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Altered Associations Between Motivated Performance and Frontostriatal Functional Connectivity During Reward Anticipation in Schizophrenia

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***Background and hypothesis*: The neuronal mechanisms that underlie deficits in effort cost computation in schizophrenia (SZ) are poorly understood. Given the role of frontostriatal circuits in valence-oriented motivation, we hypothesized that these circuits are either dysfunctional in SZ or do not appropriately predict behavior in SZ when task conditions are difficult and good performance is rewarded. *Study design*: A total of 52 people with recent onset SZ-spectrum disorders and 48 healthy controls (HCs) performed a 3T fMRI task with 2 valence conditions (rewarded vs neutral) and 2 difficulty conditions. Frontostriatal connectivity was extracted during the cue (anticipatory) phase. Individual behavior was fit using a drift-diffusion model, allowing the performance parameter, *drift rate* (DR), to vary between task conditions. Three models were examined: A group × condition model of DR, a group × condition model of connectivity, and a regression model of connectivity predicting DR depending on group and condition. *Study results*: DRs showed the expected positive correlation with accuracy and a negative association with reaction time. The SZ group showed a deficit in DR but did not differ in overall connectivity or show a valence-specific deficit in connectivity. Significant group × valence × difficulty interactions, however, were observed on the relationship between right dorsolateral prefrontal (DLPFC)-striatal connectivity and DR (DLPFC-Caudate: $F = 10.92$, $P_{FDR} = .004$; DLPFC-Putamen: $F = 5.14$, $P_{FDR} = .048$) driven by more positive relationships between DR and connectivity during cues for the difficult-rewarded condition in HCs compared to SZ. *Conclusions*: These findings suggest that frontostriatal connectivity is less predictive of performance in SZ when task difficulty is increased and a reward incentive is applied.**

Key words: caudate/dorsolateral prefrontal cortex/drift rate/psychosis/putamen/striatum

Introduction

A deficit in reward-associated motivation is a striking feature of schizophrenia (SZ), although questions remain regarding the neural mechanisms by which this process is dysfunctional in the illness. Studies suggest that individuals with SZ report normal levels of in-the-moment positive emotion and subjective arousal when exposed to pleasurable stimuli, as well as similar neural response to healthy controls (HCs) when presented with emotional stimuli and asked to report on their in-the-moment emotions.[1–3] In contrast, people with SZ also demonstrate a relative inability to perform effort vs cost predictions and computations, eg, appropriately increase their effort in difficult tasks that reward high performance.[3–5] It is postulated that this deficit arises from a relative inability to maintain value representations in the prefrontal cortex, such that cognitive control mechanisms cannot be engaged to modulate activity in other brain areas (eg, the dorsal striatum) and affect behavior.[5–8] Given that these regions are functionally and structurally connected (with the DLPFC sending inputs to the striatum to provide top-down modulation of valence-based decision-making and related processes[8,9]), it is also possible that dysconnectivity in frontostriatal circuitry in SZ[10,11] makes the prefrontal cortex less able to produce goal-directed behavior in the illness even if value representations are relatively intact. Furthermore, one may speculate that this dysconnectivity is particularly pronounced in people with SZ who show the largest deficits in goal-directed performance.

Examining the neuronal basis of behavior with high-spatial resolution requires the use of functional magnetic resonance imaging (fMRI). How might we comprehensively capture task performance in a laboratory setting? Typically, task-related fMRI studies report accuracy and reaction time (RT) as performance

metrics, with high accuracies and low reaction times usually interpreted as "ideal." This approach, however, is problematic for 2 reasons. First, accuracy and RTs are often inversely correlated (the "speed-accuracy tradeoff").[12] Second, reporting mean or median accuracies and RTs do not fully capture the underlying distributions of these values; RTs, in particular, typically show long-tailed, skewed distributions.[13] A more comprehensive approach would be able to incorporate accuracy and RT into a single, "efficiency" metric that is positively correlated with accuracy and negatively correlated with RT. This metric would also be calculated by fitting the entire distribution of individual RT values and thus would not only be based on the individual mean RT but also the individual standard deviation of the RT.

The *drift-diffusion model* (DDM) is a model fitting procedure developed by Ratcliff[14] that provides the desired unified framework to explain measures of RT (including RT distributions) and accuracy in the context of 2choice decisions, eg, pressing 1 button or another in response to stimuli.[14–16] In the DDM framework, decisions 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 1), with the rate of information accumulation referred to as the drift rate (DR). Higher DRs lead to faster and more accurate decisions, whereas lower DRs lead to slower and less accurate decisions. A person with high DRs, therefore, can quickly accumulate enough information to make a correct response, resulting in increased speed and accuracy. It also follows from the model that, in general, high-difficulty trials are expected to show lower DRs relative to low-difficulty trials. Furthermore, motivated behavior may be associated with enhanced DRs to optimize performance and maximize reward (as modeled by[17,18]). It is also important to note that DR captures more information than either accuracy or RT alone as these measures can be inversely correlated (the "speed-accuracy tradeoff'); ie, the DR can be considered a measure of performance efficiency.

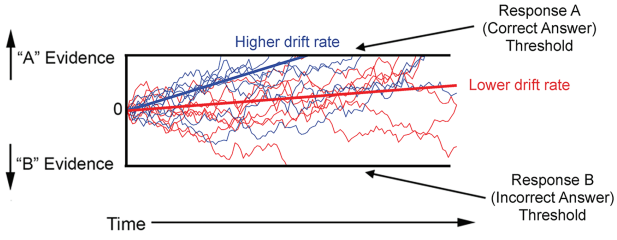

Fig. 1. Illustrative explanation of the drift-diffusion model (DDM) and DR. The DDM posits that decision making can be modeled as a function of the signal-to-noise ratio of gathering information to make a decision (DR), an information threshold for making a decision, and non-decision time (eg, motor response time). The DR is the average slope of the evidence accumulation process (solid lines). Higher DR implies increased efficiency of gathering information, eg, with simultaneously lower RT and higher accuracy. In this figure, "A" and "B" represent correct and incorrect answers, respectively.

What are the neuronal processes by which information accumulation occurs? Briefly, human fMRI studies of decision making have demonstrated that the dorsolateral prefrontal cortex (DLPFC) and dorsal striatum integrate information gathered from sensory processing areas to make categorical decisions.[19–23] Furthermore, studies incorporating DDM measures suggest both of these areas are involved in evidence accumulation.[24–27] Along these lines, disruptive low-frequency transcranial magnetic stimulation and theta burst stimulation over the DLPFC have also been shown to decrease and increase DR, respectively, suggesting that DLPFC activation may have a causal role in influencing DRs across this network.[28,29] Interestingly, higher functional connectivity has been shown to be related to faster DRs,[30,31] suggesting that in healthy populations differences in connectivity may predict performance.

Based on evidence suggesting that intact function of the DLPFC and dorsal striatum may predict DDM-associated behavioral measures, it follows that dysconnectivity between these areas may have deleterious effects on task performance (reflected by low DRs in DDM contexts). Accordingly, it is well-established that SZ is characterized by functional deficits in the DLPFC and dorsal striatum during a myriad of cognitive tasks, including working memory, cognitive control, and anticipatory reward processing.[6,32–35] Frontostriatal regions also have well-studied roles in goal-directed behavior and valence-driven performance[8,9] that may help explain why these processes are abnormal in SZ.[5] One may speculate, therefore, that either frontostriatal circuitry is functionally disconnected under certain task conditions (eg, during challenging tasks that incentivize good performance) in SZ, or (alternatively) that relationships between connectivity and performance are disrupted in SZ.

The goal of this study, therefore, was to test the hypotheses that: (1) vs HCs, people with SZ will show reduced DRs when task conditions are difficult and performance is incentivized, (2) vs HCs, people with SZ will show altered functional connectivity between the DLPFC and dorsal striatum also when conditions are difficult and performance is incentivized, and (3) vs HCs, functional connectivity between the DLPFC and dorsal striatum will be less predictive of DR in SZ when conditions are difficult and performance is incentivized. We also examined correlations between DR and accuracy/RT to determine if DR would show the expected relationships with these measures—specifically, a positive correlation with accuracy, and a negative correlation with RT.

Method

Relationship to Previous Work

This sample was taken from an ICE-T dataset that we previously analyzed for publication.[36] Unlike the present study, the prior analysis examined group differences in reward anticipation-associated activation (not connectivity) and did not examine brain–behavior relationships.

Participants

Fifty-two individuals with recent-onset SZ spectrum disorders (including SZ, schizoaffective disorder, schizophreniform disorder, and psychosis-not-otherwise-specified, hereafter referred to as the SZ group in this paper) were recruited from the UC Davis Early Psychosis Programs (EDAPT and SacEDAPT Clinics) as well as 49 demographically matched HCs from the community. SZ participants were within 2 years of their first psychotic episode. 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. All procedures involving human subjects/patients were approved by the University of California, Davis Institutional Review Board. Participants gave written informed consent and were paid for their participation.

Data from these subjects using a traditional univariate task fMRI analysis have previously been published.[36]

Task Description

The ICE-T is a delayed match-to-sample task (supplementary figure 1, parameters in supplementary table 1) that dissociates reward motivation and top-down cognitive control.[37,38] The task is composed of blocks of easy, "same" trials requiring low cognitive control and blocks of more difficult, "opposite" trials requiring high cognitive control.

Additional details are provided in the Supplement.

Behavioral Measures: Accuracy and Reaction Time

Accuracy scores were calculated as the mean percent correct in response to the probe over all blocks of trials for each condition (Same Neutral, Same Rewarded, Opposite Neutral, and Opposite Rewarded). RT was calculated as the mean RT in response to correct probes over all blocks of trials for each condition.

Behavioral Measures: Drift Diffusion Model

A DDM was used to fit the choice and accuracy data.[15,16,39,40] The decision time depends on 2 parameters: DR and decision bound. Changes in DR can account for different trial difficulties with higher DRs resulting in faster and more accurate choices. Changes in decision bound can account for the tradeoff between speed and accuracy at a particular trial difficulty with higher bounds resulting in more accurate but slower choices.[15,16,39,40] 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 difficulty conditions while having the decision bound shared across conditions. This was because, in the DDM, the pattern of differences in the distribution of RT and accuracy for each group/task condition can be explained by changes in DR but not changes in bound [16] (changes in bound are used to model RT vs accuracy tradeoffs, eg, when participants are instructed to favor accuracy over speed or vice-versa, which was not the case in this study). The full RT predicted by the model also consisted of a fixed non-decision time added to the decision time to account for sensory and motor latencies.

Additional details regarding the calculation of model parameters are provided in the supplementary methods.

fMRI Image Acquisition and Preprocessing

Please see the supplementary material for details.

Functional Connectivity Denoising

Please see the supplementary material for details.

First-level Functional Connectivity Analysis

Functional connectivity analyses were conducted using the generalized psychophysical interaction(s) tool in CONN v.20 (web.conn-toolbox.org). Reward anticipation (cue)-associated functional connectivity during correct responses for each trial type (Same Neutral, Same Rewarded, Opposite Neutral, Opposite Rewarded) was extracted from 6 ROIs: left DLPFC, right DLPFC, left caudate, right caudate, left putamen, and right putamen.

Please see the Supplement for additional details on ROIs and connectivity analysis.

Correlations Between Behavioral Measures

To determine if DR would show the expected positive correlation with accuracy and negative correlation with RT, we performed partial correlations (SPSS v. 28, IBM) between DR and these measures after controlling for diagnosis, task valence, and task difficulty. For this analysis, the significance was set to $P < .05$.

Group Analyses—Demographic and Clinical

Age, Weschler Abbreviated Scale of Intelligence (WASI)[41] score, and education were compared between groups by *t*-tests. Group differences in gender and handedness were assessed by chi-square tests. Significance for these tests was set to $P < .05$.

Group Analyses

We conducted 3 sets of mixed model ANOVA analyses (SAS v. 9.4, IBM). The restricted maximum likelihood (REML) method was used to fit all models, and all models were fully factorial (ie, included all possible main effects and interactions).

Behavioral Analysis. The first analysis set was purely behavioral, with either accuracy, RT, or DR as the dependent variable, valence (neutral vs rewarded) as a within-subjects factor, difficulty (same vs opposite) as a within-subjects factor, and group diagnosis (HC vs SZ) as a between-subjects factor.

Functional Connectivity Analysis. The second set was examined frontostriatal connectivity between each DLPFC ROI and each striatal ROI, with connectivity as the dependent variable, valence (neutral vs rewarded) as a within-subjects factor, difficulty (same vs opposite) as a within-subjects factor, and group diagnosis (HC vs SZ) as a between-subjects factor.

Functional Connectivity—Drift Rate Relationships. The third analysis set examined relationships between DR and connectivity between each DLPFC ROI and each striatal ROI, with DR as the dependent variable, connectivity as a continuous covariate, valence (neutral vs rewarded) as a within-subjects factor, difficulty (same vs opposite) as a within-subjects factor, and group diagnosis (HC vs SZ) as a between-subjects factor. Interaction effects of interest were those involving interactions between connectivity and group, ie, the connectivity × group × valence × difficulty, connectivity × group × valence, connectivity × group × difficulty, and connectivity × group interactions.

Significance for main effects and interactions was set to $P < .05$ for behavioral analysis and $P_{FDR} < .05$ for functional connectivity analyses (FDR-corrected for 4 comparisons for 4 ROI-ROI connectivity pairings). Significant group interaction effects were followed up by *t*-tests of parameter estimates to determine the nature of the interactions. Only individuals who showed at least 60% accuracy during all 4 task conditions were included in the analyses.

To examine antipsychotic effects, we examined relationships between DR and connectivity as described above while including chlorpromazine equivalent antipsychotic dose as a continuous covariate and examining the main effect of dose as well as interactions with dose. As HCs were not included in this analysis, the group was not included as a factor.

Results

Excluded Data

The initial sample consisted of the 49 HCs and 52 people with SZ that were included in our previous analysis of the ICE-T[36]. Of these, the DDM fitting procedure failed for 1 HC because bounds could not be determined, leaving 48 HCs and 52 individuals 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 WASI score and education, but not on age, biological sex, handedness, or parental education.

Behavioral Analysis

Behavioral group means, SDs, and results are presented in table 2. For accuracy, significant main effects of valence, difficulty, and diagnosis were observed, but no valence × diagnosis interaction. Main effects were characterized by higher accuracies in the "Same" (easy) conditions,

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

	HC (SD)	SZ (SD)	Statistic (*P*)
n	48	52	—
n Schizophrenia/SZ-A/SZ-P/ PNOS	—	38/10/3/1	—
Age	20.3 (3.0)	20.0 (3.8)	$t = 0.39$ (.70)
Sex M/F	33/15	39/13	$\chi^2 = 0.48$ (.49)
Handedness R/L	45/2 (1 missing)	48/4	$\chi^2 = 1.61$ (.45)
Years of education	13.8 (2.6)	12.2 (2.0)	$t = 3.27$ (.002)
Parental years of education	14.9 (3.4)	14.8 (2.8)	$t = 0.16$ (.87)
WASI IQ	118.4 (12.6)	103.8 (15.4)	$t = 4.97$ (< .001)
Length of illness, days	—	274.2 (154.9)	—
Antipsychotics typical/atypical/none	—	1/46/5	—
Antipsychotics CPZ equivalent dose mg/day	—	190.3 (139.2)	—
SANS total	—	10.2 (3.8)	—
SAPS total	—	3.8 (3.5)	—

Note: CPZ, chlorpromazine; HC, healthy control; PNOS, psychosis-not-otherwise-specified; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SD, standard deviation; SZ, Schizophrenia; SZ-A, Schizoaffective; SZ-P, Schizophreniform; WASI, Wechsler Abbreviated Scale of Intelligence.

Table 2. Adjusted Beta Estimates (Least Squares Means) of Behavioral Data (Accuracy, Reaction Time, and Drift Rate)

	HC (SE)	SZ (SE)	$F_{Valence}$ (*P*)	F_{Diff} (*P*)	F_{Dx} (*P*)	$F_{Dx \times Valence}$ (*P*)	$F_{Dx \times Diff}$ (*P*)	$F_{Dx \times Valence \times Diff}$ (*P*)
Accuracy								
Same neutral	0.93 (0.01)	0.89 (0.01)	36.93 (<.001)	172.90 (<.001)	13.16 (<.001)	0.01 (.91)	3.20 (.07)	0.62 (.43)
Same rewarded	0.95 (0.01)	0.92 (0.01)						
Opposite neutral	0.86 (0.01)	0.81 (0.01)						
Opposite rewarded	0.90 (0.01)	0.84 (0.01)						
Reaction time (ms)								
Same neutral	554.6 (8.6)	562.2 (8.3)	27.02 (<.001)	602.38 (<.001)	1.25 (.26)	3.12 (.08)	3.48 (.06)	1.18 (.28)
Same rewarded	539.8 (8.6)	550.2 (8.3)						
Opposite neutral	599.3 (8.6)	610.1 (8.3)						
Opposite rewarded	586.2 (8.6)	608.4 (8.3)						
Drift rate (higher is faster)								
Same neutral	0.070 (0.002)	0.061 (0.002)	49.79 (<.001)	595.37 (<.001)	13.60 (<.001)	0.95 (.33)	1.78 (.18)	0.74 (.39)
Same rewarded	0.077 (0.002)	0.068 (0.002)						
Opposite neutral	0.050 (0.002)	0.040 (0.002)						
Opposite rewarded	0.056 (0.002)	0.043 (0.002)						

Note: Diff, difficulty; HC, healthy control; SE, standard error; SZ, schizophrenia.

rewarded conditions, and HC vs SZ. For RT, significant main effects of valence and difficulty were observed, but no effect of diagnosis or valence × diagnosis interaction. Main effects were characterized by lower RTs in the "Same" and rewarded conditions. For DR, significant main effects of valence, difficulty, and diagnosis were observed, but no valence × diagnosis interaction. Main effects were characterized by higher DRs in the "Same" conditions, rewarded conditions, and in HC vs SZ.

Correlations Between Behavioral Measures

After controlling for group and task effects, a significant positive correlation was observed between DR and accuracy ($r = 0.73$, $P < .001$), and a significant negative correlation was observed between DR and RT ($r = -0.56$, $P < .001$).

Functional Connectivity Analysis

Groups did not differ in mean movement (supplementary table 2). Compared to HCs, people with SZ had a significantly higher of % frames scrubbed (2.56% scrubbed for HCs vs 4.82% scrubbed for SZ; see supplementary table 2 for data and supplementary methods for scrubbing criteria).

Results of mixed models examining group and task condition effects on frontostriatal functional connectivity are presented in table 3. Briefly, a significant diagnosis × difficulty interaction was observed for connectivity between the right DLPFC and right putamen, in which connectivity was lower during the difficult condition in HCs but qualitatively showed the opposite pattern in SZ. No other main effects or interactions were observed.

Functional Connectivity-drift Rate Relationships

Results of mixed models examining relationships between connectivity and DR are presented in table 4. DR was the dependent variable for these models (see supplementary methods for details).

Significant connectivity × group × valence × difficulty interactions were observed when analyzing the relationships between DR and functional connectivity between the right DLPFC and the 2 dorsal striatal areas (right caudate and right putamen). Specifically, during the difficult, rewarded condition, a more positive relationship between connectivity and DR was observed in HC's compared to people with SZ (right DLPFC—right caudate connectivity HC vs SZ estimate = 0.14 (SE = 0.05), $t = 2.57$, $P = .011$; right DLPFC—right putamen connectivity HC vs SZ estimate = 0.10 (SE = 0.05), $t = 2.02$, $P = .045$) (see figure 2 for right DLPFC seed-based statistical parametric map and representative connectivity by DR scatter plot). Within-group parameter estimates suggested a trend-level positive relationship between DR and right DLPFC—right caudate connectivity in HCs during the Opposite Rewarded condition and the converse relationship in SZ (table 4). Relationships between DR and connectivity did not differ between groups for any other task condition. No group interaction effects were observed when examining the relationships between DR and connectivity between the left DLPFC and dorsal striatum ROIs.

No main effects of dose or interactions with dose were observed on relationships between functional connectivity and DR.

Discussion

As expected, DRs were significantly positively associated with accuracy and negatively associated with RT. Reduced DRs were observed in SZ vs HCs independently of task condition. Our hypotheses that people with SZ would show exaggerated deficits in DR and reduced

Table 3. Summary of Significant Results of 3-way ANOVAs Analyzing Group Effects and Interactions Between Diagnostic Group and Task Condition for Connectivity Between Regions of Interest (ROIs). Connectivity Betas are Provided on the Right Side of the Table as Appropriate When Group Effects and/or Interactions were Significant

Connectivity ROIs			Condition	HC connectivity		SZ connectivity	
	F	P_{FDR}		Beta	SE	Beta	SE
F contrast							
Right DLPFC—right caudate							
No significant effects or interactions							
Right DLPFC—right putamen							
DX × Diff	5.08	.0498	Same	0.011	0.004	0.002	0.004
			Opposite	0.002	0.004	0.008	0.004
Left DLPFC—left caudate							
No significant effects or interactions							
Left DLPFC—left putamen							
No significant effects or interactions							

Note: Diff, difficulty; DLPFC, dorsolateral prefrontal cortex; HC, healthy control; SE, standard error; SZ, schizophrenia.

Table 4. Summary of Results of 4-way ANOVAs Analyzing Relationships Between Connectivity Between Regions of Interest (ROIs) and Drift Rate (DR). DR was the Dependent Variable for These Models. Model-Adjusted Slopes of Brain-Behavior Relationships for Each Condition and Group are Provided as Appropriate on the Right Side of the Table When Group Effects and/or Interactions Were Significant. Group Effects were FDR-corrected for 4 Comparisons

Connectivity ROIs			Condition	HC connectivity vs DR		SZ connectivity vs DR	
	F	P_{FDR}		Slope	SE	Slope	SE
F contrast							
Right DLPFC—right caudate							
DX × Valence × Diff	10.92	.004	Same neutral	0.05	0.03	−0.02	0.03
			Same rewarded	−0.08	0.05	−0.04	0.03
			Opposite neutral	−0.08	0.05	0.02	0.04
			Opposite rewarded	0.07	0.04	−0.06	0.04
Right DLPFC—right putamen							
DX × Valence × Diff	5.14	.048	Same neutral	0.01	0.04	−0.01	0.03
			Same rewarded	−0.11	0.04	0.01	0.04
			Opposite neutral	0.03	0.04	0.03	0.03
			Opposite rewarded	0.03	0.04	−0.06	0.03
Left DLPFC—left caudate							
DX × Valence × Diff	0.26	0.81					
Left DLPFC—left putamen							
DX × Valence × Diff	0.03	0.87					

Note: Diff, difficulty; DLPFC: Dorsolateral Prefrontal Cortex; HC, healthy control; SE, standard error; SZ, Schizophrenia.

connectivity when the task was difficult and incentivized was not supported, as group analyses of DR and frontostriatal functional connectivity revealed no interactions with a valence or 3-way interactions (although a group × difficulty interaction was observed on right DLPFC—right putamen connectivity). Our third hypothesis, however, was supported, in that frontostriatal connectivity was less predictive of DR in SZ (vs HC) when task conditions were difficult and incentivized but not during other task conditions. These results suggest that SZ is associated with a relative disruption in the functional ability of frontostriatal circuits to modulate DR under conditions where accurate performance during high cognitive control demands is monetarily incentivized. These results suggest a functional mechanism to explain why SZ patients have difficulty ascertaining the value of future rewards[1,42,43] and representing the value of an outcome to effectively engage cognitive control.[1,44]

Consistent with theory,[16] after controlling for group and task condition effects, a significant positive correlation was observed between DR and accuracy and a significant negative correlation was observed with DR and RT. These results suggest that DR in this study effectively captured performance "efficiency," ie, a metric in which high values implied both high accuracy and low RT, and thus was a more comprehensive measure of performance that either accuracy or RT alone.

The primary significant finding in the present study was the observation that in people with SZ, frontostriatal functional connectivity was less predictive of DR when the task was rewarding and difficult. This was evident in the significant group × difficulty × valence interactions with

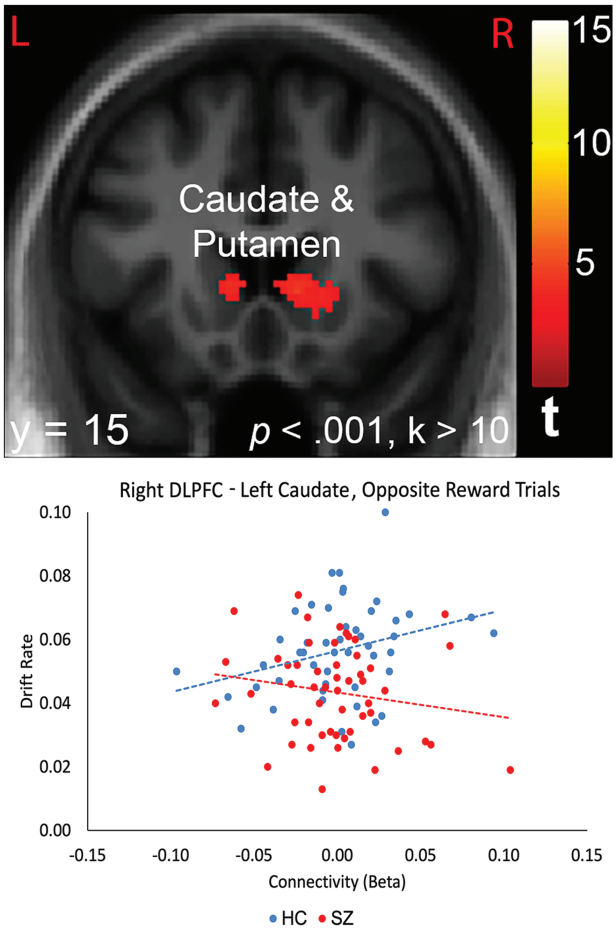

Fig. 2. ***Top:*** Right dorsolateral prefrontal cortex (DLPFC) seed-based statistical parametric map showing a greater positive relationship (ie, higher slope) between right DLPFC—dorsal striatal connectivity and drift rate (DR) in healthy controls vs patients with schizophrenia during cues of the opposite rewarded condition of the Incentivized Cue-Engagement Task. Map thresholded at $P < .001$ (voxelwise), $k > 10$ voxels for visualization. ***Bottom:*** Scatter plot showing a relationship between DR and connectivity between the right dorsolateral prefrontal cortex (DLPFC) and left caudate during opposite reward trials in healthy controls (HC) and people with schizophrenia (SZ).

connectivity between the right DLPFC and both right dorsal striatal ROIs (caudate and putamen), in which DR and connectivity were more positively associated in HCs compared to SZ. Thus, in the healthy brain, enhanced connectivity between the DLPFC and striatum (particularly the caudate) results in a relatively increased rate of evidence accumulation (ie, higher DR) when the task is difficult and good performance is rewarded compared to SZ. What may be the neural mechanism(s) by which this disruption occurs? One possibility may involve striatal dopamine. Dopaminergic signaling from midbrain pathways to the striatum and DLPFC involves both tonic and phasic release, with phasic "burst" firing occurring during particularly salient events, eg, rewards and reward cues.[45] It is also now well-established that SZ is associated with increased nigrostriatal presynaptic dopamine release capacity.[46–48] As argued by Maia and Frank,[49] hyperdopaminergia in these pathways may cause an increase in spontaneous phasic dopamine release (akin to noise) with a concurrent decrease in adaptive task-relevant phasic release. This may result in the reduced association between connectivity and behavior in SZ observed in the present study, such that high levels of striatal "noise" prevent the DLPFC from effectively modulating performance when needed to achieve reward (ie, when the task is more difficult). Related to this point, reduced ability to filter out distracting information may be one of the mechanisms contributing to poor working memory in SZ,[50] perhaps due in part to deleterious alterations in GABAergic somatostatin-expressing interneurons[51] that gate excitatory inputs to DLPFC pyramidal cells facilitating distractor resistance.[35,52–55] A second possibility may be related to DLPFC dysfunction. Postmortem studies have found cellular and subcellular changes in DLPFC morphology that may underlie related deficits in DLPFC neural synchrony and task-associated activation reviewed by Ref.[35] It is therefore possible that this pathology prevents the DLPFC from performing its role in the online maintenance of information to guide higher cognition.[35] A third possible mechanism may involve antipsychotics, which primarily act as D2 receptor antagonists in the brain and thus may affect the relationship between activation and output. Future studies comparing unmedicated vs medicated patients may help test this hypothesis, although it should be noted that we did not see any association or interactions with antipsychotic dose in this study.

Interestingly, our first hypothesis (that DR would be reduced in SZ in a condition-specific manner) was not supported. Rather, consistent with our prior analysis of accuracy and RT,[36] DRs were lower in SZ across conditions. As stated in our previous study,[36] possible reasons for the lack of condition-specific effects were that the difficult condition was not sufficiently challenging relative to the easy condition, the task was not sufficiently rewarding ($50 per correct Rewarded trial) to differentially affect performance, and the SZ group was relatively cognitively intact (mean WASI score ~100). Our second hypothesis—that connectivity would be reduced in SZ in a valence × difficulty and/or valence-specific manner—was also not supported, possibly due to the above reasons.

Our study had several limitations. First, although setting DR as the dependent variable statistically infers causality (ie, connectivity influencing behavior), truly causal effects can only be measured via externally modifying brain function, eg, using transcranial direct current stimulation. Second, the SZ group was heterogenous in regard to medication status. Although no effects of antipsychotic dose were observed, we cannot rule out potentially confounding effects of chronic antipsychotic treatment. Future studies in antipsychotic-naïve patients will be needed to determine if antipsychotic effects influenced

the pattern of findings. The SZ group also had comparatively less within-subject data vs HCs, as a higher percentage of frames were removed during preprocessing. It was also somewhat surprising that reduced DRs were observed in SZ vs HCs independently of task condition (although reduced DRs in SZ are consistent with previous observations[56,57]). Only small monetary rewards were offered in this study, however, and taken together with the possibility that the "difficult" condition may have been insufficiently taxing on cognitive control systems, it is conceivable that the task was not sensitive enough to elicit group × condition interaction effects on DR. Finally, although the present study was designed to examine the effects of extrinsic motivation (in this case, monetary reward) on the relationship between DR and frontoparietal connectivity, we cannot rule out the possibility that group differences in non-reward associated, "intrinsic" motivation (which the present study did not measure) also influenced the observed interaction effects.

In conclusion, the novel pattern of results reported in this computational model-based fMRI study suggests that DR, a measure of information accumulation that is a function of accuracy and RT at the individual subject level, is decoupled from reward anticipation-associated frontostriatal functional connectivity when task conditions require high cognitive control to obtain a reward in SZ. Further studies using the DDM and other computational modeling-based approaches will likely provide additional insights into the motivational and executive aspects of cognitive control deficits in SZ and other forms of psychosis.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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