

Altered Associations Between Task Performance and Dorsolateral Prefrontal Cortex Activation During Cognitive Control in Schizophrenia

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ABSTRACT

BACKGROUND: Dysfunctional cognitive control processes are now well understood to be core features of schizophrenia (SZ). A body of work suggests that the dorsolateral prefrontal cortex (DLPFC) plays a critical role in explaining cognitive control disruptions in SZ. Here, we examined relationships between DLPFC activation and drift rate (DR), a model-based performance measure that combines reaction time and accuracy, in people with SZ and healthy control (HC) participants.

METHODS: One hundred fifty-one people with recent-onset SZ spectrum disorders and 118 HC participants performed the AX-Continuous Performance Task during functional magnetic resonance imaging scanning. Proactive cognitive control-associated activation was extracted from left and right DLPFC regions of interest. Individual behavior was fit using a drift diffusion model, allowing DR to vary between task conditions.

RESULTS: Behaviorally, people with SZ showed significantly lower DRs than HC participants, particularly during high proactive control trial types (“B” trials). Recapitulating previous findings, the SZ group also demonstrated reduced cognitive control-associated DLPFC activation compared with HC participants. Furthermore, significant group differences were also observed in the relationship between left and right DLPFC activation with DR, such that positive relationships between DR and activation were found in HC participants but not in people with SZ.

CONCLUSIONS: These results suggest that DLPFC activation is less associated with cognitive control-related behavioral performance enhancements in SZ. Potential mechanisms and implications are discussed.

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Schizophrenia (SZ) is a multifaceted, complex disorder for which cognitive deficits are prominent debilitating features. Indeed, studies suggest that among its tripartite symptomatology of positive, negative, and cognitive symptoms, the cognitive symptoms have the most pronounced impact on everyday functioning (1). Among its cognitive symptoms, deficits in cognitive control may have substantial impact due to its regulation of a wide range of cognitive abilities (2). Cognitive control is a dorsolateral prefrontal cortex (DLPFC)-dependent process that refers to the ability to use context to guide behavior, particularly in the face of the need to overcome habitual responding (3–6). Dysfunction in cognitive control processes is now well recognized as a core feature of SZ because previous studies have consistently observed behavioral [e.g., (7,8)] as well as functional (9–12) abnormalities in cognitive control in the illness [reviewed in (3,5)].

In the current study, we used an alternative, computational modeling-based approach to examining brain-behavior relationships associated with cognitive control to determine how functional integrity of the DLPFC may translate into abnormalities in behavioral performance in SZ. Numerous models have been developed to computationally formalize individual differences in behavior that are associated with variations in

task conditions. One such example is the drift diffusion model (DDM), which provides a unified framework to model reaction time (RT) and accuracy during cognitive tasks (13,14). In the DDM framework, decisions (e.g., a motor response) are described as arising from a noisy process in which information is accumulated over time until a response boundary is reached. A decision is then made at this point (Figure S1), with the rate of information accumulation referred to as the drift rate (DR). Higher DRs are associated with faster and more accurate decisions, whereas lower DRs are associated with slower and less accurate decisions. Thus, an individual with high DRs can rapidly accumulate sufficient information to respond correctly, resulting in increased speed and accuracy. DR is computationally more informative, capturing more information than either accuracy or RT alone.

What are the neuronal mechanisms by which information accumulation occurs? Briefly, neuroimaging and electrophysiological studies have demonstrated that the DLPFC integrates information gathered from sensory processing areas to support task-relevant decisions (15–21). Furthermore, DLPFC response has been shown to be associated with DRs in healthy adults (22) and children (23). In addition, disrupting and enhancing DLPFC activity with noninvasive stimulation

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methods has been shown to decrease and increase DR, respectively, suggesting that the DLPFC may indeed play a causal role in these processes (24,25).

It is well established that SZ is characterized by significant functional deficits in DLPFC activation during cognitive control tasks (3,5,9–12). However, the relationship between DR and DLPFC activation in SZ is unknown. Therefore, the goal of this study was to examine this relationship during a well-characterized cognitive control task (the AX–Continuous Performance Task [AX-CPT]). More specifically, we 1) examined DRs associated with all trial types during this task, as well as cognitive control–associated DR, 2) recapitulated previously observed deficits in DLPFC activation during cognitive control in SZ, and 3) used linear regression to examine the extent to which DLPFC activation predicts DR in SZ and healthy control (HC) participants. Based on prior work (26), we hypothesized reduced DRs in SZ during most AX-CPT trial types. In addition, based on prior work suggesting that recruitment of the DLPFC differentially predicts DR in SZ versus HC participants during a motivated performance task (27), we hypothesized that this brain-behavior relationship might again be disrupted in SZ, particularly during conditions that require high proactive (anticipatory) cognitive control and thus typically recruit the network. We also examined relationships between DRs, cognition, and symptoms as exploratory analyses.

METHODS AND MATERIALS

Participants

The initial sample consisted of 128 HC participants and 161 patients with SZ spectrum disorders (includes SZ, schizoaffective disorder, and schizophreniform disorder; hereafter collectively referred to as SZ). Non-DDM-related AX-CPT functional magnetic resonance imaging (fMRI) data from all but 11 HC participants and 20 people with SZ have been reported in previous publications (9–12,28–34).

The University of California, Davis Early Diagnosis and Preventive Treatment (of Psychosis) research clinic performed recruitment at clinical intake. The Structured Clinical Interview for DSM-IV-TR (35) was used for the diagnosis of psychopathology at intake. All participants with SZ reported psychosis onset within 2 years prior to study enrollment and were receiving some form of treatment (e.g., antipsychotic medication, psychosocial intervention including psychoeducation and/or cognitive behavioral therapy). Participants with SZ were within 2 years of their first psychotic episode. All procedures involving human participants/patients were approved by the University of California, Davis Institutional Review Board. Participants gave written informed consent and were paid for their participation. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975 as revised in 2008.

Patient symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (36), Scale for the Assessment of Negative Symptoms (37), and Scale for the Assessment of Positive Symptoms (38). As described previously (7), three core symptom dimensions were computed: poverty, disorganization, and reality distortion. Poverty was calculated as the sum

of emotional withdrawal, motor retardation, and blunted affect from the BPRS and anhedonia/asociality, avolition/apathy, alogia, and affective flattening from the Scale for the Assessment of Negative Symptoms. Disorganization was calculated as the sum of conceptual disorganization, mannerisms and posturing, and disorientation scores from the BPRS; the attention score from the Scale for the Assessment of Negative Symptoms; and positive formal thought disorder and bizarre behavior scores from the Scale for the Assessment of Positive Symptoms. Reality distortion was calculated as the sum of grandiosity, suspiciousness, hallucinations, and unusual thought content from the BPRS and hallucinations and delusions from the Scale for the Assessment of Positive Symptoms.

Individuals with SZ were excluded for a diagnosis of major medical or neurological illness, head trauma, substance abuse during the previous 3 months and/or a positive urine drug screen on the day of scanning, Wechsler Abbreviated Scale of Intelligence (WASI) (39) score < 70, and MRI exclusion criteria (e.g., claustrophobia, metal in the body). HC participants were excluded for all of the above as well as a history of Axis I mental illness or first-degree family history of psychosis. Chlorpromazine equivalent antipsychotic doses were calculated using published guidelines for conventional (40) and atypical (41) antipsychotics.

Task Description

The AX-CPT and associated task parameters have been described in detail elsewhere (9,42–45). Briefly, participants are presented with a series of cues and probes and are instructed to make a target response (pressing a button with the index finger) to the probe letter “X” only if it was preceded by the cue letter “A.” All cues and nontarget probes require nontarget responses (pressing a button with the middle finger). Target sequence trials (i.e., “AX” trials) are frequent (60%–70% occurrence) and set up a prepotent tendency to make a target response when the probe letter X occurs. As a result, a nontarget sequence trial in which any non-A cue (collectively called “B” cues) is presented and followed by a probe letter X (i.e., “BX” trials) requires proactive cognitive control (e.g., maintenance of the inhibitory rule over the delay time) (43). Consistent with prior work (44), individual participant data were only included in analyses if results suggested that the participant understood the AX-CPT (specifically, showed accuracy >44% on AX trials, 0% on AY trials, 0% on BX trials, and 50% on BY trials). Participants were combined across two task protocols (AX-1 and AX-2) collected from two MRI scanners. Parameters for each protocol are provided in Table S1a. The task was presented using EPrime2 software (Psychology Software Tools, Inc.).

fMRI Scanning Parameters and Preprocessing

Please see the Supplement for details.

fMRI Analysis and Prespecified Region of Interest Selection

The procedures for generating first-level cognitive control–associated beta estimates were identical to those used in previous AX-CPT fMRI publications (9–11,29,34). First-level

effects were modeled with a double-gamma function with temporal derivatives using the general linear model in SPM8. Rigid-body motion parameters were included as single-participant regressors to partially account for movement effects. B > A cue (correct trials only) contrast images (parameter estimates) were generated for each participant. The B > A cue contrast measures response under conditions of high versus low proactive cognitive control (9,29). All trial types were modeled (AX/AY/BX/BY), and only correct responses were used to create first-level images, consistent with previous studies (9,29). Whole-brain analyses in the total sample (HC participants and people with SZ) using the B > A contrast were used to confirm significant (height threshold $p < .001$, cluster threshold $p < .05$ [whole-brain false discovery rate corrected]) expected activation in the bilateral DLPFC for both protocol versions (AX-1 and AX-2).

For analyzing associations between activation and the DDM DR metric, blood oxygen level-dependent response was extracted from prespecified left and right 5-mm radius spherical DLPFC regions of interest (ROIs). Although this size was chosen arbitrarily, previous work from our group suggests that varying ROI radius between 4 and 8 mm does not substantially affect AX-CPT task-associated response patterns in psychosis (11). DLPFC ROIs were taken from a previous study of an independent dataset (46). Mean task-associated response from these ROIs was extracted using the MarsBaR toolbox (47).

Behavioral Measures: Accuracy and RT

Accuracy scores were calculated as the mean percent correct in response to the probe over all blocks of trials for each condition (AX, AY, BX, BY). RT was calculated as the mean RT in response to correct probes over all blocks of trials for each condition.

Behavioral Measures: DDM

A DDM was used to fit the choice and accuracy data (13,14,48,49). The model works by accumulating momentary evidence to an upper bound (+A) or a lower bound (-B) corresponding to the two choice options (e.g., for the AX-CPT, index vs. middle finger). Positive evidence favors choice A, and negative evidence favors choice B. The momentary evidence gathered at each time step is drawn from a unit-variance Gaussian distribution with mean set by the DR parameter r . The bound reached first by the accumulated evidence determines the choice, and the decision time is determined by how long it took to reach that bound. One advantage of this model is that analytic solutions exist for both choices (13,50).

Mathematically, the probability of reaching bound A before B is given by the equation:

$$P_a(r, A, B) = \frac{e^{2rB} - 1}{e^{2rB} - e^{-2rA}} \quad (1)$$

The mean time (T) to bound A is given by the equation:

$$\langle T_a(r, A, B) \rangle = \frac{A + B}{r} \coth((A + B)r) \quad (2)$$

Symmetrical bounds were always applied such that $A = B$. Thus, in this study, the decision time depended on two

parameters: DR and decision bound. Changes in DR can account for different trial types with higher DRs resulting in more accurate and (usually) faster choices. The decision bound can account for the trade-off between speed and accuracy at a particular trial difficulty level, with higher bounds resulting in more accurate but slower choices (13,14,48,49). We fit the model to the accuracy and RT data (mean and standard deviation) for each subject by allowing the DR to vary between trial types while having the decision bound shared across conditions. The full RT predicted by the model also consisted of a fixed nondecision time added to the decision time to account for sensory and motor latencies. The best-fit parameters were found as those that maximized the likelihood of the data. Model fitting code was written in MATLAB (version 2022a; The MathWorks, Inc.) and is available upon request.

Under this framework, it is also possible to fit the model by allowing the decision bound to vary between trial types while having the DR shared across conditions. However, fitting the model in this manner resulted in significantly poorer fits (log-likelihoods) compared with the former method ($t = 4.56$, $p < .001$). It should also be noted that in the DDM, the pattern of differences in the distribution of RT and accuracy for each group/trial type can be explained by changes in DR but not changes in bound (14) (changes in bound are used to model RT vs. accuracy trade-offs, e.g., when participants are instructed to favor accuracy over speed or vice versa, which was not the case in this study). For these reasons, individual differences in bound were not analyzed in the current work.

Group Analyses: Demographic and Clinical

Age, WASI (39) score, and education were compared between groups by t tests. Group differences in sex and handedness were assessed by χ^2 tests. Significance for these tests was set to $p < .05$.

Group Analyses

We conducted three sets of analyses of variance using the general linear model implementation in SAS version 9.4 (IBM). Notably, results from the first two analyses (behavioral and fMRI activation) were expected to be similar to those of previous studies (9–12,28) primarily due to shared participants (see Participants). To our knowledge, the third analysis—the association between activation and DR—is entirely novel and is the focus of this work. Main effects of protocol version (AX-1 or AX-2) and sex (due to group sex imbalance) were also included as nuisance covariates. We also repeated the analyses including age as an additional covariate.

Behavioral Analysis. The first analysis set was an analysis of variance on purely behavioral data, with either accuracy, RT, or DR as the dependent variable, task condition as a within-subjects factor, group (HC vs. SZ) as a between-subjects factor, and the condition-by-group interaction. We also examined relationships between DR and accuracy/RT using partial correlations (controlling for group and protocol version).

Activation Analysis. The second set compared cognitive control-associated activation for the left and right DLPFC ROIs between HC participants and people with SZ.

Activation: DR Relationships. The third analysis set examined relationships between DR and left/right DLPFC activation with DR as the dependent variable, cognitive control–associated activation as a continuous covariate, group (HC vs. SZ) as a between-subjects factor, and the activation-by-group interaction. Secondary parameter estimates were also examined to test the statistical significance of these relationships within groups.

Significance for main effects and interactions was set to a Bonferroni-corrected p value of $<.025$ (for two ROIs). We also conducted a set of exploratory analyses examining relationships (Spearman's ρ correlation coefficients) between DRs, cognitive functioning (i.e., WASI score), clinical measures (reality distortion, disorganization, and poverty), and antipsychotic dose (chlorpromazine equivalent mg/day), with significance set to $p < .0125$ (Bonferroni correction for four trial types).

RESULTS

Excluded Data

Of the initial sample of 128 HC participants and 161 people with SZ, the DDM fitting procedure failed for 10 HC participants and 10 people with SZ, leaving 118 HC participants and 151 people with SZ in the final sample.

Demographics

Demographic and clinical information for participants in the final sample is shown in Table 1. Groups differed significantly on biological sex and education. Groups did not differ significantly on the ratio of AX-1 to AX-2 participants, age, handedness, parental education, or WASI score.

Behavioral and fMRI Comparison of AX-1 Versus AX-2

Behavioral and cognitive control–associated DLPFC ROI activation data segregated by protocol version are presented in Table S2. Across all participants, main effects of protocol version were observed for accuracy ($F_{1,267} = 16.08, p < .001$) and RT ($F_{1,267} = 88.69, p < .001$) but not DR ($F_{1,267} = 0.55, p = .46$). Significant or near-significant condition-by-protocol version interaction effects were also observed for accuracy ($F_{3,801} = 2.47, p = .060$), RT ($F_{3,801} = 34.40, p < .001$), and DR ($F_{3,801} = 9.77, p < .001$). The B > A cue contrast showed significant activation clusters in the left and right DLPFC of all individuals for both AX-1 and AX-2 (Table S3 and Figure S2). Cognitive control–associated (B > A cue) activation did not differ significantly between protocol versions for any ROI (Table S2).

Behavioral Group Analysis

Behavioral group means, standard errors, and results are presented in Table 2. For accuracy, significant main effects of condition and group were observed, but there was no condition-by-group interaction. Trial types in order of descending accuracy were BY > AX > BX > AY. Accuracies were lower in participants with SZ versus HC participants for all conditions. For RT, significant main effects of condition and group were observed, as well as the condition-by-group interaction. Trial types in order of ascending RT were AX < BY < BX < AY. RTs were higher in

Table 1. Demographic and Clinical Information for Participants Included in Analyses

	HC, $n = 118$	SZ, $n = 151$	Statistic (p)
SZ/SZ-A/SZ-P	–	86/33/32	–
AX-1/AX-2 Participants	46/72	69/82	$\chi^2_1 = 1.22 (.27)$
Age, Years	21.2 (2.7)	21.0 (3.4)	$t_{267} = 0.40 (.69)$
Sex, Female/Male	50/68	33/118	$\chi^2_1 = 13.07 (.001)$
Handedness, Right/ Left/Ambidextrous ^a	107/9/1	145/6/0	$\chi^2_2 = 4.35 (.23)$
Years of Education	14.0 (2.4)	12.4 (2.1)	$t_{267} = 5.99 (<.001)$
Parental Years of Education	13.7 (4.0)	13.9 (4.2)	$t_{267} = -0.37 (.71)$
WASI IQ	108.7 (29.5)	103.2 (14.3)	$t_{267} = 1.88 (.062)$
Length of Illness, Days	–	207.5 (138.6)	–
Medicated/ Unmedicated	–	132/19	–
Antipsychotics CPZ Equivalent Dose, mg/day ^b	–	241.4 (184.7)	–
Reality Distortion Symptoms ^c	–	14.15 (6.81)	–
Poverty Symptoms ^c	–	14.36 (5.73)	–
Disorganization Symptoms ^c	–	6.78 (3.37)	–

Values are presented as n or mean (SD).

AX-1, AX protocol version 1; AX-2, AX protocol version 2; CPZ, chlorpromazine; HC, healthy control participants; SZ, schizophrenia; SZ-A, schizoaffective; SZ-P, schizophreniform; WASI, Wechsler Abbreviated Scale of Intelligence.

^aMissing data: handedness = 1.

^bMissing data: CPZ equivalent dose = 9.

^cMissing data: symptoms = 4.

participants with SZ versus HC participants for all conditions and particularly during BX trials. For DR, significant main effects of condition and group were also observed, as well as the condition-by-group interaction. Trial types in order of descending DR were BY > AX > BX >>> AY. DRs were lower in participants with SZ versus HC participants for all conditions and particularly during BX trials. Including age as a covariate did not appreciably alter these results (Table S5).

Correlations Between DR and Other Behavioral Measures

Results from correlation analyses examining relationships between DR and other behavioral measures (accuracy, RT) after controlling for group (HC/SZ) and protocol version (AX-1/AX-2) are shown in Table S4. Across all trial types, DR was significantly positively correlated with accuracy and significantly negatively correlated with RT. Examining correlations separately for each trial type, significant positive correlations were observed between DR and accuracy during AX, AY, BX, and BY trials. Significant negative correlations were observed between DR and RT during AX, BX, and BY trials.

Activation Group Analysis

Significant main effects of group (in which people with SZ showed lower cognitive control–associated [B > A cue]

Table 2. Behavioral Data (Accuracy, Reaction Time, and Drift Rate)

Trial Type	HC, Mean (SD)	SZ, Mean (SD)	HC vs. SZ, t_{1017} (p)	Condition $F_{3,807}$ (p)	Group $F_{1,269}$ (p)	Condition by Group $F_{3,807}$ (p)
Accuracy						
AX Trials	0.95 (0.06)	0.91 (0.08)	2.76 (.006)	114.41 (<.001)	21.39 (<.001)	1.09 (.35)
AY Trials	0.82 (0.16)	0.79 (0.20)	2.35 (.019)			
BX Trials	0.92 (0.09)	0.86 (0.14)	4.08 (<.001)			
BY Trials	0.98 (0.04)	0.96 (0.07)	1.81 (.071)			
Reaction Time, ms						
AX Trials	486.88 (106.21)	530.70 (136.80)	-2.08 (.038)	230.04 (<.001)	13.18 (<.001)	7.79 (<.001)
AY Trials	623.29 (131.67)	681.05 (151.04)	-2.87 (.004)			
BX Trials	517.33 (173.58)	615.71 (240.69)	-5.15 (<.001)			
BY Trials	497.91 (131.52)	561.15 (160.02)	-3.17 (.002)			
Drift Rate ^a						
AX Trials	0.078 (0.020)	0.068 (0.023)	3.23 (.001)	266.07 (<.001)	29.78 (<.001)	5.22 (.001)
AY Trials	0.035 (0.019)	0.029 (0.019)	2.33 (.020)			
BX Trials	0.077 (0.036)	0.057 (0.034)	6.15 (<.001)			
BY Trials	0.082 (0.031)	0.067 (0.026)	4.92 (<.001)			

Analysis of variance (ANOVA) analyses included sex and protocol version (AX-1 or AX-2) as nuisance covariates. The t (p) values in the third column are based on comparisons of parameter estimates from ANOVA models.

HC, healthy control participants; SZ, schizophrenia spectrum disorder group.

^aHigher is faster.

activation than HC participants) were observed for the left DLPFC ROI ($F_{1,265} = 10.87, p = .001$, SZ vs. HC-adjusted beta estimate = $-0.47, SE = 0.14$), right DLPFC ROI ($F_{1,265} = 14.36, p < .001$, SZ vs. HC-adjusted beta estimate = $-0.57, SE = 0.15$). Including age as a covariate did not appreciably alter these results (Table S5).

Activation-DR Relationships

Scatterplots displaying relationships between cognitive control-associated activation ($B > A$ cue) and the equivalent DR measure ($B > A$ cue DR) for each group are presented in Figure 1. $B > A$ cue DR was the dependent variable for these models (see Methods and Materials for details). Briefly, significant activation-by-group interactions on DR were observed for both the left ($F_{1,263} = 8.77, p = .003$) and right ($F_{1,263} = 5.37, p = .021$) DLPFC ROIs, in which more positive relationships between activation and DR were observed in HC participants compared with people with SZ. Follow-up analyses of parameter estimates further suggested that activation significantly predicted DR in HC participants for the left DLPFC ROI (adjusted slope estimate = $0.010, SE = 0.002, t = 4.43, p < .001$) and right DLPFC ROI (adjusted slope estimate = $0.007, SE = 0.002, t = 2.99, p = .003$). In contrast, in people with SZ, activation did not significantly predict DR for either the left DLPFC ROI (adjusted slope estimate = $0.001, SE = 0.002, t = 0.70, p = .49$) or the right DLPFC ROI (adjusted slope estimate = $0.000, SE = 0.002, t = 0.22, p = .83$). Including age as a covariate did not appreciably alter these results (Table S5).

Notably, no significant or near-significant (all $ps > .50$) activation-by-protocol version (AX-1 or AX-2) interaction effects were observed, suggesting that the relationships between activation and DR did not differ as a function of task version. Because these interactions were nonsignificant, they were not included in the final models.

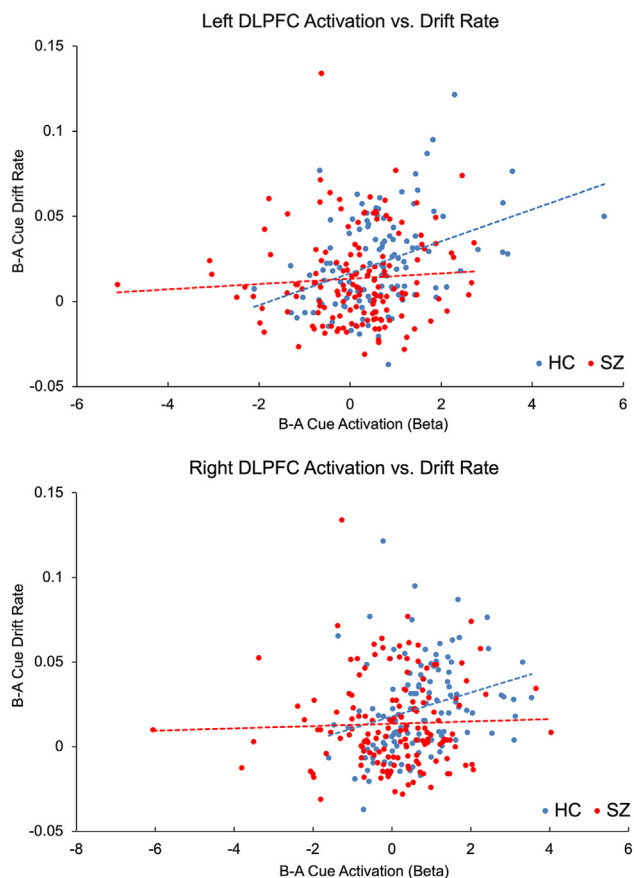


Figure 1. Scatterplots showing relationships between left (top panel) and right (bottom panel) dorsolateral prefrontal cortex (DLPFC) activation and drift rate. HC, healthy control; SZ, schizophrenia spectrum disorder group.

Cognitive and Clinical Correlations With DRs

In individuals with SZ, higher WASI scores were associated with higher DRs during BX trials ($\rho = 0.21, p = .011$) and BY trials ($\rho = 0.25, p = .002$). A qualitatively negative relationship between disorganization score and DR during AY trials approached but did not reach significance after correction for multiple comparisons ($\rho = -0.18, p = .025$). No significant clinical correlations with DRs were observed. Antipsychotic dose was also not significantly associated with DRs or DLPFC activation.

DISCUSSION

Using DDM-based analyses, in this study we found that people with SZ showed impaired performance during the AX-CPT as evidenced by lower DRs. DRs during B trials were also significantly associated with general intelligence in people with SZ. As would be expected from the DDM, DRs were positively correlated with accuracy (across and within all trial types) and negatively correlated with RT (across all trial types and within all trial types except for AY trials). Finally, we have provided new insights into the mechanisms of cognitive control impairments in SZ, showing that the typical relationships between DLPFC activation and performance are disrupted in the disorder in that cognitive control-associated recruitment of the DLPFC significantly predicts DRs in HC participants but not in people with the illness.

Behaviorally, people with SZ showed deficits in DR during all trial types, although these were particularly pronounced during high proactive cognitive control trials (B cues). We also found that DRs during B trials predicted WASI scores in individuals with SZ, which may not be surprising given that 1) proactive cognitive control processes (e.g., goal maintenance) may be recruited to help accomplish many if not most cognitive tasks (51), and 2) the primary cognitive control hub, the DLPFC, is part of a superordinate network of brain regions that supports a broad array of executive functions (2).

The main finding of this study was that unlike HC participants, participants with SZ did not show significant relationships between cognitive control-associated ($B > A$ cue) DLPFC recruitment and the equivalent DR measure. Thus, in the healthy brain, greater DLPFC response during proactive cognitive control resulted in a relatively increased rate of evidence accumulation (i.e., higher DR) compared with persons with SZ. Why might activation and DR be positively related in HC participants but not in participants with SZ? As argued by Miller and Cohen (51), the primary function of the DLPFC is to maintain goal representations during cognitive tasks to provide top-down biasing (i.e., input control, similar to a gain switch in an amplifier) of motor and/or sensory output. The DLPFC accomplishes this via its connections to accessory motor regions (e.g., the supplementary motor and premotor areas) as well as the dorsal striatum. Via these connections, the DLPFC can help overcome prepotent responses (e.g., proactively withholding button presses to stimuli as in the AX-CPT) and thus improve DR. Thus, greater DLPFC activation may be expected to be correlated with DR in HC individuals. In people with SZ, however, the DLPFC may be less able to perform its typical function in goal maintenance due to a pathological state in the region itself and/or through a relative loss in or rerouting of DLPFC connectivity to other brain areas (5). Supporting the

first hypothesis, analyses of brain tissue postmortem have found numerous and widespread differences in cellular and subcellular DLPFC morphology, which may lead to changes in DLPFC neural synchrony and cognitive control-associated activation [reviewed in (5)]. In agreement with the dysconnectivity hypothesis, structural and functional neuroimaging studies have frequently demonstrated a loss of prefrontal connectivity in SZ [e.g., (10,12,52–59); reviewed in (5,60–62)]. This hypothesis may be tested in future studies that use resting-state fMRI or white matter imaging to determine how reductions in intrinsic connectivity may result in the observed disruptions between DLPFC response and behavior during proactive cognitive control in people with SZ.

Given this result, how might deficits in proactive cognitive control be targeted in future studies? One possibility is through noninvasive brain stimulation. One recent study reported that high-frequency repetitive transcranial magnetic stimulation over the left DLPFC decreased RTs during high cognitive control BX trials in female HC participants (63), which is in conceptual agreement with the observed positive relationship between DLPFC activation and DR in unaffected individuals in this study. Work by our group has also shown that transcranial direct current stimulation over the DLPFC reduces error rates during proactive control in HC participants (64) and people with SZ (65). Meta-analytic evidence of high-frequency repetitive transcranial magnetic stimulation studies in SZ also suggests that DLPFC stimulation using this method may improve working memory, a type of goal maintenance, in the illness (66). Furthermore, DLPFC theta burst stimulation, a transcranial magnetic stimulation method involving short high-frequency stimulation bursts (that more closely mimics brain dynamics), was recently shown to improve working memory performance in SZ while modulating fractional amplitude of low-frequency fluctuations in primary/accessory visual areas (67). Meta-analyses suggest that noninvasive DLPFC stimulation in SZ also improves negative symptoms in the disorder (68). These effects may be due to stimulation-induced restoration of DLPFC connectivity to accessory visual and midbrain dopamine areas (69). Related to the current work, it is possible that noninvasive stimulation of the DLPFC specifically applied during the proactive control condition may induce task-specific plasticity in the region, thus enabling the DLPFC to perform its normal role during cognitive control in people with SZ.

Some limitations of the current study should be noted. Although our regression-based approach (in which DR was set as the dependent variable) implies causality (i.e., activation producing behavior), true causality can only be demonstrated using agents that modulate brain activity, e.g., via pharmacologic manipulation or brain stimulation. Second, most people with SZ were taking antipsychotic medication and/or undergoing various aspects of coordinated specialty care (e.g., counseling). Thus, we cannot rule out confounding effects of these factors, even though we did not observe significant correlations between medication dose and DRs or DLPFC response. Future studies involving first-episode, treatment-naïve individuals would be informative in this regard.

Conclusions

The results of this study suggest that in SZ, typically strong relationships between DLPFC activation and performance

associated with proactive cognitive control are disrupted. Future studies may examine whether targeted stimulation of the DLPFC during cognitive control tasks may be an effective method of improving this dysfunctional process in the illness.

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