



# Cognitive control network dysconnectivity and response to antipsychotic treatment in schizophrenia

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## ABSTRACT

To better understand cognitive control impairment in schizophrenia, it is vital to determine the extent of dysfunctional connectivity in the associated fronto-striatal brain network, with a focus on the connections with the anterior cingulate cortex (ACC), prior to the potential confounding effect of medication. It is also essential to determine the effects following antipsychotic medication and the relationship of those effects on psychosis improvement. Twenty-two patients with schizophrenia, initially unmedicated and after a 6-week course of risperidone, and 20 matched healthy controls (HC) performed a fMRI task twice, six weeks apart. We investigated group and longitudinal differences in ACC-related functional connectivity during performance of a Stroop color task as well as connectivity patterns associated with improvement in psychosis symptoms. Unmedicated patients with schizophrenia showed greater functional connectivity between ACC and bilateral caudate and midbrain and lower connectivity with left putamen compared to healthy controls. At baseline, greater functional connectivity between ACC and bilateral putamen predicted subsequent better treatment response. Change in functional connectivity between ACC and left putamen positively correlated with better treatment response. These results suggest that patterns of functional connectivity in fronto-striatal networks can be utilized to predict potential response to antipsychotic medication. Prior to treatment, brain function may be structured with a predisposition that favors or not treatment response.

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## 1. Introduction

Schizophrenia is associated with impairments in executive functioning, particularly cognitive control. These deficits are present before illness onset (Wood et al., 2003) and are stable over the course of the illness (Burdick et al., 2006; Tyson et al., 2004) with marginal improvement with atypical antipsychotic medication (Keefe et al., 2006; Woodward et al., 2005). Cognitive control deficits have been associated with abnormal activity in frontal, parietal, and subcortical brain regions (Minzenberg et al., 2009). A core region of the cognitive control network is the anterior cingulate cortex (ACC) (Kouneiher et al., 2009) which has consistently demonstrated reduced functional activation during cognitive control tasks in schizophrenia (Kerns et al., 2005; Minzenberg et al., 2009; Weiss et al., 2007). The ACC represents a network hub that strongly affects cognitive network processing and network connection efficiency, becoming more closely interconnected to surrounding

areas in the presence of greater inhibitory control need (Spielberg et al., 2015).

Functional connectivity analyses examine temporal correlations in neural activity between different brain regions. Dysconnectivity or abnormal connectivity has been suggested as a pathophysiological mechanism in schizophrenia. Alterations in fronto-striatal network connectivity have been frequently reported in schizophrenia during cognitive task performance (Ongur et al., 2010; Quide et al., 2013) and during resting-state (Sarpal et al., 2015). However, since most schizophrenia studies have been conducted in medicated patients, such dysfunction cannot be definitively attributed solely to alterations deriving from the disorder. This is a major confound as antipsychotic drugs (APD) have prominent neurochemical (Kessler et al., 2005) and functional effects within these regions (Lahti et al., 2003; Lahti et al., 2009; Lahti et al., 2005). It is therefore critical to characterize the extent of fronto-striatal network dysfunction in schizophrenia without the confounding effect of medication, which may also be relevant for other symptom domains, such as cognition, that are not improved with APD.

Clinical response to APD has been shown to occur within the first week of treatment, with the greatest improvement in psychotic symptoms occurring during the first two weeks (Agid et al., 2003; Leucht

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et al., 2005). Six weeks of APD is usually required for full treatment response to occur (Emsley et al., 2006). As up to 1/3 of patients do not respond to APD (Lieberman et al., 2005), predicting treatment response likelihood prior to APD administration would facilitate prescribing effective treatment. Characterization of fronto-striatal network changes associated with treatment response could also assist with determination of drug effectiveness, and help elucidate mechanisms behind the variability in treatment response.

We use a longitudinal design to evaluate ACC-dependent functional connectivity in unmedicated patients with schizophrenia (SZ) before and after a six-week trial of APD while controlling for the effect of time on ACC functional connectivity in a group of healthy controls (HC) scanned twice, six weeks apart. Our goals were to characterize (1) fronto-striatal connectivity, comprised of ACC connectivity with the striatum and substantia nigra (SN), in unmedicated SZ patients, (2) changes in fronto-striatal connectivity induced by six weeks of risperidone, a frequently used APD, and (3) fronto-striatal connectivity patterns associated with treatment response. To engage the fronto-striatal network, we used a Stroop color-naming task, a prototypical cognitive control task (Bari and Robbins, 2013) with a reliably induced effect, relatively unaffected by learning effects (Gruber et al., 2002) and easily performed by patients with schizophrenia (Carter et al., 2001; Reid et al., 2010). Supporting the relationship between the selected network and APD effects (an effect achieved through dopamine (DA) receptor blockade), the neural basis of cognitive control relies on fronto-cortical-striatal circuitry known to be under DA modulation and that both striatal DA synthesis and DA receptor availability have been shown to correlate with cognitive control performance (Ghahremani et al., 2012; Vernaleken et al., 2007). Also, a meta-analysis in Parkinson's disease indicated that Stroop task performance decrements were the largest compared to all surveyed executive tasks (Kudlicka et al., 2011). We previously characterized activation patterns in the same patient group (Cadena et al., 2018) and as an extension, now present a psychophysiological interaction analysis. Generalized psycho-physiological interaction (gPPI) is an analysis method that investigates functional connectivity between a selected brain region and the rest of the brain during the presence of task conditions. gPPI analysis is an interaction analysis that allows one to analyze connectivity changes across conditions, here between incongruent and congruent conditions, and allows more flexibility in analyses compared to standard PPI (McLaren et al., 2012).

Based on prior findings (Hadley et al., 2014; Kraguljac et al., 2014; Lesh et al., 2015), we hypothesized to find reduced functional connectivity between ACC and striatum in unmedicated SZ as well as functional connectivity patterns predictive of subsequent good response to medication. We also hypothesized that functional connectivity changes between the ACC and caudate (Sarpal et al., 2015) would correlate with treatment response.

## 2. Methods

Twenty-eight subjects with schizophrenia or schizoaffective disorder (SZ) were recruited for this study from the psychiatry clinics and emergency room at the University of Alabama at Birmingham (UAB) based on being off antipsychotic medication for at least 10 days. Twenty-five healthy controls (HC), matched on age, sex, smoking, and parental occupation, without personal or family history in a first-degree relative of psychiatric disorders were recruited using advertisements. Exclusion criteria were major medical or neurological conditions, substance use disorders (except for nicotine) within six months of imaging (drug screen was done prior to scanning), head injury with loss of consciousness >2 min, and pregnancy. Subjects gave written informed consent prior to participating in this UAB Institutional Review Board approved study.

Diagnoses were established using subjects' medical records and the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al.,

1994). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) characterized general cognitive function (Randolph et al., 1998).

SZ were scanned while unmedicated and after a six-week risperidone trial. Medication was managed by two psychiatrists (ACL and NVK), and dose determinations were based on therapeutic and side effects. Starting doses were 1–3 mg, titrated by 1–2 mg increments. Use of concomitant medications was permitted as clinically indicated. 13 subjects were prescribed bupropion, 2 were prescribed trazodone, and 1 subject each was prescribed valproic acid, mirtazapine, and amitriptyline at week six (concomitant medication data was not available for 2 subjects). Symptom severity was assessed weekly using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Medication compliance was monitored by weekly pill count. HC were scanned twice six weeks apart.

Subjects were excluded due to excess movement (>2 mm translation; 2° rotation within a run; 4 SZ, 2 HC) or lack of complete task performance, defined as no responses to more than ¼ of the total number of trials (2 SZ baseline, 2 SZ week six, 3 HC), leaving 22 SZ and 20 HC at baseline and 20 SZ and 20 HC at week six.

### 2.1. Task

Subjects performed a computerized version of the Stroop color-naming task (Becker et al., 2008). Stimuli consisted of three words: “RED”, “GREEN”, or “BLUE”, displayed in the corresponding color. Trials were either “congruent” or “incongruent,” where the word and the color of the word differed in incongruent trials. Subjects were instructed to indicate the color but ignore the word and to respond as quickly and accurately as possible. Responses were recorded by button press using an IFIS-SA system (In Vivo, Orlando, Florida) running E-Prime (version 1.2; Psychology Software Tools, Pittsburgh, Pennsylvania). The event-related design consisted of three runs of 88 trials per run (~30% incongruent, 70% congruent). The 3-second trials were comprised of a word-stimulus for 1.5 s and a fixation cross for 1.5 s. Subjects completed a practice run before each scanning session.

### 2.2. Image acquisition

Imaging was performed on a 3T head-only MRI scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany), with a circularly polarized transmit/receive head coil. fMRI data were acquired using the gradient recalled echo-planar imaging sequence (repetition time/echo time [TR/TE] = 2100/30 milliseconds, flip angle = 70°, field of view = 24 × 24 cm<sup>2</sup>, 64 × 64 matrix, 4 mm slice thickness, 1 mm gap, 26 axial slices). A high-resolution structural scan was acquired for anatomical reference (MPRAGE; TR/TE/inversion time [TI] = 2300/3.93/1100 milliseconds, flip angle = 12°, 256 × 256 matrix, 1 mm<sup>3</sup> voxel size).

### 2.3. Statistical analysis

Analyses were conducted in SPSS 20 (IBM SPSS Inc., Chicago, IL). Group comparisons were performed using chi-square or analysis of variance, as appropriate. Reaction times (RT) for correct trials [congruent, incongruent, and Stroop (incongruent–congruent)] and errors (congruent, incongruent) were analyzed using linear-mixed-models comparing fixed-effects of group (HC vs SZ), time (unmedicated vs week six), condition (congruent vs incongruent), and interactions. *Post-hoc* analyses were performed where appropriate with Bonferroni corrections.

### 2.4. Image analyses

Data analyses were implemented in SPM8 (Wellcome Trust Centre for Neuroimaging). Preprocessing included slice-timing correction, realignment, reslicing at 1.5 mm isotropic voxels, motion/artifact correction using ArtRepair (Mazaika et al., 2009), DARTEL normalization,

and smoothing (4 mm full width at half-maximum Gaussian kernel). Analysis for the Stroop task consisted of a single-subject voxel-by-voxel general linear model. Five conditions were included: incongruent, congruent, stimulus repetitions (exact repetition of a previous trial (Reid et al., 2010)), error, and no response trials. Conditions were convolved with the canonical hemodynamic response function with temporal derivatives. The contrast of interest was incongruent minus congruent correct trials, subsequently referred to as the Stroop-effect. A contrast z-map of the BOLD signal during the Stroop-effect was generated for each subject at each time point.

Stroop-effect dependent connectivity with the seed region of interest, the ACC (defined using the IBASPM 116 WFU pickatlas (Maldjian et al., 2003) with subsequent restriction of being one slice forward from the disappearance of the juncture of the anterior corpus callosum from both hemispheres and the posterior end as the first vertical slice posterior to the anterior commissure (Wheelock et al., 2014) to map into the dorsal region of the ACC, which has been shown to be activated during cognitive control tasks (Carter et al., 2001)) was assessed using the gPPI analysis toolbox (McLaren et al., 2012). The gPPI analysis included the following regressors: the psychological component (task condition: congruent, incongruent), the physiological component (time course of ACC activation) and the psychophysiological interaction of these components throughout the whole brain. The Stroop-effect gPPI connectivity (incongruent-interaction regressor minus the congruent-interaction regressor) was generated for each subject at each time point.

Between-group differences for baseline ACC-Stroop-effect functional connectivity were characterized via a two-sample *t*-test within SPM. Exploratory analyses: in regions where baseline functional connectivity was significantly different between groups, the first eigenvariate of functional connectivity was extracted for each individual via REX (CIBSR Stanford University, CA) (Whitfield-Gabrieli, 2009) using a 6 mm sphere centered on the maximum intensity projections; these values were plotted against errors and Stroop RT and  $R^2$  values (z-converted) compared between groups. Outlier values beyond two standard deviations were removed from correlation analysis and plots between connectivity values and Stroop performance (RT and errors) values.

To examine APD effects on functional connectivity, we employed a full factorial analysis. Independent variables were included for group (HC vs SZ), time (unmedicated/baseline vs week six) and the interaction (group  $\times$  time). Contrast images were generated for the group  $\times$  time interaction. To correctly partition the variance for valid interpretation of the main effects of group and time (Mee, 2009) independent-sample *t*-tests and paired-sample *t*-tests were run. In the presence of a significant group  $\times$  time interaction, functional connectivity values were extracted at the individual level using REX. For each group, we correlated the change in functional connectivity between regions identified in the group  $\times$  time interaction and compared  $R^2$  values between groups.

Linear regression was used to determine whether functional connectivity at baseline in unmedicated SZ was related to subsequent treatment response and to determine whether changes in functional connectivity over the course of 6 weeks were related to treatment response. For the latter, contrast images were created using IMCalc (Stroop week 6 – Stroop baseline) and then entered into the regression. To visualize the distribution of variance associated with these analyses, we extracted the first eigenvariate of the effect of interest in regions significantly associated with treatment response and plotted the extracted values (z-scores) against treatment response. Treatment response was defined as the percent change on the BPRS psychosis subscale from baseline (A) to six weeks of risperidone (B):  $\frac{B-A}{A} \times 100$ .

Analyses were corrected for multiple comparisons using small-volume-correction (SVC) in accordance with Gaussian random field theory ( $p < 0.05$ ). In order to observe functional connectivity in the network of interest, results were restricted with a mask containing regions of the fronto-striatal network. The mask was composed of the putamen and caudate from IBASPM 116 and midbrain from TD lobes in the WFU pickatlas (Maldjian et al., 2003) (Supplement Fig. 1).

### 3. Results

HC and SZ did not differ in age, gender, parental socioeconomic status, or smoking (Table 1). Correct response RT showed a significant effect of group ( $F_{1, 40} = 4.47, p < 0.05$ ), condition ( $F_{1, 116} = 122.88, p < 0.001$ ), and a group  $\times$  time interaction ( $F_{1, 116} = 4.00, p < 0.05$ ). HC had faster congruent RT than unmedicated SZ ( $p < 0.05$ ), and faster congruent and incongruent RT than medicated SZ ( $p < 0.05$ ). There were no differences in RT between unmedicated and medicated SZ. No significant differences in error commission or missing trials were observed for group, time, or interactions ( $p > 0.05$ ). There was a trend-level significance of condition in error commission ( $p = 0.07$ ; Table 2, Supplement Table 1).

**Table 1**  
Demographics, clinical, movement measures.<sup>a</sup>

	SZ (n = 22)	HC (n = 20)	t/ $\chi^2$	P value
<b>Demographics</b>				
Age, years	33 (9.78)	33.05 (9.31)	-0.002	0.99
Sex, M/F	17/5	14/6	0.63	0.54
Parent SES <sup>b</sup>	7.89 (5.85)	5.68 (3.92)	1.34	0.19
Smoking status (smoker/non-smoker)	19/3	10/10		
Smoking, packs per day	0.73 (0.54)	0.39 (0.57)	1.97	0.06
<b>Clinical variables</b>				
Medication naïve	n = 9			
Months off medication <sup>c</sup>	27.75 (49.99)			
<b>Diagnosis</b>				
Schizophrenia	19			
Schizoaffective disorder	3			
Risperidone dose, in mg (week 6)	4.17 (1.92)			
RBANS total <sup>d</sup> BPRS <sup>e</sup>	70.55 (12.67)	93.5 (14.81)	-2.89	0.006
<b>Total</b>				
Baseline	48.59 (10.32)			
Week 6	29.52 (8.14)			
<b>Positive</b>				
Baseline	8.86 (2.48)			
Week 6	4.52 (2.58)			
<b>Negative</b>				
Baseline	7.05 (2.38)			
Week 6	5.14 (2.31)			
<b>Motion parameters<sup>f</sup></b>				
<b>x</b>				
Baseline	-0.00 (0.02)	0.00 (0.01)		
Week 6	-0.02 (0.11)	-0.00 (0.01)		
<b>y</b>				
Baseline	0.01 (0.13)	0.02 (0.04)		
Week 6	0.02 (0.09)	-0.00 (0.03)		
<b>z</b>				
Baseline	0.05 (0.04)	0.04 (0.04)		
Week 6	0.06 (0.09)	0.04 (0.06)		
<b>Pitch</b>				
Baseline	0.00 (0.00)	0.00 (0.00)		
Week 6	0.00 (0.00)	-0.00 (0.00)		
<b>Roll</b>				
Baseline	-0.00 (0.00)	0.00 (0.00)		
Week 6	-0.00 (0.00)	-0.00 (0.00)		
<b>Yaw</b>				
Baseline	-0.00 (0.00)	-0.00 (0.00)		
Week 6	-0.00 (0.01)	-0.00 (0.00)		

No significant differences between groups or across time (all  $p > 0.05$ ). See Supplement Table 1 for summary statistics. SZ, schizophrenia; HC, healthy control.

<sup>a</sup> Mean (SD) unless indicated otherwise.

<sup>b</sup> Ranks determined from Diagnostic Interview for Genetic Studies (1–18 scale); higher rank (lower numerical value) corresponds to higher socioeconomic status; data not available for 4 SZ subjects.

<sup>c</sup> Median time off medication was 8 months with a range of 1 to 156 months.

<sup>d</sup> Repeatable Battery for Neuropsychological Status. Data not available for 5 SZ subjects.

<sup>e</sup> Brief Psychiatry Rating Scale (1–7 scale); positive (conceptual disorganization, hallucinatory behavior, and unusual thought content); negative (emotional withdrawal, motor retardation, and blunted affect); data not available for 1 SZ subject.

<sup>f</sup> Mean (SD) for X, Y, Z. Mean degree (SD) for Pitch, Roll, Yaw.

**Table 2**  
Stroop task behaviors.<sup>a</sup>

	SZ (n = 22)		HC (n = 20)	
	SZ 0	SZ 6	HC 0	HC 6
Task reaction time, sec				
Congruent	0.91 (0.18)	0.90 (0.19)	0.80 (0.10)	0.79 (0.13)
Incongruent	1.04 (0.18)	1.03 (0.23)	1.00 (0.14)	0.91 (0.10)
Stroop	0.13 (0.07)	0.13 (0.07)	0.19 (0.09)	0.14 (0.08)
Missing trials, number				
Congruent	8.45 (11.86)	6.80 (13.76)	2.85 (8.38)	2.75 (5.30)
Incongruent	4.32 (7.08)	4.20 (7.85)	1.05 (2.63)	1.25 (2.61)
Task errors, number				
Congruent	10.71 (15.83)	8.06 (12.49)	2.75 (4.28)	4.30 (7.14)
Incongruent	4.52 (5.23)	3.28 (3.75)	4.25 (5.46)	3.90 (5.09)

SZ, schizophrenia; HC, healthy control. SZ 0, unmedicated baseline schizophrenia; SZ 6, 6 weeks medicated schizophrenia. HC 0, healthy controls baseline; HC 6, healthy controls 6 weeks.

No significant differences between groups or across time (all  $p > 0.05$ ). See Supplement Table 1 for summary statistics.

<sup>a</sup> Mean (SD) unless indicated otherwise.

Image analyses between groups and across time found no significant differences in mean scan-to-scan head movement for the movement parameters (Table 1, Supplement Table 1).

### 3.1. Unmedicated SZ compared to HC

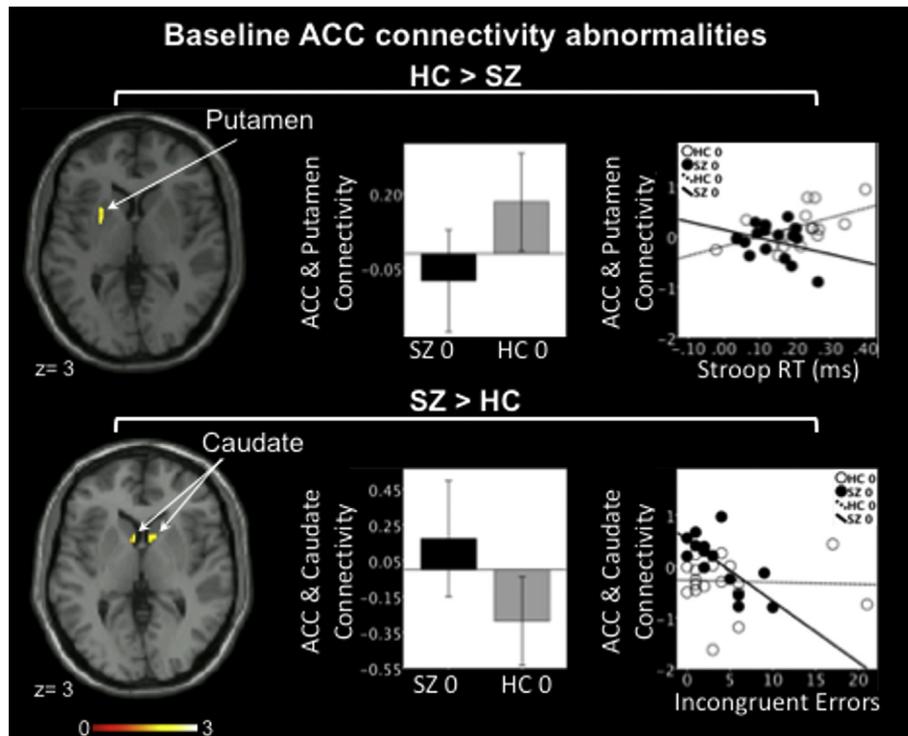
Compared to HC, unmedicated SZ displayed significantly decreased connectivity between ACC and the left putamen (Fig. 1, Table 3) and increased connectivity to the bilateral caudate (Fig. 1, Table 3). Examination of individual trials (see Supplement Fig. 2) indicates that the effect was driven by abnormal SZ connectivity patterns.

In HC, but not in SZ, Stroop RT was positively correlated with ACC to left putamen connectivity ( $r = 0.522$ ,  $p = 0.02$ ), correlations significantly differed between groups ( $z = 2.54$ ;  $p = 0.011$ ; Fig. 1). In unmedicated SZ, but not in HC, incongruent error commission was negatively correlated with ACC to bilateral caudate connectivity ( $r = -0.722$ ,  $p < 0.01$ ), correlations significantly differed between groups ( $z = 2.04$ ;  $p < 0.05$ ; Fig. 1). Also, baseline symptom severity (BPRS positive subscale) was correlated with connectivity to the left midbrain ( $r = 0.449$ ,  $p = 0.04$ ).

### 3.2. Effect of risperidone

Significant group  $\times$  time interactions were observed between ACC and bilateral putamen, left caudate and left midbrain (Fig. 2A, Table 3). Connectivity values between ACC and regions significant in the interaction were graphed in incongruent and congruent conditions for each group and at each time point in Supplement Fig. 2. Paired contrasts indicated that connectivity in SZ patients significantly decreased over the course of six weeks of risperidone from ACC to the bilateral putamen, left midbrain, and left caudate. HC connectivity significantly increased from ACC to the right putamen and midbrain (Fig. 2B, Table 3). In SZ, but not in HC, changes in ACC to caudate and changes in ACC to putamen ( $p = 0.007$ ) functional connectivity were significantly correlated (Fig. 2C, Table 3). However, correlations were not significantly different between groups.

Examining relationships between risperidone doses and clinical variables (BPRS, RBANS scores) or behavioral results (RTs or error commissions) did not reveal associations except for a negative correlation between risperidone dose and RTs for both congruent and incongruent trials on the Stroop task at week 6 (Supplement Fig. 3).



**Fig. 1.** Unmedicated baseline between-group differences in ACC functional connectivity during Stroop performance. HC > SZ shows increased connectivity between ACC and left putamen. SZ > HC shows increase connectivity between ACC and bilateral caudate (for details see Table 2). Graphs on the right show connectivity values (first eigenvalue) extracted from the significant between-group comparison. Connectivity values between ACC and putamen were significantly correlated with Stroop reaction time (RT) in SZ 0, but not in HC 0; between-group correlations were significantly different ( $p < 0.05$ ). Connectivity values between ACC and caudate were significantly correlated with incongruent errors in SZ 0, but not in HC 0; between-group correlations were significantly different ( $p < 0.05$ ). Analyses were restricted to a mask encompassing the striatum and midbrain using small-volume correction;  $p < 0.05$ , cluster threshold was 48 voxels. z coordinates refer to Montreal Neurological Institute (MNI) space. Regions labeled and indicated with arrows. ACC: anterior cingulate cortex; SZ 0: baseline schizophrenia; HC 0: baseline healthy control. Color bar on bottom indicates t-score.

**Table 3**  
Significant regions in Stroop ACC functional connectivity analyses.

Region	Hemisphere	x, y, z	Voxels	Peak t-value	p-value
Between group differences					
HC 0 > SZ 0					
Cluster 1 (putamen)	L	−26, 10, 8	113	2.79	0.016
SZ 0 > HC 0					
Cluster 1 (caudate)	L	−4, 9, 6	78	3.25	0.021
Cluster 2 (midbrain)	L	−3, −18, −19	49	2.64	0.029
Cluster 3 (caudate)	R	9, 15, 0	67	2.16	0.026
Full factorial group × time interaction					
Putamen	L	−30, 0, −3	37		0.042
Putamen	R	31, 12, −3	32		0.036
Midbrain	L	−2, −20, −19	86		0.021
Midbrain	R	14, −17, −7	48		0.028
Caudate	L	−4, 9, 6	25		0.030
Baseline ACC connectivity associated with treatment response					
Cluster 1 (putamen)	R	27, −3, 11	239	5.37	0.013
Cluster 2 (putamen, caudate)	L	−15, 6, −6	69	4.07	0.034
Cluster 3 (caudate)	R	22, 7, 17	68	3.86	0.029
Cluster 4 (putamen)	L	−16, 15, −1	65	3.63	0.036
Cluster 5 (midbrain)	R	14, −15, −10	67	3.16	0.022
Cluster 6 (caudate)	L	−14, 0, 15	150	2.80	0.014
Change in ACC connectivity associated with treatment response					
Cluster 1 (putamen)	L	−27, −3, 0	74	2.79	0.031

Significant brain regions for functional connectivity analyses, the main brain regions comprising the cluster is indicated in parenthesis. Analyses include between group differences in unmedicated baseline ACC connectivity, full factorial group × time interaction, unmedicated schizophrenia predicting treatment response, and schizophrenia changes correlated with treatment response.

SZ, schizophrenia; HC, healthy control. SZ 0, unmedicated baseline schizophrenia; HC 0, healthy controls baseline. L = left; R = right. x, y, z, refer to Montreal Neurological Institute coordinates. Functional connectivity was striatum and midbrain restricted.  $p < 0.05_{\text{SVC}}$ .

### 3.3. Treatment response

In unmedicated SZ, greater connectivity between the ACC and bilateral putamen was predictive of subsequent treatment response ( $p < 0.05$ ; Fig. 3A, Table 3). Additionally, greater change in connectivity between the ACC and left putamen was positively correlated with treatment response ( $p < 0.05$ ; Fig. 3B, Table 3). Risperidone dose significantly correlated with congruent and incongruent RT at 6 weeks (Supplement Fig. 3) and showed no significant correlations with baseline RTs or error commissions across time.

## 4. Discussion

To our knowledge, this is the first longitudinal study investigating functional connectivity in the cingulo-nigro-striatal network during cognitive task performance in unmedicated SZ and examining the effects of APD on this network. In unmedicated SZ, we observed greater functional connectivity between the ACC and bilateral caudate and reduced connectivity with the left putamen compared to HC. In unmedicated SZ, we also observed altered relationships in unmedicated SZ between fronto-striatal functional connectivity and measures of reaction time and error commission. At baseline, greater functional connectivity between the ACC and bilateral putamen was associated with good treatment response. Greater connectivity changes between ACC and left putamen was significantly correlated with treatment response.

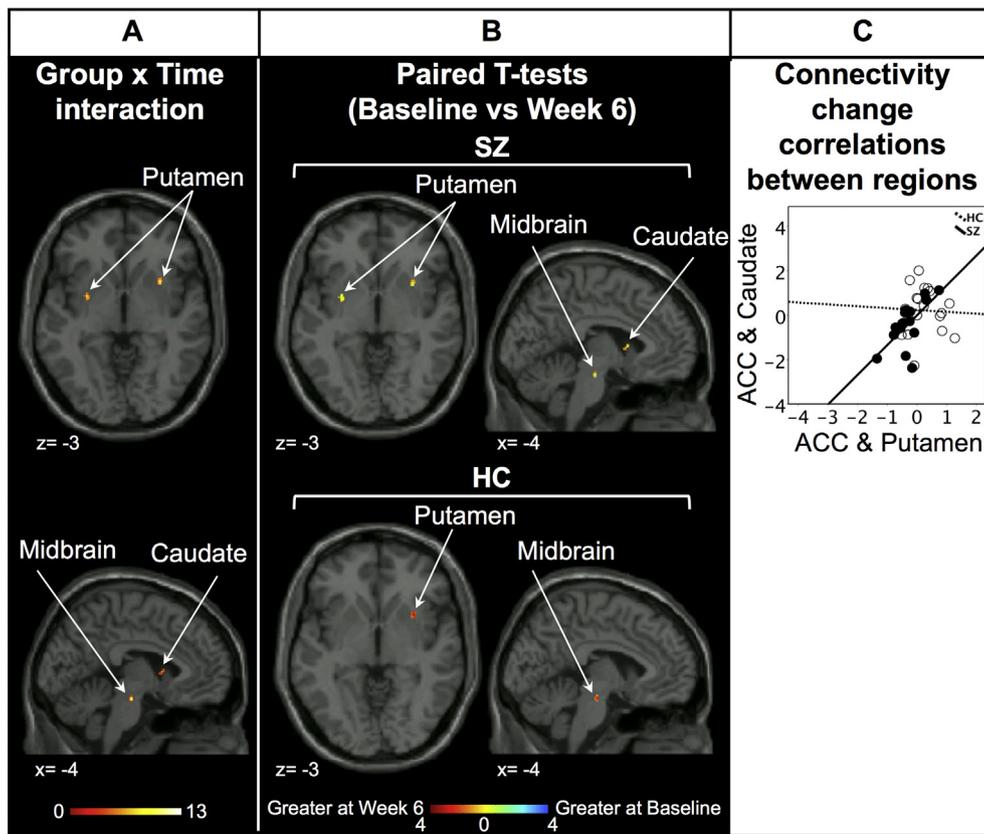
### 4.1. Behavior and stroop performance

HC responded faster than unmedicated SZ for the congruent trials and for the Stroop-effect (an effect driven by the faster congruent reaction time). There was no significant difference in RTs between HC and SZ for the incongruent trials at either time point. Because patients were unmedicated, increased RT cannot be ascribed to a medication effect. Abnormal RTs in schizophrenia have been observed in a large variety of paradigms and are thought to implicate either a dysfunction in

basic motor processes or a deficit in exerting control over response-related processing (Kappenman et al., 2015). In terms of error commission, there was no difference between groups, or across time in error commission (total, incongruent, congruent) beyond trends for HC to make more congruent errors than unmedicated SZ and medicated SZ to make fewer incongruent errors than unmedicated. There were no significant differences in RTs or performances between SZ at baseline and after six weeks of treatment. While it is usually assumed that antipsychotic medication impairs performance, slight cognitive function improvement has been observed in patients treated with second-generation antipsychotic medication (Keefe et al., 2006) and a recent study comparing first-episode medicated and unmedicated patients and healthy controls reported better behavioral performance in the medicated compared to the unmedicated patients (Lesh et al., 2015).

### 4.2. Functional connectivity

We evaluated the functional connectivity of the ACC during performance of the Stroop task with gPPI analysis. Compared to HC, unmedicated SZ presented altered ACC/striatal functional connectivity and an abnormal relationship between these connectivity patterns and behavior. In HC, ACC/putamen functional connectivity increased as Stroop RT increased, while the opposite pattern was seen in SZ. In SZ, ACC-caudate functional connectivity decreased as error commission increased, a pattern not seen in HC. During cognitive performance, dopamine-depleted subjects have shown impaired fronto-striatal functional connectivity and an alteration of the normal relationship between prefrontal-putamen functional connectivity and RT (Nagano-Saito et al., 2008). Of course, the PPI maps in our analysis may already include the influence of reaction time. It is therefore possible that the correlations between PPI analysis and reaction time are confounded by this. Collectively, these results suggest that altered dopaminergic transmission, consistently demonstrated in unmedicated SZ, modifies fronto-striatal connectivity patterns and their relationships to task performance.



**Fig. 2.** Effects of antipsychotic medication on ACC functional connectivity. A). ACC functional connectivity Full Factorial Model (Group  $\times$  Time interaction). Significant group  $\times$  time interactions in ACC functional connectivity were identified in bilateral putamen, left caudate, and bilateral midbrain (for details see Table 2). Color bar on bottom indicates F-score, cluster threshold was 54 voxels. B). Post hoc paired *t*-tests (baseline versus Week 6) for each group (SZ: patients with schizophrenia; HC: healthy controls). Color bar on bottom indicates *t*-scores with associated scale underneath, cluster threshold was 47 voxels. Warm colors indicate a greater functional connectivity at Week 6 compared to baseline and cold colors indicate the opposite. Connectivity from ACC to bilateral putamen, left midbrain, and left caudate decreased over the course of six weeks of risperidone in SZ, with the opposite pattern observed in HC. All analyses were restricted to a mask encompassing the striatum and midbrain using small-volume correction;  $p < 0.05$ . *x* and *z* coordinates refer to Montreal Neurological Institute (MNI) space. C). In each group independently, changes in ACC functional connectivity over the course of six weeks were correlated between each of the significant regions. In SZ, but not in HC, ACC connectivity changes in caudate and in putamen were significantly correlated. Regions labeled and indicated with arrows. ACC: anterior cingulate cortex.

#### 4.3. Effect of antipsychotic medication

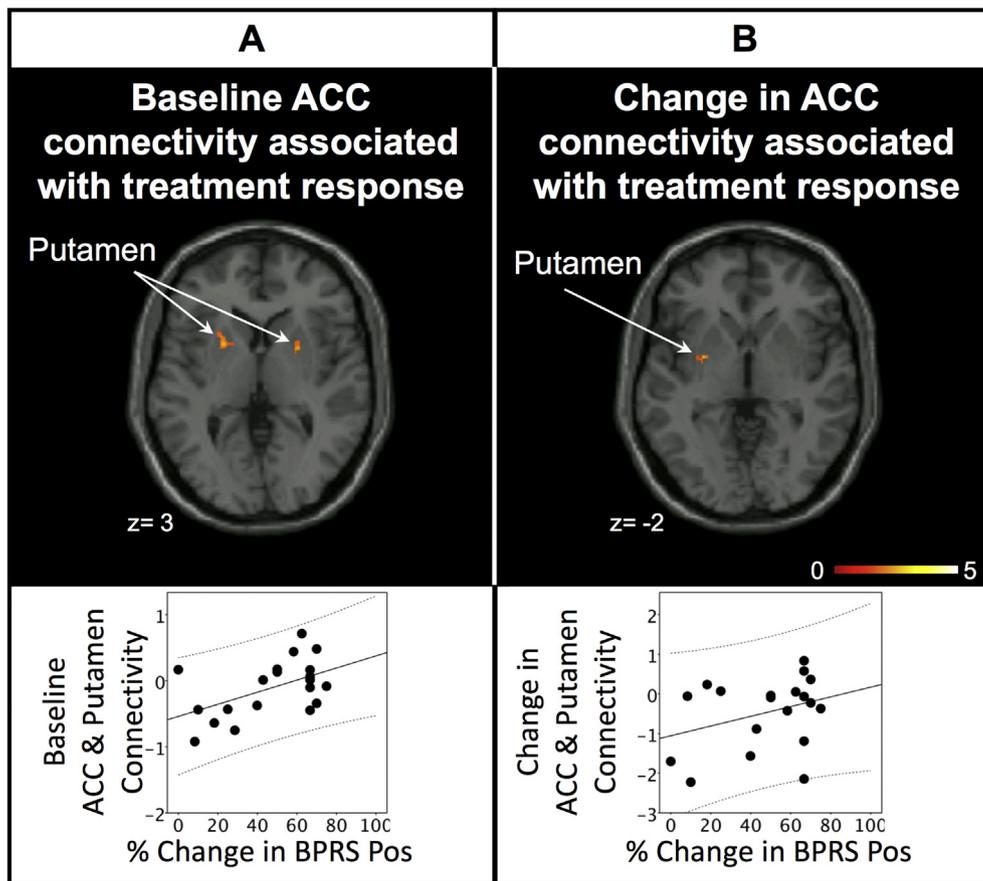
To disentangle the effect of medication and time, we conducted a group by time interaction on ACC gPPI functional connectivity and observed significant interactions in the caudate, putamen, and midbrain. Post-hoc contrasts indicated that in SZ, drug administration was associated with ACC connectivity decreases in these regions. Interestingly, while functional connectivity changes in those regions were not correlated with each other in HC, some were in SZ, suggesting a drug driven effect. A group by time interaction was found between ACC/dorsal caudate functional connectivity at the same location (*x*, *y*, *z*:  $-4, 9, 6$ ) where between groups differences were observed at baseline. In SZ, ACC/dorsal caudate functional connectivity changed from a positive pattern at baseline to a negative one at week six similar to that seen in HC. In contrast to baseline, the relationship between ACC/dorsal caudate functional connectivity and error commission was not statistically different between groups at week six. Essentially, we observed that altered ACC-dorsal caudate functional connectivity at baseline “normalized” with treatment along with its relationship with behavior. It is appealing to speculate that these findings parallel abnormal dopaminergic transmission at baseline and normalization with antipsychotic treatment. Our findings suggest a mechanism, by way of the ACC and its influence on cognitive control, in which antipsychotic medication may marginally improve cognition (Keefe et al., 2007). Supporting the significance of including time, a component lacking in many studies (Snitz et al., 2005), our results indicate variability of gPPI functional connectivity in HC

over time, which may be driven by factors including habituation to task or scanner environment.

#### 4.4. Relationship with treatment response

Reported findings on treatment response relationships with baseline schizophrenia in varying brain imaging methods have been primarily restricted to structural associations (review in (Dazzan et al., 2015), with continual sparse findings on the relationship with functional connectivity patterns. We report that, prior to treatment, greater ACC-striatum functional connectivity was associated with greater chances of symptom improvement, indicating that, prior to treatment, brain function is prearranged in a manner that does or does not favor treatment response. While it is possible that symptom severity at baseline contributes to the observed relationship between connectivity and treatment response, the spatial patterns of brain areas associated with symptom severity at baseline are different from those associated with treatment response. These results are consistent with previous findings (Hadley et al., 2014; Kraguljac et al., 2016). Using the criterion of a 30% decrease in the BPRS total score (Correll et al., 2003; Madaan et al., 2011), 70% of patients in the study responded to treatment.

In addition, as psychosis improved, we observed increased ACC-putamen gPPI functional connectivity. Sarpal and colleagues reported a positive relationship between right dorsal caudate-ACC resting state functional connectivity change and psychosis symptom improvement in first episode patients (Sarpal et al., 2015). While we did not identify that



**Fig. 3.** Associations between baseline ACC functional connectivity (unmedicated) (A), changes in functional connectivity over six weeks and treatment response (% change in BPRS Positive) (B). In unmedicated patients, greater connectivity between ACC and bilateral putamen was predictive of subsequent better treatment response (improvement in BPRS Positive subscale score). Changes in connectivity between ACC and left putamen over the course of six weeks were positively correlated with better treatment response (for details see Table 2). Analyses were restricted to a mask encompassing the striatum and midbrain using small-volume correction;  $p < 0.05$ , cluster threshold was 48 voxels. z coordinates refer to Montreal Neurological Institute (MNI) space. Color bar on bottom indicates t-score. Connectivity values of significant regions for SZ subjects were plotted against treatment response. Solid lines indicate linear regressions and dashed lines indicate 95% confidence intervals. Regions labeled and indicated with arrows. ACC: anterior cingulate cortex; BPRS Pos: Brief Psychiatric Rating Scale (BPRS) Positive subscale.

specific functional connectivity change being correlated with psychosis improvement, we did find a significant group by time interaction on this connectivity pattern. These results underscore the importance of proper ACC modulation in order to reach effective treatment response.

#### 4.5. Strengths and limitations

To avoid confounding medication effects and minimize data variance, we only enrolled unmedicated SZ, matched groups on several key factors, and used a rigorous longitudinal design with a single antipsychotic medication. Also, we attempted to control for the effect of time by scanning a HC group six weeks apart. Changes in patient symptoms could be credited to non-medication factors, such as placebo effects or treatment compliance. Potential cognition changes, reflected in cognitive control changes over 6 weeks, may stem from positive symptom improvements, attention (Wang et al., 2013), or practice effects (Goldberg et al., 2007) since APDs only marginally affect cognitive symptoms. Since patients in this study were able to successfully perform a task, as well as provide consent for and tolerate scanning procedures, our patient sample may not be representative of the schizophrenia population. Stringent subject motion-based exclusionary criteria found no significant group or time differences in head motion (Supplement Table 1). Our prefrontal cortex connectivity analysis was restricted to the ACC region, given the nature of the task and the physiological component for the gPPI analysis. While midbrain subregions could not definitively be identified due to the level of smoothing performed, all regions midbrain labeled in our results fell within a mask

limited to the SN and ventral tegmental area (VTA) (Murty et al., 2014). Clinical outcome was measured after six weeks of treatment, which may be considered a short time period, but has been proven to be a reliable reflection of maximum effective APD response (Emsley et al., 2006).

#### 5. Conclusion

In conclusion, in unmedicated schizophrenia patients, we found altered functional connectivity using gPPI analysis of fronto-striatal networks as well as an abnormal relationship between fronto-striatal connectivity and behavior. In addition, patterns of functional connectivity in unmedicated patients were associated with greater chances of symptom improvement, supporting the idea that brain function is set in a way that does or does not favor treatment response even before drug administration. As imaging research in the schizophrenia field progresses, the relationship between in vivo neural activity and neuropsychological symptoms has the potential for use as an imaging-based biomarker for schizophrenia and psychosis spectrum conditions and for unraveling schizophrenia's known heterogeneity.

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### Author contributions

Lahti contributed to the study concept and design. Study supervision was conducted by Lahti and White. Cadena, White, Kraguljac, Reid, Pixley, and Lahti contributed to the acquisition, analysis, or interpretation of the data. Cadena, White, Kraguljac, and Lahti drafted the manuscript. Cadena, White, and Lahti performed the statistical analysis. All authors contributed to and have approved the final manuscript.

### Author conflicts of interest

Medication for this study was donated to Dr. Lahti by Janssen Pharmaceuticals, Inc. Dr. Lahti received an investigator initiated grant from Janssen Pharmaceuticals, Inc. All other authors declare no conflicts of interest, including relevant financial interests, activities, relationships, and affiliations.

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