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One-Year Stability of Frontoparietal Cognitive Control Network Connectivity in Recent Onset Schizophrenia: A Task-Related 3T fMRI Study

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Kraepelinian theory posits that schizophrenia (SZ) is a degenerative disorder that worsens throughout the lifespan. Behavioral studies of cognition have since challenged that viewpoint, particularly in the early phases of illness. Nonetheless, the extent to which cognition remains *functionally* stable during the early course of illness is unclear, particularly with regard to task-associated connectivity in cognition-related brain networks. In this study, we examined the 1-year stability of the frontoparietal control network during the AX-Continuous Performance Task (AX-CPT) from a new baseline sample of 153 participants scanned at 3T, of which 29 recent onset individuals with SZ and 42 healthy control (HC) participants had follow-up data available for analysis. Among individuals that had both baseline and follow-up data, reduced functional connectivity in SZ was observed between the dorsolateral prefrontal cortex (DLPFC) and superior parietal cortex (SPC) during the high control (B cue) condition. Furthermore, this deficit was stable over time, as no significant time × diagnosis interaction or effects of time were observed and intraclass correlation coefficients were greater than 0.6 in HCs and SZ. Previous 1.5T findings showing stable deficits with no evidence of degeneration in performance or DLPFC activation in an independent SZ sample were replicated. Overall, these results suggest that the neuronal circuitry supporting cognitive control is stably impaired during the early course of illness in SZ across multiple levels of analysis with no evidence of functional decline.

Key words: AX-CPT/dorsolateral prefrontal cortex/functional connectivity/intraclass correlation coefficient/longitudinal/superior parietal cortex

Introduction

Over 100 years after Kraepelin coined it "Dementia Praecox,"[1] the question remains: to what extent is schizophrenia (SZ) a degenerative disorder, ie which process(es), if any, manifest at illness onset and then worsen over time? In contrast, are there processes more consistent with a neurodevelopmental viewpoint, in which changes begin early in development and then stabilize before the first psychotic break? This question is of particular importance for cognitive symptoms of the illness, considering that cognitive deficits are the greatest predictors of poor functional outcome.[2] Behavioral studies suggest cognition is relatively intact for the first few years following illness onset (reviewed by Bora et al[3,4]), although by 10 years follow-up modest declines have been observed in some domains.[5] Behavioral studies themselves, however, are insufficient evidence to prove or disprove the degeneration hypotheses, because the neuronal mechanisms that underlie cognition may be disrupted without detectably altering performance (depending on task sensitivity or due to cognitive reserve).

To gain a deeper longitudinal understanding of the underlying biology, researchers have used structural and functioning neuroimaging to study SZ. Structural imaging studies have painted a multifaceted picture in that although accelerated loss of structural integrity (eg gray matter loss) has been frequently observed (eg Kasai et al[6]; reviewed by Shenton et al[7,8]), results are potentially confounded by effects nonspecific to the disease process (eg antipsychotic effects).[9] Functional imaging studies (which are less frequently performed) suggest functional abnormalities (eg reduced activation in networks important for cognition) are relatively stable in the first months to years following illness onset,[10,11] although accelerated decline of functional network organization (efficiency in some resting state networks) has also been reported.[12]

Although SZ affects almost all cognitive domains, cognitive control, the ability to maintain contextual information needed to guide complex behaviors through

frontoparietal-dependent mechanisms,[13,14] has been an area of increasing focus in recent years because the frontoparietal networks associated with control influence a wide range of other cognitive functions.[15] Previous studies have consistently observed performance deficits (eg Barch et al,[16] who found increased error rates (even after controlling for generalized deficits)) and functional abnormalities (eg reduced dorsolateral prefrontal cortex (DLPFC) and superior parietal cortex (SPC) activity[17–19] and frontoparietal network connectivity[18]) during cognitive control tasks in SZ (reviewed by Lesh et al[13]). Using 1.5T fMRI, our group has also recently reported (in an independent sample) that these deficits in behavior and activation do not worsen at up to 2-year follow-up in recent onset SZ.[20] The longitudinal stability of previously reported reductions in frontoparietal functional connectivity during the task,[18,21] however, remains unknown. Furthermore, stability metrics (eg intraclass correlation coefficients (ICCs)) have not been examined for any cognitive control-associated functional measures across these lengths of time.

The goals of this study, therefore, were to (1) examine the as yet uncharacterized longitudinal time course of frontoparietal connectivity during cognitive control and (2) determine if our previous findings showing no decline in cognitive control performance and associated prefrontal activation during the first few years of illness in SZ at 1.5T are replicated in an independent sample using 3T fMRI. Our study focused on recent onset illness because early intervention is associated with improved outcomes.[22]

Materials and Methods

Participants

One hundred fifty-three participants (ages 16–30) were studied—84 unhospitalized individuals with either SZ, schizophreniform, or schizoaffective disorder and 69 healthy controls (HCs). The University of California, Davis (UCD) Early Diagnosis and Preventive Treatment (of Psychosis) (EDAPT) research clinic performed recruitment at clinical intake. The Structured Clinical Interview for DSM-IV-TR (SCID)[23] was used for diagnosis of psychopathology at intake. All SZ participants reported psychosis onset within 2 years prior to study enrollment and were receiving some form of treatment (eg antipsychotic medication, psychosocial intervention including psychoeducation and/or cognitive behavioral therapy). All participants provided written informed consent and were compensated for their participation. The UCD Institutional Review Board approved the study.

See Supplementary Material for exclusion criteria and description of clinical measures.

Study Design

This longitudinal study involved a baseline visit followed by a follow-up visit. The follow-up visit was designed to occur ~1 year following the baseline visit but due to scheduling constraints was allowed to vary over a period of ~8–20 months. Participants performed the AX-CPT while undergoing fMRI scanning at both visits. Clinical ratings were obtained no more than 1 month from each scanning visit. Data collection were performed between March 2011 and January 2019.

Task Description

The AX-CPT and associated task parameters have been described in detail elsewhere[17,24] and are provided in Supplementary Material (text), Supplementary Table 1a, and Supplementary Figure 1. Cue and probe durations were both 500 ms.

fMRI Scanning Parameters

3 T (Siemens) functional images were acquired with a gradient-echo T2* Blood Oxygenation Level Dependent (BOLD) contrast technique as outlined in Supplementary Table 1b.

fMRI Preprocessing

Please see Supplementary Material for details (including movement criteria).

ROI to ROI Functional Connectivity Analysis

Connectivity during the high control, B cue condition (correct trials only) was analyzed using DLPFC ROIs (MNI Left $(x,y,z) = -(42, 26, 37)$; Right $(x,y,z) = (42, 26, 37)$) taken from a previous Stroop (another cognitive control task)-based study in an independent dataset[25] and SPC ROIs mapped in a 2009 meta-analysis of executive function in SZ[26] (MNI coordinates: Left $(x,y,z) = (-28, -75, 50)$; Right $(x,y,z) = (35,-64, 46)$). Connectivity was analyzed between these areas because they are the primary cortical regions of the cognitive control network.[13] Connectivity between the left DLPFC—left SPC and right DLPFC—right DLPFC ROIs was calculated using hemodynamic response function-convolved, concatenated beta time series from each ROI. Connectivity analysis focusing on the B cue condition is consistent with a previous cross-sectional study in SZ by our group.[18] See Supplementary Material for denoising steps.

Region-of-Interest (ROI)-Defined Extraction of BOLD Response

See Supplementary Material.

Longitudinal Analysis

See Supplementary Material for details. Briefly, we performed the following analyses in a manner consistent with previous longitudinal analyses in our laboratory[27]:

1. Repeated measures ANOVAs.
2. Hedges bias-corrected[28] effect size comparisons with HC baseline data as a reference group.
3. Within-group paired *t*-tests.
4. ICCs within each group between baseline and follow-up.

Participants that did not have complete datasets (ie baseline and follow-up behavioral and neuroimaging data that met criteria) were excluded from stability analyses. To examine missing data effects, baseline comparisons (*t*-tests) between participants with complete data and participants lost to follow-up were performed for each diagnostic group.

Results

Demographic and Clinical

Of the 153 participants (69 HC, 84 SZ) studied, 24 HCs and 43 individuals with SZ were lost to follow-up. In addition, 6 participants with SZ did not meet performance or MRI motion criteria (see Materials and Methods section) and/or had excessive image artifacts at follow-up. Furthermore, 3 HCs and 6 participants with SZ did not meet performance criteria at baseline, leaving a final sample of 42 HCs and 29 individuals with SZ for longitudinal analyses (ANOVA and stability). Baseline data from 37 HCs and 21 individuals with SZ in the final sample have been used as part of a previously published analysis.[29]

Demographic and clinical information for participants included in the final sample are shown in Tables 1 and 2. At baseline, groups did not differ by age, sex, handedness, or parental education; groups did differ by education. Individuals with SZ had lower WASI-II IQ compared with HCs. No group difference was observed on the number of days between baseline and follow-up. No significant effects of diagnosis, time, or time × diagnosis interactions were observed for fMRI overall movement or for any of the 6 rigid-body motion parameters in the final sample (Supplementary Table 2). Participants with SZ significantly improved between baseline and follow-up on GAF score and poverty symptoms (Table 2). Auxiliary behavioral data (number of correct trials, accuracy, and reaction time for each trial type) with corresponding ANOVA values are provided in Supplementary Table 3.

Repeated Measures ANOVA Analyses

Raw (unstandardized) values for DLPFC-SPC connectivity, d' context, and DLPFC activation are provided in

Table 1. Demographic Information for Participants Included in Primary Analyses

	HC (n = 42)	SZ (n = 29)	t or $^2(p)$
Age	21.02 (3.08)	21.69 (3.70)	0.82 (.41)
Sex (M/F)	26/16	19/10	0.10 (.76)
Handedness (L/R)	5/37	3/26	0.04 (.84)
Education level (years)	14.22 (2.04)	12.72 (1.79)	3.17 (.002)*
Parental education level (years)	14.65 (3.22)	13.75 (2.50)	1.24 (.22)
IQ (WASI-2)	117.72 (11.90)	103.62 (16.70)	4.07 (<.01)*
n SZ/SZ-A/SZ-P	–	19/8/2	–
Duration of illness (days)	–	312.55 (181.21)	–
Days between baseline and follow-Up	347.69 (86.99)	334.17 (79.44)	0.67 (.51)

Note: Information taken from baseline unless otherwise specified. Numbers in parentheses represent the standard deviation unless noted in the column heading. HC, healthy controls; SZ, schizophrenia; SZ-A, schizoaffective disorder; SZ-P, schizophreniform disorder; WASI-2, Weschler Abbreviated Scale of Intelligence, 2nd Edition. Education data were unavailable for 1 HC. Parental education data were unavailable for 3 HCs and 1 individual with SZ. WASI-2 scores were unavailable for 3 HCs.
*$p < .05$.

Table 2. Raw Patient Clinical Information for Individuals Included in Primary Analysis (n = 29)

	Baseline	1 year	t or ^{2} (p)
Medicated/Unmedicated	27/2	22/7	0.79 (.38)
CPZ equivalent dose (mg/day)	241.92 (172.68)	255.86 (180.52)	0.46 (.65)
GAF score	45.76 (6.60)	53.61 (11.19)	4.10 (<.01)*
Poverty symptoms	16.00 (6.53)	12.59 (6.09)	3.11 (<.01)*
Disorganization symptoms	7.90 (3.74)	6.86 (2.59)	1.55 (.13)
Reality distortion symptoms	12.46 (6.13)	10.55 (6.05)	1.48 (.15)

Note: Numbers in parentheses represent the standard deviation unless noted in the column heading. Complete clinical data were unavailable at baseline for 2 individuals with SZ and follow-up for 3 individuals with SZ. CPZ, chlorpromazine.
*$p < .05$.

Table 3. Longitudinal Analysis of AX-CPT Data

Dx	*Z* Scores, Mean (SD)		Effect Size (Hedges Bias Corrected Cohen's *d*) vs Baseline HC {95% CI}		Within-Dx Follow-Up vs Baseline Comparison and Stability			
	Baseline	Follow-Up	Baseline	Follow-Up	*t*	*p*	ICC {95% CI}	*p*
Left DLPFC—Left SPC Connectivity, Cue B								
HC**	0.00 (1.00)	−0.02 (0.90)	n/a	−0.02 {−0.45−0.41}	0.16	.87	0.77 {0.58−0.88}	<.01*
SZ**	−0.07 (1.13)	−0.19 (1.22)	−0.06 {−0.54−0.41}	−0.17 {−0.65−0.30}	0.56	.58	0.65 {0.25−0.84}	<.01*
Right DLPFC—Right SPC Connectivity, Cue B								
HC**	0.00 (1.00)	0.01 (1.13)	n/a	0.01 {−0.42−0.43}	0.04	.97	0.72 {0.48−0.85}	<.01*
SZ**	−0.37 (0.85)	−0.49 (0.79)	−0.39 {−0.86 − 0.09}	−0.53 {−1.01−−0.05}	0.78	.44	0.62 {0.19−0.82}	<.01*
Left DLPFC BOLD Response, Cue B > Cue A								
HC	0.00 (1.00)	0.32 (0.67)	n/a	0.38 {−0.06−0.81}	1.88	.07	0.25 {−0.35−0.59}	.17
SZ	−0.21 (0.67)	−0.16 (0.90)	−0.23 {−0.71−0.24}	−0.16 {−0.64−0.31}	0.24	.81	NC	−
Right DLPFC BOLD Response, Cue B > Cue A								
HC	0.00 (1.00)	0.13 (1.00)	n/a	0.13 {−0.30−0.56}	0.66	.51	0.24 {−0.42−0.59}	.19
SZ	−0.69 (0.89)	−0.48 (1.30)	−0.71 {−1.20−−0.22}	−0.42 {−0.90−0.06}	0.75	.46	0.24 {−0.65−0.64}	.25
D' Context								
HC	0.00 (1.00)	0.27 (0.99)	n/a	0.27 {−0.16−0.70}	2.34	.02*	0.82 {0.65−0.90}	<.01*
SZ**	−0.53 (0.99)	−0.37 (1.17)	−0.53 {−1.01−−0.05}	−0.34 {−0.82−0.14}	0.80	.43	0.66 {0.29−0.84}	<.01*

Note: Data were normalized to healthy control (HC) baseline levels for each measure prior to analysis. CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; ICC, intraclass correlation coefficient (parameters: two-way random, absolute agreement); SD, standard deviation; SPC, superior parietal cortex; SZ, schizophrenia; NC, negative correlation (violates reliability assumptions).

*$p < .05$.

**Shows both non-significant time effect and good to excellent stability (ICC > 0.60).

Supplementary Table 3. Standardized values used for stability analyses are provided in Table 3 and Figure 2.

Neuroimaging data were first examined within groups (across both time points) using a whole-brain voxelwise threshold of $p < .05$ (FWE-corrected) to confirm that the AX-CPT was associated with frontoparietal connectivity and recruiting the DLPFC. For connectivity, both the right and left DLPFC seeds showed significant (voxelwise whole-brain FWE-corrected $p < .05$) connectivity with the right and left SPC (respectively) during B cue trials for both groups (right DLPFC connectivity maps shown in Supplementary Figure 2 as an illustrative example). For cognitive control-associated activation (B > A cue contrast), robust (voxelwise whole-brain FWE-corrected $p < .05$) recruitment of the bilateral DLPFC was observed for HCs but not individuals with SZ (Supplementary Figure 3).

For right DLPFC—right SPC connectivity, a significant main effect of diagnosis ($F(1,69) = 4.40$, $p = .040$) was observed. The effect was most strongly driven by lower connectivity at follow-up ($p = .045$) in SZ (Figures 1A and

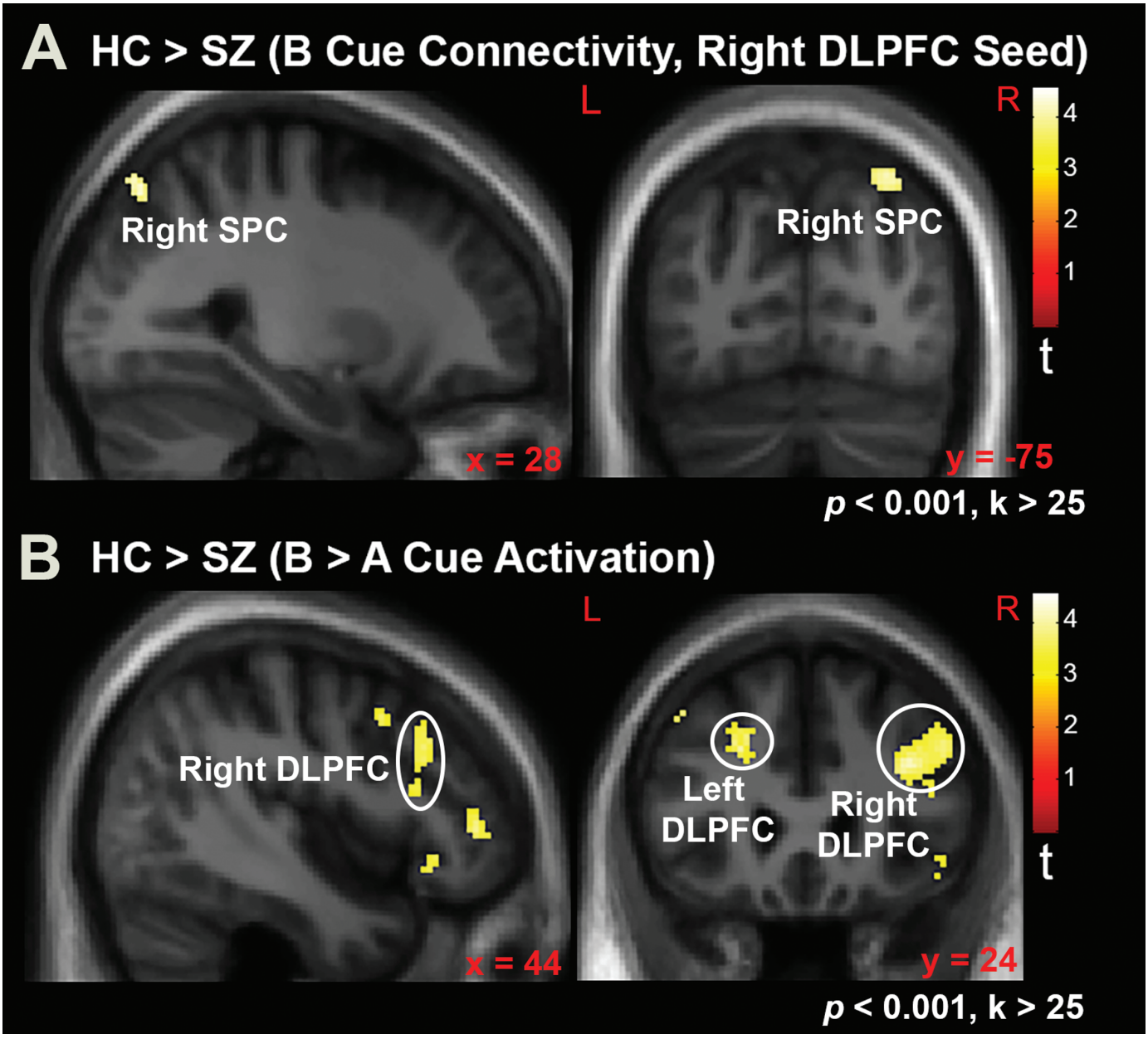

Fig. 1. (A) Statistical parametric map showing increased connectivity (the average connectivity across baseline and follow-up) during correct B cue trials between the right dorsolateral prefrontal cortex (DLPFC) seed and the right superior parietal cortex (SPC) in healthy controls (HCs) vs individuals with schizophrenia (SZ). Image thresholded at $p < .001$, $k > 25$ voxels for visualization. (B) Statistical parametric map showing increased task-associated (B > A cue) activation (the average activity across baseline and follow-up) in the bilateral dorsolateral prefrontal cortex (DLPFC) in healthy controls (HCs) vs individuals with schizophrenia (SZ). Image thresholded at $p < .001$, $k > 25$ voxels for visualization.

2A left column). No main effect of time ($F(1,69) = 0.27$, $p = .60$) or time × diagnosis interaction ($F(1,69) = 0.33$, $p = .57$) was observed. For left DLPFC—left SPC connectivity, no main effect of time ($F(1,69) = 0.37$, $p = .55$), diagnosis ($F(1,69) = 0.29$, $p = .59$), or time × diagnosis interaction ($F(1,69) = 0.19$, $p = .66$) was observed.

For right DLPFC cognitive control-associated activation (B > A Cue), a significant main effect of diagnosis ($F(1,69) = 11.63$, $p = .001$) was observed. The effect was driven by lower activation at baseline ($p = .004$) and follow-up ($p = .028$) in SZ (Figures 1B and 2B left column). No main effect of time ($F(1,69) = 1.03$, $p = .32$) or time × diagnosis interaction ($F(1,69) = 0.04$, $p = .84$) was observed. For left DLPFC activation, a significant main effect of diagnosis ($F(1,69) = 5.39$, $p = .023$) was also observed. This effect was most strongly driven by lower activation at follow-up in SZ ($p = .012$). Mirroring the right DLPFC result, no main effect of time ($F(1,69) = 1.92$, $p = .17$) or time × diagnosis interaction ($F(1,69) = 1.03$, $p = .31$) was observed.

For *d'* context, a significant main effect of diagnosis ($F(1,69) = 6.87$, $p = .011$) was observed. This effect was driven by lower *d'* context in SZ vs HC at both baseline ($p = .031$) and follow-up ($p = .015$) (Figure 2C left column). The main effect of time also approached significance ($F(1,69) = 3.97$, $p = .050$), driven by a trend-level ($p = .054$) increase at follow-up in HC but no change in SZ ($p = .34$). No time × diagnosis interaction ($F(1,69) = 0.26$, $p = .061$) was observed.

Effect sizes between patients and controls were moderate for right DLPFC activation, right frontoparietal network connectivity, and *d'* context at both time points (Table 3). No associations were observed between time to follow-up or duration of illness and change in connectivity, activation, or d' context for either group (where applicable). Behavioral and fMRI results were not appreciably altered by removing individuals with schizoaffective or schizophreniform disorder from the analysis.

No associations were observed between antipsychotic dose or duration of illness and any measure of cognitive control at either baseline or follow-up.

Stability Analyses

Stability was good to excellent for d' context and functional connectivity as evidenced by (1) effect sizes (relative to control baseline data) that stayed within the 95% confidence interval of the effect size of the opposing time point, (2) no significant *p* values from paired *t*-tests for any measure within either group (except for d' context in HCs), and (3) ICCs of 0.6 or greater (Table 3; Figures 2A and 2C right column). Stability was comparatively poor, however, for cognitive control-associated activation of the right and left DLPFC as evidenced by low ICC values (~0.25) for both groups (Table 3; Figure 2B right column).

Behavioral correlates and results of missing data analyses are provided in Supplementary Material. Baseline comparison of SZ vs HC in all subjects with baseline data also yielded significant deficits in *d'* context and right DLPFC activation but not right frontoparietal connectivity.

Discussion

The goal of this study was to determine if connectivity and activation of frontoparietal network during cognitive control in SZ improves, worsens, or remains stable during the early course of illness. Consistent with previous work,[16,17,19] individuals with SZ showed significant deficits in prefrontal recruitment as well as d' context (the primary behavioral measure of cognitive control) at baseline. Also consistent with prior findings,[18,21] reduced frontoparietal connectivity was also observed in SZ in participants with both baseline and follow-up data. No evidence of decline between baseline and follow-up was observed for network connectivity, as evidenced by (1) no significant main effects of time or time × diagnosis interactions, (2) overlapping effect sizes between each time point, (3) lack of significant differences (using paired *t*-tests) between time-points, (4) ICCs of at least 0.60. Replicating our previous 1.5T study in an independent sample,[20] no evidence of decline was also observed for cognitive control-associated DLPFC activation or behavioral performance.

Consistent with previous work (including a study conducted with 10-year follow-ups),[3–5,20,27] we found no evidence for decline of any functional process associated with cognitive control in SZ. Along with a large body of literature suggesting that cognitive deficits are stable in recent onset individuals with SZ and consistent with our previous activation study in an independent sample at 1.5T,[3,4,20,27] this finding supports the neurodevelopmental hypothesis of SZ, in which cognitive dysfunction occurs early in the illness and then remains stable throughout the early course of the disorder. Taken together with previous work showing deficits in cognitive control in at-risk individuals and unaffected first-degree relatives,[30,31] our findings suggest that deficits in control may occur developmentally (before the onset of psychosis). Given that early intervention is associated with improved outcome in SZ, physicians may seek to identify and target abnormal cognitive control processes as soon as possible in at-risk (prior to psychotic break) individuals. Our findings further suggest that an effective treatment for these deficits in early SZ should seek to normalize cognitive control to healthy levels rather than "preventing" a (nonexistent) decline.

A major strength of this work is the inclusion of longitudinal neuroimaging connectivity data, bolstering the link between brain and behavior in an established cognitive deficit in SZ. Longitudinal neuroimaging studies in

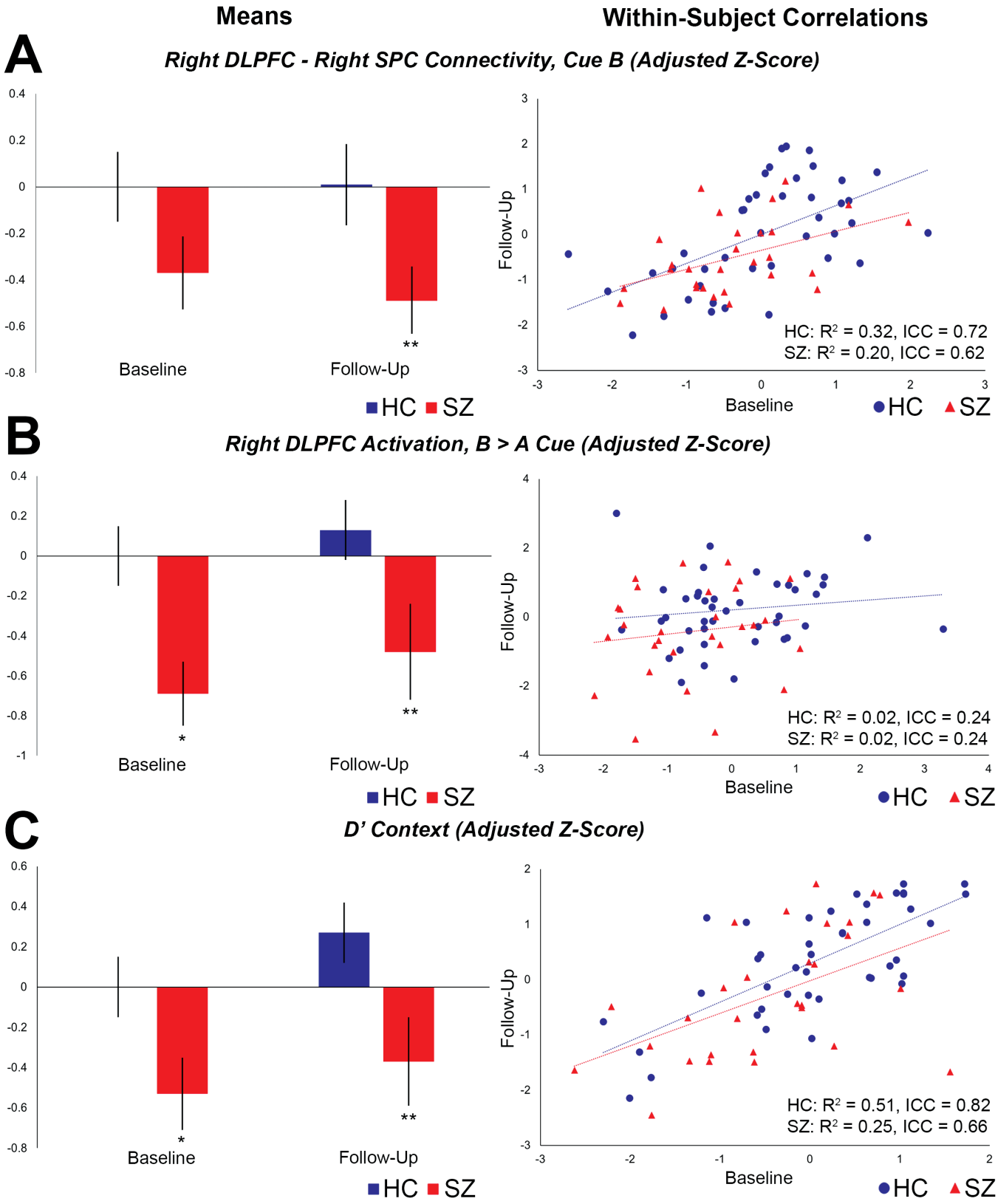

Fig. 2. *Left column*: ANOVA analyses of cognitive control measures of interest (A: right dorsolateral prefrontal cortex (DLPFC)—right superior parietal cortex (SPC) connectivity, (B) right DLPFC activation, (C) D' context). *$p < .05$ vs healthy control (HC) baseline. **$p < .05$ vs HC follow-up. *Right column*: relationships between baseline and follow-up data for cognitive control measures of interest (A: right DLPFC—right SPC connectivity, B: right DLPFC activation, C: D' context). R^2 values are provided for illustrative purposes, but only intraclass correlation coefficients (ICCs) should be considered measures of stability.

mental illness are rare, likely due to their inherent difficulties (eg high-attrition rate). In combination with previous cross-sectional fMRI studies on cognitive control,[9,13,17,19,25,32] the finding that both *d'* context and control-associated functional connectivity show similarly stable patterns of deficits in SZ strongly ties together consistent impairment of this important cognitive ability and related neuronal processes. Interestingly, functional activation was a less stable measure than connectivity. The reason(s) for this discrepancy are unclear, although a previous study of implicit face emotion processing in teenagers also found greater reliability for connectivity than activation between fMRI scans scheduled 2.5 months apart.[33] The difference in stability between activation and connectivity suggests that connectivity may be a better biomarker for cognitive control than activation, although this result requires replication due to the relatively small sample size in this study. Furthermore, a limitation of the connectivity finding was that significant differences were not observed at baseline when all participants (including those lost to follow-up) were compared by diagnosis. The reason(s) for this discrepancy are unclear, although SZ individuals lost to follow-up were qualitatively less symptomatic than those with complete datasets.

Although our results suggest cognitive control is stable in the first few years following illness onset in SZ, the disease may still have as an aspect of its pathophysiology a neurodegenerative process. In re cognition, although our results are in line with a previous study showing stable deficits in executive function in first-episode SZ at up to 10-years follow-up, the same study also showed significant deterioration (relative to HC) in other cognitive domains (verbal knowledge and memory).[5] It is notable, however, that the individuals in the previous study were considerably older (~30 years) at baseline than is typical for first-episode SZ.[34] Regarding neuronal processes, structural imaging studies have frequently reported accelerated gray matter loss, even in early onset SZ (eg Kahn[34]; reviewed by Shenton et al[7,8]). Functional deterioration has been observed as well; a recent pseudo resting-state study, eg, found accelerated decline of global and local efficiency (measures of information transfer) in SZ.[12] Interestingly, this study also reported that efficiency measures did not mediate the relationship between age and cognitive function in SZ, helping to explain why efficiency may decline in the face of stable cognition. Future studies may examine the relationships between deteriorating and nondeteriorating measures in SZ to better understand why stability may be specific to particular aspects of the disease. One possibility is that cognition may be stable in early SZ despite gray matter loss due to neuronal "reserve" (ie increased neuronal density acting as a buffer), as has been hypothesized to explain why cognition may be normal in individuals with SZ whose brains show evidence of Alzheimer's pathology (amyloid plaques and neurofibrillary tangles).[35]

Unexpectedly, significant group differences were only observed in the right hemisphere, suggesting right lateralization of pathology. We caution against overinterpreting our findings in this manner, however. First, unlike the bilateral activation observed in HCs, cognitive control-associated DLPFC activation was not apparent in either hemisphere in SZ. Second, whole-brain connectivity maps (available upon request) comparing HC vs SZ connectivity from the left DLPFC seed revealed a cluster (k = 153 voxels, peak coordinates x = −30, y = −66, z = 34) in the left parietal cortex when using a lenient threshold ($p < .01$, uncorrected). The finding that group differences were slightly weaker in the left vs right hemispheres may be due to unknown task-specific effects (eg use of letter stimuli) as there is no strong evidence to suggest that left vs right hemispheres are differentially affected during cognitive control in SZ.

Several potential limitations should be considered while interpreting our findings. First, we cannot rule out potentially confounding practice effects, as HCs showed near significant improvement in *d'* context at follow-up. The age range of participants (early adulthood) in this study coincides with a well-characterized period of neurocognitive improvement, which suggests that it is possible that the observed increase in *d'* context in HC was a purely neurodevelopmental effect. Although nonsignificant, *d'* context scores over time in SZ also were in the direction of improvement, suggesting similar trajectories for both groups; furthermore, no significant group × time interaction was observed for *d'* context, suggesting no difference in practice effects (if such effects truly exist). The period of time (~1 year on average) between baseline and follow-up, however, is not likely conducive to practice effects. In addition, a much shorter term (~2 week) longitudinal study that examined AX-CPT performance (*d'* context) did not report practice effects in individuals with SZ whose ages most closely matched those in the present study (only much older individuals with SZ in that work demonstrated practice effects).[36] An additional limitation was that one-third of the included sample had either schizoaffective or schizophreniform disorder, potentially increasing the heterogeneity of the sample. Excluding individuals with schizoaffective or schizophreniform disorder from the analysis, however, did not appreciably alter the results. Other potential limitations are potentially confounding effects of medications (besides antipsychotics) that may impact cognition, the relatively small sample size, the fact that only outpatients were studied, group differences in education and cognitive functioning (WASI), and variability in treatment engagement between timepoints. Future fMRI studies with longer follow-up periods will also be required to more fully illustrate into the functional trajectory of cognitive control in SZ. The high-attrition rate also reduced the potential power of the study to find a time × diagnosis interaction. Notably, however, assuming a relatively modest

effect size of partial $\eta^2 = 0.03$, 87% power for this analysis is achieved with $\alpha = 0.05$, $n = 71$ (the number of individuals with complete datasets) (G*Power 3.1 (www.gpower.hhu.de)). As a final note, the high-attrition rate (36% for HC, 63% for SZ) was not unexpected as this study recruited participants in an age range where they are relatively difficult to schedule follow-up visits (eg working or in school).

In conclusion, our findings found no evidence for degeneration of cognitive control in either performance of any of its associated functional processes in SZ, consistent with the neurodevelopmental hypothesis of cognitive dysfunction in the illness. These results also support the continued investigation of the AX-CPT and other paradigms of cognitive control as biomarkers of cognitive deficits in SZ. Given that functional neuroimaging studies are plagued by low reproducibility,[37] our findings represent an important replication of previous work as well as a novel illustration of the functional stability of cognitive control in SZ.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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Conflict of Interest

The authors declare no conflicts of interest.

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