### Title

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# Baseline Frontoparietal Task-Related BOLD Activity Predicts Improvement in Clinical Symptoms During Early Psychosis Specialty Care at One Year Follow-Up in Recent Onset Psychosis

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## Abstract

**Objective.—**The early course of illness in psychotic disorders is highly variable, and predictive biomarkers of treatment response have been lacking to date. Trial and error remains the basis for care in early psychosis and poor outcomes are common. Early prediction of non-improvement in response to treatment could help identify those who would benefit from alternative and/or supplemental interventions. The goal of this study, therefore, was to evaluate the ability of fMRI-based measures of cognitive control-related brain circuitry collected at baseline to predict symptomatic response in patients after one year.

**Method.—**Patients with recent (< 2 year) onset psychotic disorders ($n$ = 82) were classified as Improvers (> 20% improvement on Brief Psychiatric Rating Scale (BPRS) Total Score at one-year follow-up vs. baseline) or Non-Improvers. Behavioral (d-prime context) and fMRI (proactive control-associated activation in *a priori* frontoparietal regions of interest) measures of cognitive control were then evaluated on their ability to predict BPRS improvement using linear and logistic regression.

**Results.—**Cognitive control-associated measures significantly predicted BPRS improvement (r = 0.38, $p$ = 0.002) and Improver status ($\chi^2$ = 9.5, $p$ < 0.01) with 70% positive predictive value, 60% negative predictive value, and 66% accuracy. Only the fMRI-based measure (and not the behavioral measure) significantly predicted status.

**Conclusions.—**These results suggest that frontoparietal activation during cognitive control performance at baseline significantly predicts subsequent symptomatic improvement during early psychosis specialty care. Potential implications for fMRI-based personalized patient treatment are discussed.

## Introduction

Although Kraepelin postulated that schizophrenia (SZ) was a degenerative disorder characterized by deterioration and inevitably poor outcomes (1), longitudinal studies have found great heterogeneity in symptomatic progression over the lifespan. An early study by Ciompi (2), for example, identified eight course types based on their suddenness of onset, symptom stability (simple or undulating), and end state (recovered or otherwise). Later work

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by Fenton and Mcglashan (3) attempted to reclassify SZ based on illness progression, finding that stability varied as a function of “classic” illness subtype (paranoid, hebephrenic, undifferentiated) with paranoid patients, who (by definition) have fewer disorganization and negative symptoms, showing the most improvement. Nonetheless, no consensus guidelines or biomarkers have been developed that can effectively predict disease progression. Development of such biomarkers would be clinically invaluable as they would not only provide mechanistic insights into what influences symptomatic response to treatment but also help identify patients who may require non-standard treatment approaches to optimize outcome.

Ideally, such predictive biomarkers would be inexpensive, noninvasive, readily administered, and suitable for use in the majority of patients (including adolescents). Functional magnetic resonance imaging (fMRI) has been used extensively in efforts to develop neurophysiological biomarkers for SZ and other psychotic illnesses. Surprisingly, however, very few fMRI studies have examined the potential for brain activation to predict treatment outcomes. In a very small sample ($n$ = 23), Van Veelen et al. (4) found that first-episode patients who showed >30% symptom reduction after 10 weeks of treatment had significantly greater dorsolateral prefrontal cortex (DLPFC) function during working memory (specifically using the contrast practice > novel stimulus set) at baseline compared to those who did not ($n$ = 12). A 2015 report by Anticevic and coauthors (5) in unmedicated patients observed a significant relationship between resting-state prefrontal hyperconnectivity and 12-month symptom improvement. In a 2016 study Sarpal and colleagues (6) found that resting state striatal functional connectivity distinguished between treatment responders ($n$ = 24) and non-responders ($n$ = 17) in SZ with 76% and 79% positive and negative predictive values, respectively. Finally, Cao et al. (7) recently reported that resting state connectivity between the superior temporal cortex and other cortical regions predicted treatment responders ($n$ = 25; $n$ = 13 non-responders) after 10 weeks of risperidone treatment with 83% accuracy.

Although promising, these studies are limited by small sample sizes and brief follow-up periods. Furthermore, they were designed to predict acute treatment response in antipsychotic naive individuals; to our knowledge, no previous studies have used fMRI to predict change in symptoms over a year or more in a naturalistic sample undergoing early psychosis specialty care. To that end, in this study we examined the ability of baseline brain activity during an established, validated cognitive control task, the AX Continuous Performance Task (AX-CPT), to predict symptomatic improvement after one-year follow-up in a sample of recent onset patients with SZ. Based on the two preliminary fMRI studies cited above and the association with better outcomes in patients with the paranoid subtype we hypothesized frontoparietal activation (which has been shown to be impaired in early psychosis and associated with behavioral disorganization and cognitive dysfunction (8–10)) would be a potential predictive biomarker of treatment response. As an additional exploratory analysis, we also examined the ability of baseline symptom dimensions (reality distortion, poverty, and disorganization) to contribute to logistic model prediction, as previous work suggests that long-term outcome may be influenced by symptom severity at presentation (3, 11).

## Methods

### Sample

Baseline neuroimaging AX-CPT data were available for 171 patients (139 SZ, 32 Type I bipolar disorder (BD) with psychotic features). Of this sample, follow-up clinical data were available for 82 patients (65 SZ, 17 BD). 138 healthy controls were included to verify the task was activating expected frontoparietal regions (see "fMRI Analysis and Pre-Specified ROI Selection", below). Neuroimaging AX-CPT data from the 82 patients with complete (baseline and follow-up) datasets have been used in previous studies as follows: (9) – 53 controls and 18 patients, (12) – 34 controls and 20 patients, (13) – 23 controls and 11 patients, (14) – 52 controls and 43 patients, (10) – 21 controls and 6 patients. Imaging data from 70 (of 138) controls and 36 (of 82) patients in the final sample have not been previously published. Individuals were recruited as outpatients from the University of California, Davis (UCD) Early Diagnosis and Preventive Treatment (of Psychosis) (EDAPT) research clinic (http://earlypsychosis.ucdavis.edu). Treatment in the clinic follows a coordinated specialty care (CSC) for early psychosis model delivered by an interdisciplinary treatment team. Treatment includes detailed clinical assessments using gold-standard structured clinical interviews and medical evaluations, targeted pharmacological treatments including low dose atypical antipsychotic treatment, individual and family-based psychosocial education and support, cognitive behavioral therapy for psychosis, and support for education and employment. The Structured Clinical Interview for DSM-IV-TR (SCID) (15) was used for diagnosis of psychopathology. Diagnoses were confirmed by a group of trained clinicians during case-conferences. All patients reported psychosis onset within two years of the date of informed consent. Patients were excluded for a diagnosis of major medical or neurological illness, head trauma, substance abuse in the previous three months (as well as a positive urinalysis on the day of scanning), Weschler Abbreviated Scale of Intelligence-2 score (WASI-2) (16) score < 70, and magnetic resonance imaging (MRI) exclusion criteria (e.g. claustrophobia, metal in the body). Control participants were excluded for all of the above as well as a history of Axis I mental illness or first-degree family history of psychosis. All participants provided written informed consent and were compensated for participation. The UCD Institutional Review Board approved the study. Medication regimen (type and dose) was assessed by clinical records at baseline and follow-up. Medication compliance was based on self-report. Medicated patients at follow-up all self-reported at least medium compliance with antipsychotic medication during the treatment period (except for two SZ individuals who were missing compliance data at follow-up). Symptoms were assessed using the 24-point Brief Psychiatric Rating Scale (BPRS) (17) rescaled to a lowest score of zero (i.e. score of 24 = score of 0). At baseline, all patients had BPRS scores >= 5 to ensure sufficient resolution to detect a 20% improvement in score at follow-up. Consistent with prior work (18), syndrome scores from three core symptom dimensions were also calculated. "Poverty" combined emotional withdrawal, motor retardation, and blunted affect from the Brief Psychiatric Rating Scale (BPRS) (17) with anhedonia/asociality, avolition/apathy, alogia, and affective flattening from the Scale for the Assessment of Negative Symptoms (SANS) (19). "Disorganization" combined conceptual disorganization, mannerisms and posturing, and disorientation scores from the BPRS with attention score from the SANS as well as positive formal thought disorder, and

bizarre behavior scores from the Scale for the Assessment of Positive Symptoms (SAPS) (20). “Reality distortion” combined grandiosity, suspiciousness, hallucinations, and unusual thought content from the BPRS with hallucinations and delusions from the SAPS (18).

## Task Description

The AX-CPT and associated task parameters have been described in detail elsewhere (9, 21–24). Briefly, participants are presented with a series of cues and probes and are instructed to make a target response (pressing a button with the index finger) to the probe letter “X” only if it was preceded by the cue letter “A.” All cues and nontarget probes require nontarget responses (pressing a button with the middle finger). Target sequence trials (i.e. “AX” trials) are frequent (60–70% occurrence) and set up a prepotent tendency to make a target response when the probe letter X occurs. As a result, a nontarget sequence trial in which any Non-A cue (collectively called “B” cues) is presented and followed by a probe letter X (i.e. “BX” trials) requires proactive cognitive control (e.g. maintenance of the inhibitory rule over the delay time) (22). Consistent with prior work (23), individual subject data was only included in analyses if results suggested the subject understood the AX-CPT (specifically, accuracy greater than 44% on AX trials and 50% on BY trials at both baseline and follow-up). Participants were combined across two task protocols collected from two MRI scanners over a 14-year period. Parameters for each protocol (AX-1 and AX-2) are provided in Supplementary Table 1a. The task was presented using EPrime2 software (Psychology Software Tools, Inc.). The behavioral index of proactive cognitive control was d-prime context, a function of AX hits minus BX false alarms (21).

## fMRI Scanning Parameters and Preprocessing

Functional images were acquired with a gradient-echo T2* Blood Oxygenation Level Dependent (BOLD) contrast technique as outlined in Supplementary Table 1b. AX-1 was performed in a 1.5T scanner (GE Healthcare), and AX-2 in a 3.0T scanner (Siemens).

fMRI data were preprocessed using SPM8 (Wellcome Dept. of Imaging Neuroscience, London). Briefly, images were slice-timing corrected, realigned, normalized to the Montreal Neurological Institute template using a rigid-body transformation followed by non-linear warping, and smoothed with an 8 mm full-width-half-maximum Gaussian kernel. All individual fMRI runs had less than 4 mm of translational within-run movement, 3 degrees of rotational within-run movement, and 0.45 mm of average framewise displacement (calculated using the fsl_motion_outliers tool) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers). Mean displacement did not differ between Improvers and Non-Improvers ($t = 1.42$, $p = 0.16$). All participants had at least two fMRI runs surviving these criteria. Preprocessing pipelines were identical for AX-1 and 2.

## fMRI Analysis and Pre-Specified ROI Selection

First-level effects were modeled with a double-gamma function, with temporal derivatives, using the general linear model in SPM8. Rigid-body motion parameters were included as single-subject regressors in order to partially account for movement effects. B > A Cue (correct trials only) contrast images (parameter estimates) were generated for each subject. The B > A Cue contrast measures response under conditions of high vs. low proactive

cognitive control (9, 12). All trial types were modeled (AX/AY/BX/BY) and only correct responses were used to create first-level images, consistent with previous studies (9, 12). Whole-brain analyses across the final sample (healthy controls and patients with follow-up data) using the B > A contrast were used to confirm significant (height threshold $p < 0.001$, cluster threshold $p < 0.05$ (whole brain FDR-corrected)) activation in expected brain regions (bilateral DLPFC/SPC) for both protocol versions (AX-1 and AX-2).

For logistic regression using first-level images, BOLD response was extracted from pre-specified bilateral, 5 mm radius spherical DLPFC and SPC ROIs (i.e. left and right regions combined to make a single ROI). Although this size was chosen arbitrarily, previous work from our group suggests varying ROI radius between 4–8 mm does not substantially affect AX-CPT task-associated response patterns in psychosis (14). The DLPFC ROI was taken from a previous study from an independent dataset (25). The SPC ROIs was taken from a meta-analysis of executive function in SZ (26). Mean task-associated response from these ROIs was extracted using the Marsbar toolbox (27). Task-associated behavioral and functional measures were adjusted for differences in protocol version prior to further analysis by calculating standardized residuals from the linear regression of protocol version by each measure. Adjustments were calculated separately for the sample that included all subjects (i.e. 171 patients and 138 controls) and only controls and patients with follow-up data (i.e. 82 patients and 138 controls) as these datasets were used for different analyses (missing data comparisons (t-tests) vs. logistic regression, respectively).

### Linear Regression

Linear regression was performed in SPSS25 (IBM, Armonk, NY). For this analysis, the linear dependent variable was clinical improvement (increase in Total BPRS score) at follow-up, and independent (predictor) variables were the behavioral and functional measures from the proactive cognitive control-based feature set (see preceding section). Threshold for statistical significance of the overall model and individual predictors was set to $p < 0.05$.

### Logistic Regression

Logistic regression was also performed in SPSS25 (IBM, Armonk, NY). For primary analyses, the binary dependent variable was clinical improvement at follow-up. Clinical “improvement” was defined as >20% decrease in Total BPRS score from baseline rescaled to a lowest score of zero (28). An initial model was constructed using a proactive cognitive control-based feature set. An exploratory secondary model was also evaluated that added baseline core symptom dimension scores (reality distortion, poverty, disorganization) as predictors. SPSS classification cutoff was set to the ratio of Improvers/Non-Improvers. Models were evaluated for fit, specificity, sensitivity, predictive value, and accuracy.

## Results

### Demographic and Clinical

Demographic information for individuals in the study sample is presented in Table 1a. Clinical information at baseline and follow-up is presented in Table 1b. Mean BPRS score at

baseline for all patients was 42.7 (standard deviation = 9.7). Mean BPRS score at follow-up for all patients was 37.3 (standard deviation = 9.0). 47% of BD and 60% of SZ patients showed greater than 20% decrease in total BPRS score (scaled to a lowest value of zero) at follow-up and were classified as “Improvers”. Mean improvement in BPRS score for Improvers was 12.7 (standard deviation = 7.3), corresponding to a 59% decrease.

## Behavioral and Functional AX-CPT Results

Results of comparisons between patients with vs. those without follow-up data are presented in Supplementary Table 2. No differences were observed on d-prime context, task-associated DLPFC or SPC response, or total BPRS score.

Across healthy controls and patients with follow-up clinical data (i.e. patients included in logistic regression analyses), significant (see Methods for threshold) activation was observed in the DLPFC/SPC for both protocol versions (Supplementary Table 3, Supplementary Figure 1). Raw behavioral and fMRI ROI data segregated by protocol version are presented in Supplementary Table 4.

## Linear Regression

We then examined the linear relationship between BPRS improvement and baseline cognitive control measures using linear regression. Due to high covariance (0.62) between DLPFC and SPC ROI activity for the B > A Cue (proactive control) fMRI contrast, BOLD response in these regions were combined into a single frontoparietal factor score. The overall model (with two predictors, behavioral and functional) was significant ($F(2,81) = 6.50$, $R = 0.38$, $p = 0.002$), although only the fMRI-based predictor (frontoparietal factor score) significantly contributed ($B = 3.88$, standardized coefficient (beta) = 0.35, $t = 3.36$, $p = 0.001$). The linear relationship (Pearson’s correlation coefficient) between BPRS improvement and functional factor score is illustrated in Figure 1.

## Logistic Regression

We next evaluated the ability of baseline proactive control measures (adjusted for protocol version) to predict BPRS improvement on a previously identified (28), clinically relevant binary scale (with an “Improver” defined as a patient with >20% decrease in total BPRS score (rescaled to a lowest score of zero) from baseline) using logistic regression. DLPFC and SPC activation was again combined into a single factor score as described for linear regression. Significance values, fit indices, and odds ratios for logistic regression models are presented in Table 2. Predictive capacity (specificity, sensitivity, positive predictive value, negative predictive value, and accuracy) for these models are presented in Table 3.

An initial model was constructed that included only proactive control-associated variables (behavioral and functional) as predictors. The overall model was significant (Table 2, top row), explained 15% of the variance in BPRS outcome (Nagelkerke $R^2 = 0.15$), and was 65.9% accurate using the SPSS log-likelihood-based regression algorithm (Table 3, top row). Only the functional MRI predictor significantly contributed to the model (beta = 0.8 ($p = 0.01$), change in −2 log-likelihood if removed = 9.5 ($p < 0.01$); Table 2, top row).

As an exploratory measure, on top of the initial model we then evaluated a secondary model that included baseline symptom core dimension scores (reality distortion, poverty, disorganization) as additional predictors. These additional predictors did not significantly improve fit (step $\chi^2 = 4.49$, $p = 0.21$), although accuracy was slightly improved (69.5%; Table 3, bottom row).

## Discussion

The results of the present study suggest that patients with greater frontoparietal activation during proactive cognitive control are more likely to show symptomatic improvement at one-year follow-up and that, conversely, poor treatment response is associated with poor activation in this circuitry. To our knowledge, this is the first study to use functional neuroimaging of cognitive control to predict 1-year treatment responder status in recent-onset psychotic illness and may have important implications for understanding disease mechanisms and for treatment. Our results also demonstrate the potential clinical utility of fMRI-based measures of cognition related brain activity. Indeed, only functional (and not behavioral) measures associated with the task distinguished between Improvers and Non-Improvers.

If frontoparietal executive dysfunction is a significant predictor of outcome, how may it be targeted? Currently, clozapine is typically prescribed in patients who do not respond to more conventional forms of treatment (29) (no patients were taking clozapine at any point in this study). Interestingly, clozapine has demonstrated effects on prefrontal function which may help explain its effectiveness, including increasing P3b amplitude (an electrophysiological measure of top-down attention) (30) and decreasing resting metabolism (31). Nonetheless, clozapine has a number of highly deleterious side effects, including weight gain, agranulocytosis, seizures, and cardiomyopathy (32). Although research is still in the very early stages, potential alternative methods of targeting prefrontal dysfunction in psychosis include brain stimulation (33–35) and cognitive remediation (36). Future prospective studies or retrospective analyses may examine if effects of these developmental interventions can improve outcomes in patients who show significant functional pathology at intake.

The best model in this study (fMRI + baseline syndrome scores) correctly classified 70% of patients as being Improvers. While good, to be an effective diagnostic tool fMRI should demonstrate at least 80% accuracy. Furthermore, although the correlation was significant, baseline frontoparietal activation only explained 11% of the variance in BPRS improvement, suggesting additional measures are necessary to fully understand why symptoms change in some patients and not others. Related to this point, a number of fMRI studies in early psychosis have used classification-based analyses to differentiate patients and controls (or segregate patients by diagnosis) and performed in the range of classification accuracy of the present study. This work has often been criticized as having statistical but not clinical significance, since clinical or even lay interviewers can perform at equivalent levels of diagnostic accuracy. Unlike these studies, however, our study sought to forecast long-term symptomatic improvement - a measure impossible to predict using any established method in early psychosis patients. We would argue, therefore, that despite not reaching an optimum level of accuracy the present work may represent an important preliminary step towards

clinical utility. Future studies using larger samples, and additional predictive markers (e.g. frontal parietal pathophysiology, structural imaging, and molecular imaging) may take us toward higher levels of prediction and closer to a precision psychiatry of early psychosis care.

A potential limitation in interpreting the present findings is that, as a prospective naturalistic study, we did not impose strict guidelines on medication status at either baseline or follow-up (the majority of recent-onset outpatients who enter treatment in our clinic have had some brief prior medication treatment). Furthermore, medication compliance was ascertained by self-report. Therefore, we cannot state with certainty if differences in BPRS symptom change from baseline vs. follow-up are due to antipsychotics or another aspect of treatment (e.g. psychoeducation, psychotherapy). For this reason, we labeled our groups as "Improvers" and "Non-Improvers" rather than responders/non-responders. An important follow-up study, therefore, would be to perform the same analyses in a sample of first-episode patients whose medication intake and level of psychotherapy engagement was more objectively monitored and accounted for. A second limitation was that functional outcomes (social, academic, occupational) were not examined. Given the established link between cognition and functional outcomes in schizophrenia (8, 37), additional research that evaluates the ability of fMRI neurocognitive data to predict these outcomes is strongly warranted. Despite these limitations, we believe that the present results provide important new evidence that cognitive control related frontal-parietal brain activity may serve as a meaningful predictor of clinical improvement in early psychosis patients and that they may represent an important first step in developing much needed imaging biomarkers of treatment outcomes in this important patient population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Kraepelin E: Psychiatrie Ein Lehrbuch für Studirende und Aertze. Leipzig, Barth; 1899.
2. Ciompi L The natural history of schizophrenia in the long term. Br J Psychiatry. 1980;136:413–420. [PubMed: 7388247]
3. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. I. Longitudinal study of paranoid, hebephrenic, and undifferentiated schizophrenia. Arch Gen Psychiatry. 1991;48:969–977. [PubMed: 1747020]

4. van Veelen NM, Vink M, Ramsey NF, van Buuren M, Hoogendam JM, Kahn RS. Prefrontal lobe dysfunction predicts treatment response in medication-naive first-episode schizophrenia. Schizophr Res. 2011;129:156–162. [PubMed: 21497488]
5. Anticevic A, Hu X, Xiao Y, Hu J, Li F, Bi F, Cole MW, Savic A, Yang GJ, Repovs G, Murray JD, Wang XJ, Huang X, Lui S, Krystal JH, Gong Q. Early-course unmedicated schizophrenia patients exhibit elevated prefrontal connectivity associated with longitudinal change. J Neurosci. 2015;35:267–286. [PubMed: 25568120]
6. Sarpal DK, Argyelan M, Robinson DG, Szeszko PR, Karlsgodt KH, John M, Weissman N, Gallego JA, Kane JM, Lencz T, Malhotra AK. Baseline Striatal Functional Connectivity as a Predictor of Response to Antipsychotic Drug Treatment. Am J Psychiatry. 2016;173:69–77. [PubMed: 26315980]
7. Cao B, Cho RY, Chen D, Xiu M, Wang L, Soares JC, Zhang XY. Treatment response prediction and individualized identification of first-episode drug-naive schizophrenia using brain functional connectivity. Mol Psychiatry. 2018.
8. Lesh TA, Niendam TA, Minzenberg MJ, Carter CS. Cognitive control deficits in schizophrenia: mechanisms and meaning. Neuropsychopharmacology. 2011;36:316–338. [PubMed: 20844478]
9. Lesh TA, Westphal AJ, Niendam TA, Yoon JH, Minzenberg MJ, Ragland JD, Solomon M, Carter CS. Proactive and reactive cognitive control and dorsolateral prefrontal cortex dysfunction in first episode schizophrenia. Neuroimage Clin. 2013;2:590–599. [PubMed: 24179809]
10. Yoon JH, Minzenberg MJ, Ursu S, Ryan Walter BS, Wendelken C, Ragland JD, Carter CS. Association of dorsolateral prefrontal cortex dysfunction with disrupted coordinated brain activity in schizophrenia: relationship with impaired cognition, behavioral disorganization, and global function. Am J Psychiatry. 2008;165:1006–1014. [PubMed: 18519527]
11. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. Arch Gen Psychiatry. 1991;48:978–986. [PubMed: 1747021]
12. Lesh TA, Tanase C, Geib BR, Niendam TA, Yoon JH, Minzenberg MJ, Ragland JD, Solomon M, Carter CS. A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. JAMA Psychiatry. 2015;72:226–234. [PubMed: 25588194]
13. Niendam TA, Lesh TA, Yoon J, Westphal AJ, Hutchison N, Ragland Daniel J, Solomon M, Minzenberg M, Carter CS. Impaired context processing as a potential marker of psychosis risk state. Psychiatry Res. 2014;221:13–20. [PubMed: 24120302]
14. Smucny J, Lesh TA, Newton K, Niendam T, Ragland JD, Carter CS. Levels of Cognitive Control: A Functional Magnetic Resonance Imaging-Based Test of an RDoC Domain Across Bipolar Disorder and Schizophrenia. Neuropsychopharmacology. 2017.
15. First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. New York, Biometrics Research, New York State Psychiatric Institute; 2002.
16. Weschler D: Weschler Abbreviated Scale of Intelligence (WASI). San Antonio, TX, Harcourt Assessment; 1999.
17. Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, Shaner A. Manual for the expanded brief psychiatric rating scale. International Journal of Methods in Psychiatric Research. 1993;3:227–244.
18. Barch DM, Carter CS, MacDonald AW 3rd, Braver TS, Cohen JD. Context-processing deficits in schizophrenia: diagnostic specificity, 4-week course, and relationships to clinical symptoms. J Abnorm Psychol. 2003;112:132–143. [PubMed: 12653421]
19. Andreasen NC: Scale for the assessment of negative symptoms (SANS). Iowa City, IA, Department of Psychiatry, College of Medicine, The University of Iowa; 1984.
20. Andreasen NC: Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA, Department of Psychiatry, College of Medicine, the University of Iowa; 1984.
21. Cohen JD, Barch DM, Carter C, Servan-Schreiber D. Context-processing deficits in schizophrenia: converging evidence from three theoretically motivated cognitive tasks. J Abnorm Psychol. 1999;108:120–133. [PubMed: 10066998]

22. Braver TS, Paxton JL, Locke HS, Barch DM. Flexible neural mechanisms of cognitive control within human prefrontal cortex. Proc Natl Acad Sci U S A. 2009;106:7351–7356. [PubMed: 19380750]

23. Henderson D, Poppe AB, Barch DM, Carter CS, Gold JM, Ragland JD, Silverstein SM, Strauss ME, MacDonald AW 3rd. Optimization of a goal maintenance task for use in clinical applications. Schizophr Bull. 2012;38:104–113. [PubMed: 22199092]

24. Phillips RC, Salo T, Carter CS. Distinct neural correlates for attention lapses in patients with schizophrenia and healthy participants. Front Hum Neurosci. 2015;9:502. [PubMed: 26500517]

25. MacDonald AW 3rd, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science. 2000;288:1835–1838. [PubMed: 10846167]

26. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry. 2009;66:811–822. [PubMed: 19652121]

27. Brett M, Anton J-L, Valabregue R, Poline J-B. Region-of-interest analysis using an SPM toolbox. Neuroimage. 2002;8th International Conference on Functional Mapping of the Human Brain.

28. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, Bloomfield MA, Bressan RA, Buchanan RW, Carpenter WT, Castle DJ, Citrome L, Daskalakis ZJ, Davidson M, Drake RJ, Dursun S, Ebdrup BH, Elkis H, Falkai P, Fleischacker WW, Gadelha A, Gaughran F, Glenthoj BY, Graff-Guerrero A, Hallak JE, Honer WG, Kennedy J, Kinon BJ, Lawrie SM, Lee J, Leweke FM, MacCabe JH, McNabb CB, Meltzer H, Moller HJ, Nakajima S, Pantelis C, Reis Marques T, Remington G, Rossell SL, Russell BR, Siu CO, Suzuki T, Sommer IE, Taylor D, Thomas N, Ucok A, Umbricht D, Walters JT, Kane J, Correll CU. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry. 2017;174:216–229. [PubMed: 27919182]

29. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Comparative Effectiveness of Clozapine and Standard Antipsychotic Treatment in Adults With Schizophrenia. Am J Psychiatry. 2016;173:166–173. [PubMed: 26541815]

30. Schall U, Catts SV, Chaturvedi S, Liebert B, Redenbach J, Karayanidis F, Ward PB. The effect of clozapine therapy on frontal lobe dysfunction in schizophrenia: neuropsychology and event-related potential measures. Int J Neuropsychopharmacol. 1998;1:19–29. [PubMed: 11281941]

31. Molina V, Gispert JD, Reig S, Sanz J, Pascau J, Santos A, Desco M, Palomo T. Cerebral metabolic changes induced by clozapine in schizophrenia and related to clinical improvement. Psychopharmacology (Berl). 2005;178:17–26. [PubMed: 15365682]

32. Young CR, Bowers MB Jr., Mazure CM. Management of the adverse effects of clozapine. Schizophr Bull. 1998;24:381–390. [PubMed: 9718630]

33. Mervis JE, Capizzi RJ, Boroda E, MacDonald AW 3rd. Transcranial Direct Current Stimulation over the Dorsolateral Prefrontal Cortex in Schizophrenia: A Quantitative Review of Cognitive Outcomes. Front Hum Neurosci. 2017;11:44. [PubMed: 28210217]

34. Barr MS, Farzan F, Rajji TK, Voineskos AN, Blumberger DM, Arenovich T, Fitzgerald PB, Daskalakis ZJ. Can repetitive magnetic stimulation improve cognition in schizophrenia? Pilot data from a randomized controlled trial. Biol Psychiatry. 2013;73:510–517. [PubMed: 23039931]

35. Lett TA, Voineskos AN, Kennedy JL, Levine B, Daskalakis ZJ. Treating working memory deficits in schizophrenia: a review of the neurobiology. Biol Psychiatry. 2014;75:361–370. [PubMed: 24011822]

36. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry. 2011;168:472–485. [PubMed: 21406461]

37. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry. 1996;153:321–330. [PubMed: 8610818]

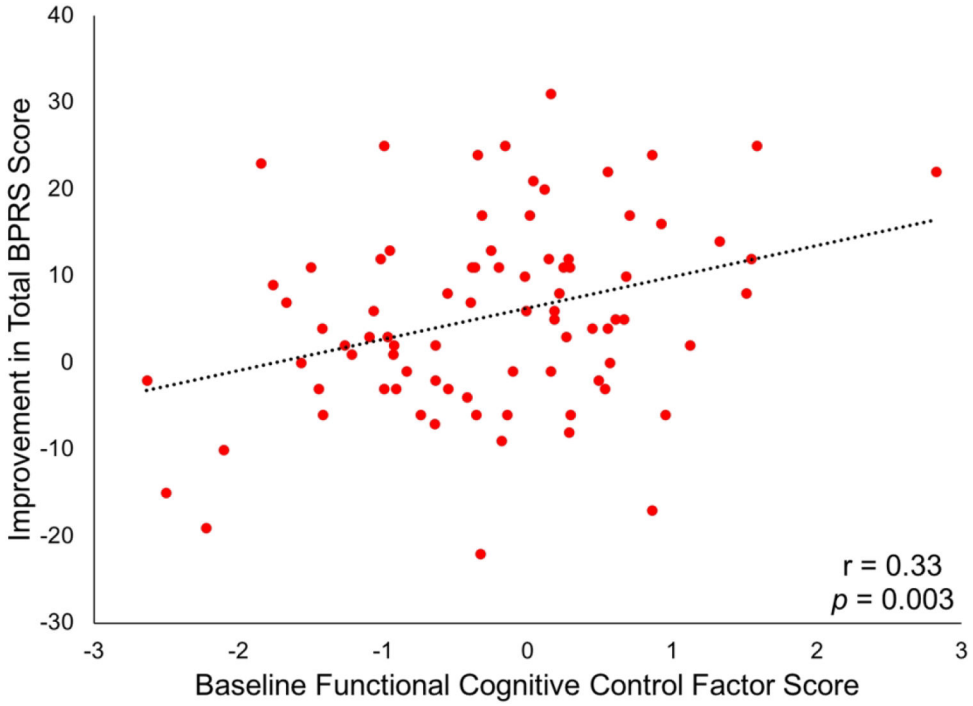


**Figure 1.**
Linear relationship between BPRS improvement (from baseline) and baseline frontoparietal factor score.

**Table 1a.**

Demographic information. Numbers in parentheses represent the standard deviation.[a]

| | HC | BD | SZ |
|---|---|---|---|
| **N** | 138 | 17 | 65 |
| **Age** | 20.4 (2.7) | 21.6 (2.8) | 20.8 (3.3) |
| **Gender (M/F)** | 85/53 | 10/7 | 49/16 |
| **AX-1/AX-2 Protocol Participants** | 73/65 | 14/3 | 38/27 |
| **Days to Follow-Up** | - | 429.7 (113.0) | 384.7 (143.7) |

[a]Abbreviations: BD = Bipolar Disorder, HC = Healthy Controls, SZ = Schizophrenia.

**Table 1b.**

Clinical information at baseline and follow-up. Numbers in parentheses represent the standard deviation[b].

| | BD | | SZ | | All | |
|---|---|---|---|---|---|---|
| | **Baseline** | **Follow-Up** | **Baseline** | **Follow-Up** | **Baseline** | **Follow-Up** |
| **Antipsychotics (Med/Unmed)** | 14/3 | 10/7 | 55/10 | 50/15 | 69/13 | 60/22 |
| **Antipsychotics (CPZ Equivalent Dose, Mg/Day)** | 302.3 (156.4) | 342.5 (358.2) | 207.2 (148.0) | 300.7 (298.9) | 227.4 (154.4) | 307.3 (305.9) |
| **BPRS Improved/Did Not Improve**[c] | 8/9 (47.1% Improved) | | 39/26 (60.0% Improved) | | 47/35 (57.3% Improved) | |

[b]Abbreviations: BD = Bipolar Disorder, BPRS = Brief Psychiatric Rating Scale, CPZ = Chlorpromazine, HC = Healthy Controls, SZ = Schizophrenia.

[c]Clinical “improvement” was defined as showing >20% decrease (with lowest possible score (24) set to zero) on Total BPRS score at follow-up (vs. baseline). Only patients with Total BPRS score >= 29 at baseline were included in the sample.

**Table 2.**

Logistic regression results.[a]

| Predictors | Model $\chi^2$ (*p*) | Step[b] $\chi^2$ (*p*) | Model −2 LL | Model C-S $R^2$ | Model Nagel $R^2$ | Predictor | | | Predictor OR {95% CI} | If Predictor Removed | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | B | SE | *p* | | Δ−2LL | *p* |
| • *Functional Cognitive Control Factor Score (DLPFC + SPC B > A Cue Activation)* | 9.5 (<0.01) | | 102.4 | 0.11 | 0.15 | 0.8 | 0.3 | 0.01 | 2.2 {1.3 – 3.7} | 9.5 | <0.01 |
| • *D-Prime Context (Adjusted Z- Score)* | | | | | | −0.1 | 0.2 | 0.69 | 0.9 {0.6 −1.4} | 0.2 | 0.68 |
| • *Constant* | | | | | | 0.5 | 0.3 | 0.05 | 1.7 {-} | | |
| • *Functional Cognitive Control Factor Score (DLPFC + SPC B > A Cue Activation)* | 14.0 (0.02) | 4.49 (0.21) | 97.9 | 0.16 | 0.21 | 0.8 | 0.3 | <0.01 | 2.1 {1.2 – 3.8} | 8.0 | <0.01 |
| • *D-Prime Context (Adjusted Z- Score)* | | | | | | 0.3 | 0.2 | 0.90 | 1.0 {0.7 – 1.6} | 0.02 | 0.90 |
| • *Reality Distortion* | | | | | | 0.1 | 0.0 | 0.21 | 1.1 {1.0 – 1.1} | 1.6 | 0.20 |
| • *Disorganization* | | | | | | 0.1 | 0.1 | 0.40 | 1.1 {0.9 – 1.3} | 0.7 | 0.40 |
| • *Poverty* | | | | | | 0.1 | 0.1 | 0.31 | 1.1 {1.0 – 1.2} | 1.0 | 0.31 |
| • *Constant* | | | | | | −1.3 | 1.0 | 0.18 | 0.3 {-} | | |

[a] Abbreviations: B = Beta, C-S = Cox and Snell, LL = Log likelihood, Nagel = Nagelkerke, OR = Odds Ratio, SE = Standard Error.

[b] Step $\chi^2$ is for adding in the baseline syndrome scores (reality distortion, disorganization, poverty) to the initial model (Functional Cognitive Control Factor Score + Constant).

**Table 3.**

Predictive metrics for each model using SPSS logistic regression.

| Predictors | %Specificity | %Sensitivity | %PPV[a] | %NPV | %Accuracy |
|---|---|---|---|---|---|
| • *Functional Cognitive Control Factor Score (DLPFC+ SPC B > A Cue Activation)* | 60.0 | 70.2 | 70.2 | 60.0 | 65.9 |
| • *D-Prime Context (AdjustedZ-Score)* | | | | | |
| • *Constant* | | | | | |
| • *Functional Cognitive Control Factor Score (DLPFC+ SPC B > A Cue Activation)* | 68.6 | 70.2 | 75.0 | 63.2 | 69.5 |
| • *D-Prime Context (AdjustedZ-Score)* | | | | | |
| • *Reality Distortion* | | | | | |
| • *Poverty* | | | | | |
| • *Disorganization* | | | | | |
| • *Constant* | | | | | |

[a]"Positive" status for positive predictive value (PPV) was defined as showing >20% improvement in Brief Psychiatric Rating Scale (BPRS) score at follow-up.