	11.9%		

Values are presented as mean (SD) or n.

BPRS, Brief Psychiatric Rating Scale; CRLB, Cramér–Rao lower bounds; FEP, first-episode psychosis; GABA, gamma-aminobutyric acid; HC, healthy control subject; IU, international units; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; SES, socioeconomic status.

[a]SES not available for 1 patient. Ranks determined from the Diagnostic Interview for Genetic Studies (1–18 scale); higher rank (lower numerical value) corresponds with higher SES.

[b]RBANS scores not available for 3 patients and 3 control subjects.

[c]BPRS rating not available for 2 patients. Scored on a 1–7 scale. Positive subscale: conceptual disorganization, hallucinatory behavior, and unusual thought content. Negative subscale: emotional withdrawal, motor retardation, and blunted affect.

[d]Behavioral data were not obtained or were unusable for 2 FEP patients.

[e]This analysis failed Levene's test. Accordingly, degrees of freedom were reduced from 36; only participants with usable functional magnetic resonance imaging were included in this analysis.

weight indicates a positive relationship between the BOLD Stroop effect and the neurometabolite. The white matter fraction of the MRS voxel was included as a covariate of no interest to control for partial volume effects. Tests for positive and negative relationships with each neurometabolite were made.

A third whole-brain multiple regression analysis was used to test for an interaction between the BOLD Stroop effect, diagnosis, and each neurometabolite according to the following equation:

$$\begin{aligned}\text{BOLD Stroop effect} = {} & \beta_1 \times \text{Group} + \beta_2 \times \text{Glu} + \beta_3 \\ & \times \text{Glu} \times \text{Group} + \beta_4 \times \text{GABA} + \beta_5 \\ & \times \text{GABA} \times \text{Group} + \beta_6 \times \text{Gln} + \beta_7 \\ & \times \text{Gln} \times \text{Group} + \beta_8 \times \text{WM\_fraction} \\ & + \text{Error}\end{aligned} \quad (2)$$

This equation was used to test for an interaction between the BOLD Stroop effect, diagnosis, and each neurometabolite. The diagnosis variable consisted of ones for HCs and twos for FEP patients. The beta weights of interest were β_3, β_5, and β_7. A positive beta weight indicates that the relationship between the BOLD Stroop effect and the neurometabolite was more positive in FEP patients. Tests for significant beta weights were made at $p_{FWE} < .05$. Tests for voxels where the relationship between the BOLD Stroop effect and glutamate, GABA, and glutamine were made in both directions (HCs > FEP patients and FEP patients > HCs).

For all fMRI and fMRI/MRS analyses, the significance was assessed at a cluster-level threshold of $p < .05$ FWE corrected across the whole brain, using a cluster-forming threshold of $p < .05$ (uncorrected).

RESULTS

Behavior/MRS

Groups did not differ with regard to demographic variables (Table 1). FEP patients were significantly slower to respond to both incongruent and congruent trials. The Stroop effect RT was greater in FEP patients, indicating that FEP patients slowed down relatively more during incongruent trials.

We previously reported that age was related to glutamine and sex was related to GABA and glutamate (38). In FEP patients but not in HCs, GABA negatively correlated with the Stroop effect RT (r = .48, p = .04), indicating that high GABA levels were associated with a slower inhibitory response.

Functional Magnetic Resonanace Imaging

In each group, BOLD activation was observed in regions of the executive network [bilateral dorsolateral prefrontal cortex (DLPFC)], bilateral parietal cortex, and supplementary motor area (SMA) (Figure 1A, B). The cluster containing the SMA extended to the middle cingulate cortex in FEP patients and the middle cingulate cortex and dorsal ACC in HCs. The bilateral insula, a salience network component, and the basal ganglia were also activated in both groups. The posterior cingulate cortex (PCC) and the precuneus (both regions of the posterior DMN) were activated in FEP patients. In HCs, DMN regions (PCC, precuneus, and medial prefrontal cortex) were deactivated. No regions were deactivated in FEP patients ($p_{FWE} > .05$).

There was a significantly greater BOLD Stroop effect in FEP patients in regions of the executive network, salience network, basal ganglia, and DMN (bilateral DLPFC, bilateral parietal cortex, SMA, ACC, right insula, right putamen, PCC, and precuneus) (Figure 1C). No regions had a greater BOLD Stroop effect in HCs than in FEP patients ($p_{FWE} > .05$) (Supplemental Tables S1–S3).

Combined MRS/fMRI

Glutamate. In HCs there was a negative relationship between dorsal ACC glutamate and the BOLD response within the PCC and precuneus extending into the occipital cortex and cerebellum (Supplemental Figure S1A, B). In FEP patients the relationship was positive and included the PCC, precuneus,

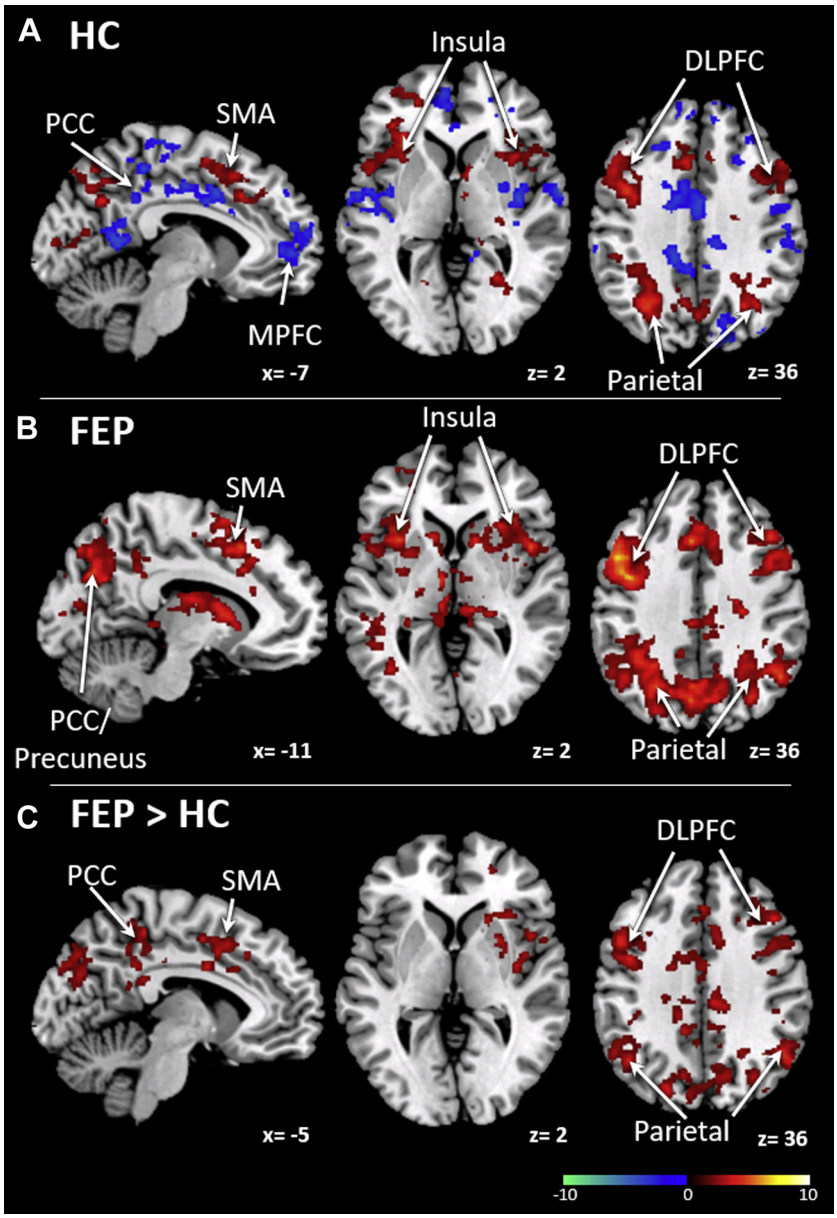

Figure 1. The blood oxygen level–dependent (BOLD) Stroop effect. **(A)** The BOLD Stroop effect in healthy control subjects (HCs) showed significant activation in areas of the executive control network (dorsolateral prefrontal cortex [DLPFC] and parietal cortex), the insula, and the supplemental motor area (SMA). There was a significant reverse contrast within regions of the default mode network (medial prefrontal cortex [MPFC], precuneus, and posterior cingulate cortex [PCC]). **(B)** First-episode psychosis (FEP) patients showed a significant BOLD Stroop effect within the insula and regions of the executive network (bilateral DLPFC and parietal cortex). In addition, areas of the posterior default mode network also showed a Stroop effect. No areas showed a significant reverse contrast. **(C)** Areas where the BOLD Stroop effect was greater in FEP patients compared with HCs. Regions include the executive control network (bilateral DLPFC and parietal cortex), middle cingulate cortex, PCC, and precuneus. No regions had a greater BOLD Stroop effect in HCs than FEP patients. The BOLD Stroop effect is defined as the difference between the BOLD responses to incongruent and congruent trials of the Stroop color-naming task (incongruent > congruent). A threshold of p familywise error < .05 was used for all analyses. Regions with a significant Stroop effect are indicated by warm colors, and cool colors represent a significant reverse contrast (congruent > incongruent).

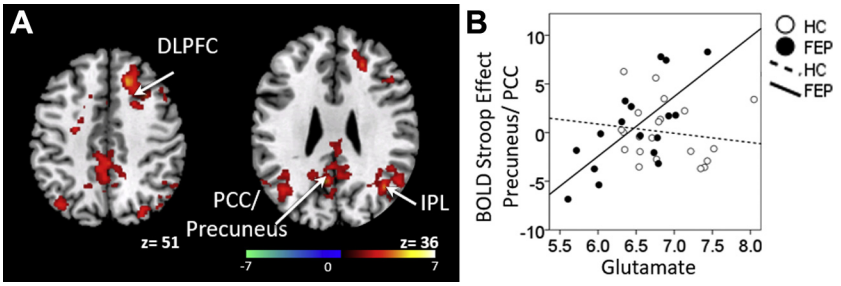

Figure 2. Difference in the relationship between glutamate levels and the blood oxygen level–dependent (BOLD) Stroop effect between healthy control subjects (HCs) and first-episode psychosis (FEP) patients. **(A)** Areas where the relationship between glutamate levels and the BOLD Stroop effect differs between groups. **(B)** Group interaction plot of relationships between glutamate levels and the BOLD Stroop effect in the precuneus/posterior cingulate cortex (PCC) in HCs and FEP patients. The BOLD Stroop effect is defined as the difference between the BOLD responses to incongruent and congruent trials of the Stroop color-naming task (incongruent > congruent). A threshold of p familywise error < .05 was used for all analyses. Regions where the relationship is significantly more positive in FEP patients are indicated by warm colors. DLPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobe.

and right DLPFC (Supplemental Figure S1C, D). Significant clusters extended into the occipital cortex and bilateral thalamus. The between-group analysis revealed that the relationship was more positive in FEP patients than in HCs within the right DLPFC, PCC, precuneus, and bilateral inferior parietal lobe (Figure 2). There were no regions where this relationship was positive in HCs, negative in FEP patients, or more positive in HCs than in FEP patients ($p_{FWE} > .05$).

GABA. In HCs there was a negative relationship between GABA and the BOLD Stroop effect in the left parietal cortex and left DLPFC (Figure 3A, B). In FEP patients there was a positive relationship within the ACC that extended to the caudate and thalamus and a negative relationship within the right somatosensory cortex that extended to the superior temporal lobe and insula (Supplemental Figure S2C, D). The relationship was more positive in the ACC and more negative in the SMA, insula, DLPFC, superior temporal lobe, and pre- and postcentral central gyrus in FEP patients (Figure 3).

Glutamine. The relationship between ACC glutamine and the BOLD Stroop effect was negative for both groups. Significant regions for HCs included the bilateral SMA, pre- and postcentral gyrus, ACC, middle cingulate cortex, insula, and right DLPFC (Supplemental Figure S3A, B). In FEP patients significant regions included the right insula, DLPFC, thalamus, and putamen (Supplemental Figure S3C, D). The between-groups analysis revealed that the glutamine relationship was more negative in HCs within the dorsal ACC, SMA, and superior frontal lobe (Figure 4).

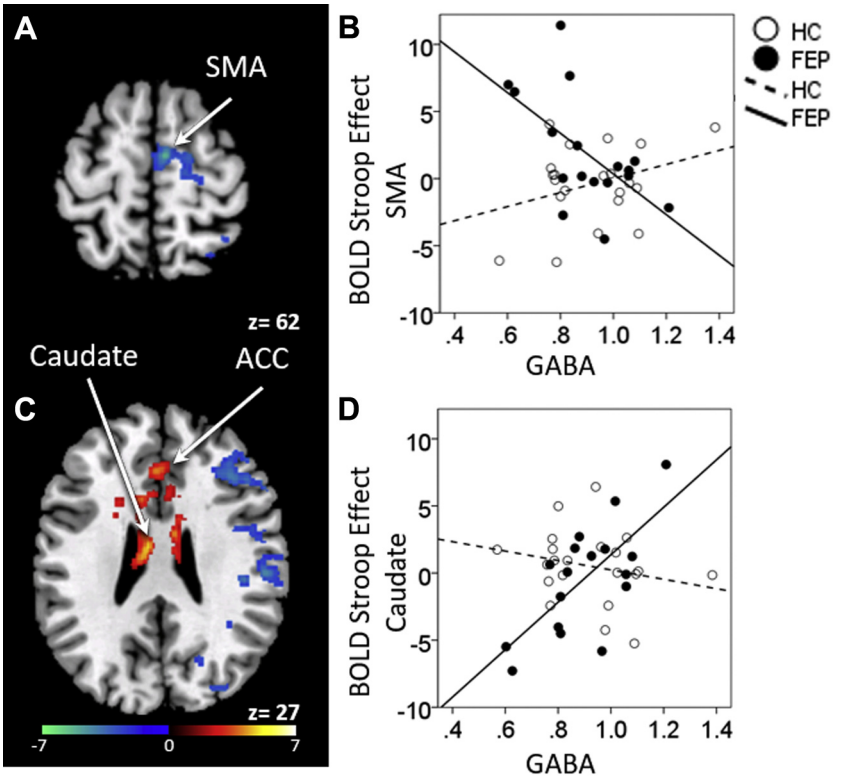

Figure 3. Difference in the relationship between gamma-aminobutyric acid (GABA) levels and the blood oxygen level–dependent (BOLD) Stroop effect between healthy control subjects (HCs) and first-episode psychosis (FEP) patients. **(A)** The relationship between GABA levels and the BOLD Stroop effect differs between groups in the supplemental motor area (SMA). **(B)** Group interaction plot of relationships between GABA levels and the BOLD Stroop effect in the SMA in HCs and FEP patients. **(C)** The relationship between GABA levels and the BOLD Stroop effect differs between groups in the caudate and in the anterior cingulate cortex (ACC). **(D)** Group interaction plot of relationships between GABA levels and the BOLD Stroop effect in the caudate in HCs and FEP patients. The BOLD Stroop effect is defined as the difference between the BOLD responses to incongruent and congruent trials of the Stroop color-naming task (incongruent > congruent). A threshold of p familywise error < .05 was used for all analyses. Regions where the relationship is significantly more positive in HCs are indicated by cool colors. Areas where the relationship is significantly more positive in FEP patients are not shown.

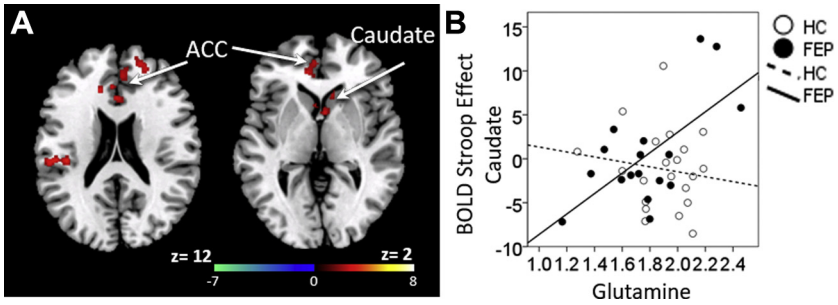

Figure 4. Difference in the relationship between glutamine levels and the blood oxygen level–dependent (BOLD) Stroop effect between healthy control subjects (HCs) and first-episode psychosis (FEP) patients. **(A)** Areas where the relationship between glutamine levels and the BOLD Stroop effect differs between groups. **(B)** Group interaction plot of relationships between glutamine levels and the BOLD Stroop effect in the caudate in HCs and FEP patients. The BOLD Stroop effect is defined as the difference between the BOLD responses to incongruent and congruent trials of the Stroop color-naming task (incongruent > congruent). A threshold of p familywise error < .05 was used for all analyses. Regions where the relationship is significantly more positive in FEP patients are indicated by warm colors. ACC, anterior cingulate cortex.

Glutamine/Glutamate. The relationship between the glutamine/glutamate ratio was more positive in FEP patients. Significant regions included the postcentral gyrus, precentral gyrus, and inferior parietal lobe. These regions were within the significant regions found in the glutamine between-groups analysis. This cluster spatially overlapped with one of the two clusters identified in above reported glutamine analysis (Supplemental Figure S4).

Relationship Between BOLD and RT. A significant group × BOLD × RT interaction was found in the left DLPFC; in that region, the relationship between the BOLD signal and RT was positive in FEP patients and negative in HCs (Supplemental Figure S5). Complete lists of significant regions for BOLD/MRS analyses can be found in Supplemental Tables S4, S5, and S6.

DISCUSSION

To our knowledge, this is the first combined 7T MRS/fMRI study in FEP patients and the first to investigate BOLD/GABA and BOLD/glutamine relationships. The main findings are as follows: 1) FEP patients showed an increased BOLD response in regions of the executive network and the DMN; 2) in FEP patients, the relationship between ACC glutamate levels and the BOLD response in regions of the posterior DMN was opposite to that of HCs; 3) in FEP patients, but not HCs, GABA correlated positively with the ACC BOLD response; 4) in both groups, glutamine levels negatively correlated with the BOLD response in diverse regions, but these relationships were stronger and broader in HCs; and 5) in FEP patients, but not HCs, GABA correlated with the Stroop RT.

Stroop fMRI

The executive network response was greater in FEP patients in the DLPFC, parietal cortex, and SMA. The DMN response was also greater in FEP patients in the PCC and precuneus. Although many studies in schizophrenia reported a decreased BOLD response in executive network during cognitive performance (43,45–48), increases have also been observed (37,49–52). Interestingly, only HCs deactivated the DMN while FEP patients showed activation in the posterior DMN. Failure to deactivate the DMN has been observed previously in schizophrenia (45,53,54), and greater DMN deactivation is associated with greater task performance (28). These data suggest that both executive network and DMN abnormalities are associated with cognitive deficits. In the left DLPFC, there was a positive relationship between the BOLD signal and RT in FEP patients, but not in HCs. It is thus possible that in that region, longer RT in FEP patients is related to greater BOLD activation, which may in part explain group differences in the BOLD Stroop effect (55); however, despite consistent findings of longer RT in schizophrenia (56), the majority of cognitive control imaging studies have found a decreased BOLD response (57).

Resting MRS

In the same participants, we reported that glutamate, but not glutamine or GABA, was significantly lower in FEP patients versus HCs (38).

Combined Stroop fMRI and Resting MRS

Glutamate. As hypothesized, in HCs, we found a significant correlation between ACC glutamate and BOLD response within the posterior DMN; higher ACC glutamate levels predicted greater deactivation of the DMN. A similar ACC glutamate modulation of BOLD response in posterior DMN regions has been reported in HCs (39). In contrast, also in HCs, higher levels of glutamate in the posterior DMN predicted less deactivation of the DMN during task performance (58). Speculatively, both posterior DMN glutamate and dorsal ACC glutamate appear to modulate the dynamic of activation/deactivation of the BOLD response in posterior DMN. Together, these data support the role of glutamate in the local and long-range modulation of the BOLD response in DMN regions. Known glutamatergic projections between the ACC and posterior DMN are hypothesized to support this modulation.

In FEP patients, we found an opposite relationship between ACC glutamate and posterior DMN compared with HCs: in FEP patients, higher glutamate predicted greater BOLD response in the posterior DMN. Like us, others found an opposite relationship between dorsal ACC glutamate levels and inferior parietal BOLD response between HCs and schizophrenia (negative in HCs and positive in schizophrenia) (37). We identified this aberrant relationship in a more inferior part of the parietal cortex, precuneus, and PCC. Together, our results suggest a long-range connection between the ACC and posterior DMN that is mediated by glutamate and that is aberrant in FEP patients.

ACC glutamate levels were decreased in FEP patients (38). It is possible that, regardless of diagnosis, low ACC glutamate could alter the relationship between task difficulty and the posterior DMN BOLD response. In support of this, in the Falkenberg *et al.* (39) study, HCs with low glutamate, but not those with high glutamate, showed increases in BOLD response in the posterior DMN as the task became more difficult.

GABA. Contrary to our hypothesis, in HCs, we did not find a negative correlation between ACC GABA and ACC BOLD but identified a negative correlation between ACC GABA and the parietal cortex, suggesting that GABA is also associated with long-range connections. We speculate that higher local GABA levels could facilitate the inhibition of glutamatergic projections to other cortical regions.

In FEP patients, but not in HCs, ACC GABA positively correlated with the BOLD response in the ACC. In previous HC studies, resting-state GABA levels were negatively related to the local BOLD response in the visual cortex (59–62), PCC (63), perigenual ACC (64), and rat somatosensory cortex (65). A functional MRS study of the dorsal ACC found that although both glutamate and GABA increased during a Stroop task, the magnitude of the GABA increase negatively correlated with the task-related BOLD response (66). Together, these findings suggest that higher GABA levels (likely related to increased inhibition) are associated with a decreased local BOLD response. Although we did not find a negative relationship between ACC GABA and the local BOLD response in HCs, we did find a positive correlation in FEP patients. This aberrant relationship in FEP patients may be relevant to understand cognitive impairment, and is further supported by our findings of relationships between higher GABA and slower Stroop RT and negative correlations between GABA and Repeatable Battery for the Assessment of Neuropsychological Status total scores in FEP patients but not HCs (38).

While local neurochemical concentrations are bound to affect local neural activity, it can also be argued that they are likely to contribute to the activity of distant projection areas; this will involve complex synaptic transmission. One might speculate that the overall regional ratio of excitation/inhibition, modulated by a number of neurotransmitters, including glutamate and GABA, might tune the neuronal projections and thus affect the BOLD signal in distant regions. Differences in FEP patients might emerge as a consequence of altered excitation/inhibition balance as well as of known abnormal functional and structural connectivity between brain regions (30,67). Just as positron emission tomography/fMRI studies have revealed relationships between dopamine measured in the striatum and BOLD signal in cortical areas (68), MRS/fMRI can provide insight into the relationship between the BOLD signal and glutamatergic and GABAergic neurotransmission.

Glutamine. In HCs, resting-state glutamine levels were negatively related to the BOLD response in a variety of regions of both task-positive networks and the DMN. As with glutamate, task-negative regions included the precuneus and the PCC. The strongest correlation was found in the ACC, and other significant regions include the insula, primary motor cortex, and caudate. This suggests that in HCs, ACC glutamine is related to neural activity both locally and in distant regions. FEP patients glutamine levels were also negatively related to the BOLD response in several regions, albeit fewer than in HCs; these include the insula and the DLPFC. Unlike with glutamate, the relationship between the BOLD response and glutamine appears to be mostly conserved in FEP patients, except for the ACC and caudate.

Limitations

All patients were treated with antipsychotic medications, which may affect metabolite levels (69) and the BOLD response (70). For spectroscopy, we used a stimulated echo acquisition mode sequence that was not optimized for GABA measurements, although this sequence has been used by Wijtenburg *et al.* (71) at 7T using a larger voxel. Both GABA and glutamine measurements had a large range; further MRS studies ascertaining normative metabolite levels and ranges will be important to obtain. Spectroscopy was done during rest, so the correlations with the BOLD signal obtained during task cannot be interpreted as being causal. Further studies combining fMRI with functional MRS might provide a more fine-grained understanding of the link between metabolites and cognitive processes. It is possible that in some regions group differences in BOLD might be driven by increased RT in FEP patients; however, despite consistent findings of longer RT in schizophrenia (56), the majority of cognitive control imaging studies have found a decreased BOLD response (57). Other limitations include our modest sample size and failure to control for smoking status; however, a prior study did not find differences in the BOLD response to a task between smoking and nonsmoking patients with schizophrenia (72).

Conclusions

Our results suggest a mechanism whereby alterations in the relationship between cortical glutamate/GABA and BOLD response is disrupting the dynamic of major neural networks, possibly affecting cognition. Screening glutamatergic/GABAergic compounds for their ability to reestablish a proper dynamic of activation/deactivation of the BOLD response is suggested. In addition, our results add to the growing amount of research showing that the local neurochemical environment can affect neural activity in distant brain regions, suggesting that MRS/BOLD studies may be useful when studying brain connectivity.

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