UC Davis
UC Davis Previously Published Works

Title

A Multimodal Analysis of Antipsychotic Effects on Brain Structure and Function in First-Episode Schizophrenia

Permalink

https://escholarship.org/uc/item/98z1h86d

Journal

JAMA Psychiatry, 72(3)

ISSN

2168-622X

Authors

Lesh, Tyler A
Tanase, Costin
Geib, Benjamin R
et al.

Publication Date

2015-03-01

DOI

10.1001/jamapsychiatry.2014.2178

Peer reviewed

A Multimodal Analysis of Antipsychotic Effects on Brain Structure and Function in First-Episode Schizophrenia

Tyler A. Lesh, PhD, **Costin Tanase, PhD**, **Benjamin R. Geib, MS**, **Tara A. Niendam, PhD**, **Jong H. Yoon, MD**, **Michael J. Minzenberg, MD**, **J. Daniel Ragland, PhD**, **Marjorie Solomon, PhD**, and **Cameron S. Carter, MD**

Department of Psychiatry, University of California, Davis (Lesh, Tanase, Geib, Niendam, Yoon, Minzenberg, Ragland, Solomon, Carter);MIND (Medical Investigation of Neurodevelopmental Disorders) Institute, University of California, Davis (Solomon); Department of Psychology, University of California, Davis (Carter); Imaging Research Center, University of California, Davis (Carter).

Abstract

IMPORTANCE—Recent data suggest that treatment with antipsychotics is associated with reductions in cortical gray matter in patients with schizophrenia. These findings have led to concerns about the effect of antipsychotic treatment on brain structure and function; however, no studies to date have measured cortical function directly in individuals with schizophrenia and shown antipsychotic-related reductions of gray matter.

OBJECTIVE—To examine the effects of antipsychotics on brain structure and function in patients with first-episode schizophrenia, using cortical thickness measurements and administration of the AX version of the Continuous Performance Task (AX-CPT) during event-related functional magnetic resonance imaging.

DESIGN, SETTING, AND PARTICIPANTS—This case-control cross-sectional study was conducted at the Imaging Research Center of the University of California, Davis, from November 2004 through July 2012. Participants were recruited on admission into the Early Diagnosis and Preventive Treatment Clinic, an outpatient clinic specializing in first-episode psychosis. Patients

with first-episode schizophrenia who received atypical antipsychotics (medicated patient group) (n = 23) and those who received no antipsychotics (unmedicated patient group) (n = 22) and healthy control participants (n = 37) underwent functional magnetic resonance imaging using a 1.5-T scanner.

MAIN OUTCOMES AND MEASURES—Behavioral performance was measured by trial accuracy, reaction time, and d′-context score. Voxelwise statistical parametric maps tested differences in functional activity during the AX-CPT, and vertexwise maps of cortical thickness tested differences in cortical thickness across the whole brain.

RESULTS—Significant cortical thinning was identified in the medicated patient group relative to the control group in prefrontal (mean reduction [MR], 0.27 mm; $P < .001$), temporal (MR, 0.34 mm; $P = .02$), parietal (MR, 0.21 mm; $P = .001$), and occipital (MR, 0.24 mm; $P = .001$) cortices. The unmedicated patient group showed no significant cortical thickness differences from the control group after clusterwise correction. The medicated patient group showed thinner cortex compared with the unmedicated patient group in the dorsolateral prefrontal cortex (DLPFC) (MR, 0.26 mm; $P = .001$) and temporal cortex (MR, 0.33 mm; $P = .047$). During the AX-CPT, both patient groups showed reduced DLPFC activity compared with the control group ($P = .02$ compared with the medicated group and $P < .001$ compared with the unmedicated group). However, the medicated patient group demonstrated higher DLPFC activation ($P = .02$) and better behavioral performance ($P = .02$) than the unmedicated patient group.

CONCLUSIONS AND RELEVANCE—These findings highlight the complex relationship between antipsychotic treatment and the structural, functional, and behavioral deficits repeatedly identified in schizophrenia. Although short-term treatment with antipsychotics was associated with prefrontal cortical thinning, treatment was also associated with better cognitive control and increased prefrontal functional activity. This study adds important context to the growing literature on the effects of antipsychotics on the brain and suggests caution in interpreting neuroanatomical changes as being related to a potentially adverse effect on brain function.

In the 40 years since the classic study by Johnstone and colleagues,[1] schizophrenia has been understood as a disorder characterized by alterations in brain structure, with the most robust findings including ventricular enlargement and reductions in overall gray matter volume.[2] Studies of cortical thickness and surface area have also revealed consistent patterns of frontotemporal thinning in patients with chronic[3–5] and first-episode[6–10] schizophrenia. In recent years, accumulating evidence suggests that antipsychotics may contribute to observed structural brain changes, including the cortical and subcortical structures.[11,12] Some studies suggest that typical antipsychotics may be associated with more dramatic structural changes (ie, larger reductions in gray matter volume, increased caudate and putamen volume) than atypical agents,[5,13] whereas others fail to find a structural relationship with specific medications.[3,14] In addition, studies of brain volume, cortical thickness, and surface area in antipsychotic-naive[8,15] and prodromal[16] individuals reveal that structural abnormalities are present before the initiation of antipsychotic therapy. These findings suggest that antipsychotics may contribute to findings of gray matter reduction in schizophrenia, but measurable changes are also caused by the illness itself.

Although antipsychotic therapy has the clear benefits of reducing psychotic symptoms and relapse in schizophrenia,[17] recent findings of an association between gray matter loss and antipsychotic treatment in schizophrenia has raised concerns about the potential adverse effects of antipsychotics that may need to be taken into consideration when prescribing these agents.[18] Recent studies have identified relationships among brain structure abnormalities, cognition, and brain function early in the course of schizophrenia,[19] including the association of white matter volume loss and cognitive impairment.[20] Therefore, examining the influence of antipsychotics on measures of brain structure and function (ie, task-related brain activity) is of critical importance to understand adequately how these factors contribute to the illness. However, to our knowledge, no studies to date have examined conjointly whole-brain cortical thickness and functional engagement of the prefrontal cortex (PFC) in groups of patients with first-episode schizophrenia who have or have not received antipsychotics. Our study seeks to address this clinically significant gap in knowledge.

More specifically, this investigation examines cortical structure and function within 1 year of psychosis onset in individuals who had not received antipsychotics (unmedicated patient group) or had been treated for a number of weeks with atypical antipsychotics (medicated patient group). Given numerous studies identifying structural alterations in the frontal regions, we hypothesized that antipsychotic treatment would be associated with a thinner cortex in the PFC. The AX version of the Continuous Performance Task (AX-CPT)[21] was used to evaluate cognitive control performance and PFC recruitment because it is a robust and reliable measure of a known executive deficit in schizophrenia.[22] Some studies have found marginal improvement in neuropsychological measures in patients taking atypical antipsychotics,[23] and we anticipated that the medicated patient group would show AX-CPT performance intermediate to those of the healthy control group and the unmedicated patient group. In addition, animal studies showed increased prefrontal dopamine release as a consequence of antipsychotic administration[24,25] and evidence of medication related increases in the blood oxygen level–dependent (BOLD) response in the PFC after starting antipsychotic treatment or after switching to an atypical antipsychotic[26–28]; we therefore anticipated that patients receiving medication would show BOLD activity intermediate to that of the control group and the unmedicated patient group. In short, we anticipated that atypical antipsychotic treatment may be associated with a net positive response in terms of higher behavioral performance and brain activity even in the context of cortical thinning.

Methods

Participants

The study was approved by the institutional review board of the University of California, Davis. Participants provided written informed consent after receiving a complete description of the study and were compensated.

Forty-five patients with first-episode schizophrenia (36 with schizophrenia, 5 with schizoaffective disorder, and 4 with schizophreniform disorder) were recruited from the Early Diagnosis and Preventive Treatment Clinic at the University of California, Davis, along with 37 healthy control participants aged 15 to 26 years. Table 1 outlines the participants' demographic and clinical status at the time of testing. Participants with

schizophrenia were outpatients within 1 year of the onset of psychotic symptoms. Twenty-three patients were currently treated with atypical antipsychotics (medicated patient group), and the remaining 22 patients were not receiving antipsychotics (unmedicated patient group). Of the 22 patients in the unmedicated patient group, 17 were antipsychotic naive and the remaining 5 had discontinued medication more than 1 month before the study. Detailed inclusion and exclusion criteria are described in eAppendix 1 in the Supplement.

Measures and Data Analysis

The AX-CPT has been described in great detail previously,[21] and the task parameters specific to this implementation are shown in Figure 1. The task was presented using E-prime software (http://www.pstnet.com/eprime.cfm). Briefly, the 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 are frequent and set up a prepotent tendency to make a target response when the probe letter *X* occurs. As a result, nontarget sequence trials in which any non-*A* cue (collectively called *B cues*) is presented and followed by a probe letter *X* require the most cognitive control.

A specific measure of cognitive control performance, d′-context,[21] was computed from AX hits and BX false alarms and analyzed using a 1-way analysis of variance (ANOVA). Analyses of AX-CPT accuracy and reaction time are reported in eAppendix 2 in the Supplement. Measures passing significance in the overall ANOVA underwent pairwise *t* tests (2-tailed) between groups, with the exception of comparisons between patient groups, which included duration of illness as a covariate in the analysis of covariance. We used the Holm-Bonferroni method[29] to correct for multiple comparisons on post hoc pairwise tests. Group comparisons on measures that violated sphericity assumptions were adjusted using the Greenhouse-Geisser correction.[30]

Functional Imaging Parameters and Data Analysis

Functional magnetic resonance imaging data were obtained using a 1.5-T scanner (Signa; GE Healthcare). For the AX-CPT, T2-weighted echoplanar imaging sessions used the following settings: repetition time, 2000 milliseconds; echo time, 40 milliseconds; flip angle, 90°; and field of view, 22 cm. Functional images consisted of 24 contiguous and interleaved 4.0-mm axial sections with a 3.4-mm^2 in-plane resolution. Preprocessing steps are outlined in eAppendix 1 in the Supplement. Functional imaging analysis was performed in statistical parametric mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) using the general linear model. All trial types were modeled, and only correct responses were included in the reported contrasts. Regressors included all cues, probes, and error trials. Translational and rotational movement data were included as covariates of noninterest. Group-level random- effects comparisons were performed between groups for the AX-CPT contrast subtracting cue *A* from cue *B* (cue *B* − cue *A* contrast) to measure activation under conditions of high vs low cognitive control. Contrasts were thresholded at the voxel level ($P < .01$), and clusters were considered significant if they survived cluster-level family wise error correction ($P < .05$).

In addition to whole-brain analyses, a priori hypotheses regarding the dorsolateral PFC (DLPFC) prompted the interrogation of left and right DLPFC regions of interest. Details concerning the selection of regions of interest and analysis are included in eAppendix 1 in the Supplement.

Cortical Thickness Data Analysis

Spoiled gradient recalled images were collected in the same session using the following parameters: repetition time, 9 milliseconds; echo time, 2 milliseconds; flip angle, 15°; field of view, 22 cm; one hundred twenty-four 1.5-mm axial sections; and 0.86-mm^2 in-plane resolution. Images were processed with the FreeSurfer software package (version 4.3; http://surfer.nmr.mgh.harvard.edu)[31,32] using the processing stream described in eAppendix 1 in the Supplement.

Measurements of cortical thickness were obtained for each vertex and mapped on a common spherical coordinate system. Maps were smoothed with a 10-mm gaussian kernel, and right and left hemispheres were tested separately. To correct for multiple comparisons, a cluster analysis was conducted using a Monte Carlo simulation with 10 000 iterations. The vertexwide threshold was set at $P < .01$ for simulation and clustering, and clusters were considered significant if they survived a clusterwise probability of $P < .05$. Duration of illness was included as a covariate of noninterest in the patient subgroup comparison.

Results

Demographic and Clinical Characteristics

Participant demographic and clinical information is presented in Table 1. The groups did not differ significantly by age, sex, handedness, or parental educational level. We found a trend for groups to differ on participant educational level ($F_{2,79} = 2.82$; $P = .07$). Post hoc independent-sample t tests revealed that the controls completed significantly more years of education compared with participants in the unmedicated patient group ($t_{57} = 2.44$; $P < .05$); the difference between the control group and the medicated patient group had a trend for more years of education ($t_{58} = 1.76$; $P = .08$). The medicated and unmedicated patient groups did not differ on years of education ($t_{43} = 0.65$; $P = .65$). Significant group differences emerged for estimated IQ ($F_{2,77} = 7.02$; $P < .01$). The control group showed a significantly higher estimated IQ compared with the medicated ($t_{58} = 3.48$; $P < .01$) and unmedicated ($t_{57} = 2.97$; $P < .01$) patient groups. The IQ did not differ between the medicated and unmedicated patient groups ($t_{43} = 0.27$; $P = .79$). The medicated and unmedicated patient groups also did not differ on duration of illness ($t_{43} = 1.75$; $P = .09$) or on scores from the modified Global Assessment of Functioning ($t_{43} = 0.75$; $P = .46$),[33] Brief Psychiatric Rating Scale ($t_{43} = 0.35$; $P = .73$),[34] Schedule for the Assessment of Negative Symptoms ($t_{43} = 0.09$; $P = .93$),[35] or Schedule for the Assessment of Positive Symptoms ($t_{43} = 1.62$; $P = .11$).[36]

Cortical Thickness Results

Between-group cortical thickness comparisons are presented in Table 2 and rendered in Figure 2 (cluster-corrected) and eFigure 1 in the Supplement (uncorrected). Comparison of

the control group with both schizophrenia patient groups revealed significant cortical thinning in the schizophrenia groups in the left supramarginal gyrus, right rostral middle frontal gyrus, right superior parietal cortex, right middle temporal gyrus, and right lateral occipital cortex. Compared with the control group, the medicated patient group showed cortical thinning in the bilateral rostral middle frontal gyrus (0.22- and 0.27-mm mean reduction in right and left hemisphere, respectively), left orbitofrontal cortex (0.22-mm mean reduction), left pars opercularis (0.24-mm mean reduction), left fusiform gyrus (0.22-mm mean reduction), left supramarginal gyrus (0.23-mm mean reduction), left precuneus (0.22-mm mean reduction), right superior frontal gyrus (0.25-mm mean reduction), right lateral occipital cortex (0.24-mm mean reduction), right superior parietal cortex (0.21-mm mean reduction), and right superior temporal sulcus (0.34-mm mean reduction). In contrast, the unmedicated patient group showed no significant differences in cortical thickness compared with controls. Finally, comparing the medicated with the unmedicated patient groups revealed thinner cortex in the medicated patient group in 2 regions of the left rostral middle frontal gyrus (0.26-mm mean reduction), in the left middle temporal gyrus (0.33-mm mean reduction), and in the right pars opercularis (0.16-mm mean reduction).

AX-CPT Behavioral Results

Table 1 provides behavioral data; eAppendix 2 in the Supplement provides an analysis of all AX-CPT conditions. However, the primary analysis focused on d′-context. One-way ANOVA of d′-context scores revealed significant group differences ($F_{2,79} = 13.61$; $P < .001$). Pairwise tests revealed lower d′-context scores in the unmedicated patient group compared with the control group ($t_{57} = 5.68$; $P < .001$) and medicated patient group ($F_{1,42} = 5.53$; $P = .02$) and lower d′-context scores in the medicated patient group compared with the control group ($t_{33} = 2.17$; $P = .04$), all of which remained significant after correcting for multiple comparisons.

AX-CPT Functional Magnetic Resonance Imaging Results

Within-group results with significant clusters are described in detail in the eTable in the Supplement. Whole-brain comparison (Figure 3) of the controls with all patients with schizophrenia revealed higher activity in the controls in the right DLPFC and bilateral inferior parietal cortex under conditions requiring high cognitive control. The medicated patient group showed no significant differences compared with the control group, although the controls showed higher frontal and parietal activity at lower thresholds. In contrast, comparison of the unmedicated patient group with the control group revealed robust differences, with controls showing significantly higher activity in the bilateral DLPFC and inferior parietal cortex. Finally, a comparison of the medicated and unmedicated patient groups revealed significantly higher activity in the bilateral DLPFC of patients in the medicated group.

The ANOVA of the DLPFC regions of interest (Figure 3) revealed a significant between-group difference in cue B − cue A activity on the right ($F_{2,78} = 13.62$; $P = .001$) and left ($F_{2,78} = 6.22$; $P = .003$) DLPFC. Post hoc t tests revealed significantly higher activity in the control group compared with the medicated ($t_{58} = 2.38$; $P = .02$) and unmedicated ($t_{56} = 5.50$; $P < .001$) patient groups in the right DLPFC. Within the left DLPFC, the control group

showed higher activity compared with the unmedicated patient group ($t_{56} = 3.72$; $P = .001$) but not the medicated patient group ($t_{58} = 1.21$; $P = .23$). The medicated patient group showed higher activity compared with the unmedicated patient group in the right ($F_{1,41} = 6.34$; $P = .02$) and left ($F_{1,41} = 4.89$; $P = .03$) DLPFC. All significant findings remained so after correction for multiple comparisons.

Supplemental Analyses

Three additional analyses were performed and are presented in the Supplement. First, follow-up cortical thickness and functional magnetic resonance imaging analyses performed only on the subgroup of 17 antipsychotic-naive patients revealed results similar to those of the whole sample (eAppendix 2 in the Supplement). Second, we explored relationships between functional and behavioral data and identified a significant positive relationship between d′-context and left DLPFC BOLD activity when looking at the patient group as a whole (eFigure 2 in the Supplement). Finally, we included DLPFC β values in a vertexwise analysis of cortical thickness and identified no significant relationships between the functional and structural variables.

Discussion

As expected, the medicated patient group showed significant thinning in the PFC and middle temporal regions when compared with the unmedicated patient group and in the prefrontal, middle temporal, parietal, and occipital regions when compared with the control group. Despite these effects on cortical thickness, we saw no evidence of deleterious effects of atypical antipsychotic treatment on cognition and brain activity in this group of patients with first-episode schizophrenia. To the contrary, examination of behavioral performance and BOLD activity during the AX-CPT revealed better performance and increased DLPFC activity in the medicated compared with the unmedicated patient groups. In addition, both patient groups showed significantly reduced DLPFC activity and performance decrements compared with the control group. We also identified a significant positive relationship between behavioral performance and left DLPFC BOLD activity in the patient groups. This combination of structural, functional, and behavioral findings adds to an already substantial literature identifying DLPFC impairment in schizophrenia[37,38] and contributes novel findings related to the effects of medication on the brain and behavior in this illness.

The cortical thickness results we described are consistent with those of other studies of patients who received antipsychotics and have shown cortical thinning in samples with first-episode schizophrenia.[6,10] Although Narr and colleagues[9] implemented different study methods, their findings of thinning are similar to ours and complement region of interest–based studies of anterior cingulate cortex thinning.[7] Our findings are also generally consistent with those of studies of cortical volume in which antipsychotic treatment was associated with decreased gray matter volume in the frontal cortex and overall reduced gray matter volume.[12,13,18] However, some studies have identified preserved or even increased cortical volume or thickness in patients treated with atypical antipsychotics.[13,39,40]

Long-term and even relatively brief exposure to antipsychotics has been linked to widespread loss of gray matter volume in macaque monkeys[41] and rodents,[42] with the most

robust findings in the frontal and parietal cortices. Konopaske and colleagues[43] demonstrated that these volume losses in nonhuman primates can be explained by fewer glial cells and higher densities of neurons.[44] However, the mechanism by which antipsychotics may produce these effects remains unclear and will likely be the focus of significant future work.

Our finding of increased prefrontal activity in the present study's medicated patient group is consistent with that of previous work by Jones and colleagues,[28] who identified increased PFC activity in a small group of medicated patients compared with a drug-naive group during a verbal fluency task. A similar finding was also identified using a prospective design in which untreated patients who underwent subsequent testing after 12weeks of quetiapine fumarate treatment showed increased PFC activity during a working memory task.[26] However, both of these studies used relatively small samples, and other work using positron emission tomography[45] provides conflicting evidence of the effect of antipsychotics on prefrontal cerebral blood flow.

Although the mechanism for antipsychotic treatment effects on brain structure and function is unclear, neuroinflammatory models provide a potential link. A growing body of evidence implicates neuroinflammation in the pathophysiological features of schizophrenia,[46] including elevations in proinflammatory cytokine levels[47] and microglia activation[48] and increased extracellular volume in white and gray matter.[49] However, antipsychotic treatment has been associated with an anti-inflammatory effect,[50] which could promote decreases in extracellular volume and activated glia and improve neuronal function and consequently cognition. Thus, the interaction of antipsychotic treatment and neuroinflammatory processes at the first episode reflects one potential mechanism to address our findings. Another potential mechanism to explain improved cognitive performance and BOLD activity in the medicated patient group would be the effect of second-generation antipsychotics on the dopaminergic and serotonergic systems. Several studies[24,25] have found increased prefrontal dopamine release as a consequence of serotonin$_{2A}$ and D$_2$ receptor blockade. Given that schizophrenia has been associated with decreased dopaminergic activity within the mesocortical system,[51] atypical antipsychotics could improve dopaminergic tone in the prefrontal cortex, with beneficial effects on cognition and potentially BOLD activity.[26,52] The absence of a significant relationship between BOLD activity and cortical thickness suggests that thinning per se is an unlikely explanation for increases in BOLD activity in patients who use antipsychotics. The mechanism by which antipsychotics are associated with thinning and functional/behavioral performance improvements may therefore be different. Nonetheless, higher performance and greater BOLD activity in the medicated sample of patients highlight the potentially positive effects of antipsychotics in what traditionally might have been interpreted as a detrimental effect if cortical thickness was examined in isolation.

Limitations include the naturalistic between-subject design of the study. The spoiled gradient recalled images collected in a 1.5-T scanner represent lower resolution than can be obtained on 3-T scanners. Consequently, the reduced precision of these data may underestimate the differences between groups. Although this study demonstrates no detrimental effect of medication on performance of the AX-CPT, the possibility exists that

medication has a different effect on other behavioral tasks. However, the importance of cognitive control for goal-directed behavior would lead to the prediction that other cognitive tasks with superordinate goals (ie, memory and language tasks) would show comparable medication effects. In addition, a prospective, within-subject, counterbalanced drug/placebo design would be preferable to the naturalistic design of the present study, but such a study would not be feasible or ethically justified. Important pathophysiological differences may exist between patients who went untreated before entering the study and those who received atypical antipsychotic treatment that could account for improved cognition and prefrontal recruitment in the medicated patient group. We believe that such differences are highly unlikely for a number of reasons. First, all patients were quite early in the course of their illness (mean duration of 6 months) and were well matched on variables such as age, sex, IQ, socioeconomic status, and clinical symptoms. Second, the mean duration of antipsychotic treatment was brief (99 days) and the mean dose was low (190-mg chlorpromazine equivalent). Finally, the only clinical difference between the medicated and unmedicated patient groups was a nonsignificant difference in positive symptoms, which would be consistent with the known clinical effects of these agents.

Conclusions

The present study provides important new data to inform the debate regarding the functional significance of the effects of antipsychotics on cortical gray matter. In addition to replicating previous reports of reduced cortical thickness in a cohort of patients with briefly medicated first-episode schizophrenia, we find no evidence of a deleterious effect of this treatment on higher cognition or on underlying neurophysiological features. Short-term treatment with atypical antipsychotics was associated with better cognition and functional brain activity in these individuals. Additional data regarding the longer-term effects of antipsychotics on brain structure and function are needed to inform this debate, with further data from animal models that might provide additional insights into the neurobiological features of the antipsychotic effects on brain structure and function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

REFERENCES

1. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet. 1976; 2(7992):924–926. [PubMed: 62160]

2. Shepherd AM, Laurens KR, Matheson SL, Carr VJ, Green MJ. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci Biobehav Rev. 2012; 36(4): 1342–1356. [PubMed: 22244985]

3. Kuperberg GR, Broome MR, McGuire PK, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry. 2003; 60(9):878–888. [PubMed: 12963669]

4. Rimol LM, Hartberg CB, Nesvåg R, et al. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol Psychiatry. 2010; 68(1):41–50. [PubMed: 20609836]

5. van Haren NE, Schnack HG, Cahn W, et al. Changes in cortical thickness during the course of illness in schizophrenia. Arch Gen Psychiatry. 2011; 68(9):871–880. [PubMed: 21893656]

6. Schultz CC, Koch K, Wagner G, et al. Reduced cortical thickness in first episode schizophrenia. Schizophr Res. 2010; 116(2–3):204–209. [PubMed: 19926451]

7. Fornito A, Yung AR, Wood SJ, et al. Anatomic abnormalities of the anterior cingulate cortex before psychosis onset: an MRI study of ultra–high-risk individuals. Biol Psychiatry. 2008; 64(9):758–765. [PubMed: 18639238]

8. Venkatasubramanian G, Jayakumar PN, Gangadhar BN, Keshavan MS. Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naive schizophrenia. Acta Psychiatr Scand. 2008; 117(6):420–431. [PubMed: 18479318]

9. Narr KL, Bilder RM, Toga AW, et al. Mapping cortical thickness and gray matter concentration in first episode schizophrenia. Cereb Cortex. 2005; 15(6):708–719. [PubMed: 15371291]

10. Crespo-Facorro B, Roiz-Santiáñez R, Pérez-Iglesias R, et al. Global and regional cortical thinning in first-episode psychosis patients: relationships with clinical and cognitive features. Psychol Med. 2011; 41(7):1449–1460. [PubMed: 20942995]

11. Navari S, Dazzan P. Do antipsychotic drugs affect brain structure? a systematic and critical review of MRI findings. Psychol Med. 2009; 39(11):1763–1777. [PubMed: 19338710]

12. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? a meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev. 2013; 37(8):1680–1691. [PubMed: 23769814]

13. Lieberman JA, Tollefson GD, Charles C, et al. HGDH Study Group. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry. 2005; 62(4):361–370. [PubMed: 15809403]

14. Gur RE, Cowell PE, Latshaw A, et al. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. Arch Gen Psychiatry. 2000; 57(8):761–768. [PubMed: 10920464]

15. Crespo-Facorro B, Kim J, Andreasen NC, O'Leary DS, Magnotta V. Regional frontal abnormalities in schizophrenia: a quantitative gray matter volume and cortical surface size study. Biol Psychiatry. 2000; 48(2):110–119. [PubMed: 10903407]

16. Jung WH, Kim JS, Jang JH, et al. Cortical thickness reduction in individuals at ultra–high-risk for psychosis. Schizophr Bull. 2011; 37(4):839–849. [PubMed: 20026559]

17. Meltzer HY. Update on typical and atypical antipsychotic drugs. Annu Rev Med. 2013; 64:393–406. [PubMed: 23020880]

18. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry. 2011; 68(2):128–137. [PubMed: 21300943]

19. Schultz CC, Fusar-Poli P, Wagner G, et al. Multimodal functional and structural imaging investigations in psychosis research. Eur Arch Psychiatry Clin Neurosci. 2012; 262(suppl 2):S97–S106. [PubMed: 22940744]

20. Andreasen NC, Nopoulos P, Magnotta V, Pierson R, Ziebell S, Ho BC. Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. Biol Psychiatry. 2011; 70(7):672–679. [PubMed: 21784414]

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(1):120–133. [PubMed: 10066998]

22. Strauss ME, McLouth CJ, Barch DM, et al. Temporal stability and moderating effects of age and sex on CNTRaCS Task Performance. Schizophr Bull. 2014; 40(4):835–844. [PubMed: 23817024]

23. Keefe RS, Seidman LJ, Christensen BK, et al. HGDH Research Group. Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. Biol Psychiatry. 2006; 59(2):97–105. [PubMed: 16140282]

24. Iyer RN, Bradberry CW. Serotonin-mediated increase in prefrontal cortex dopamine release: pharmacological characterization. J Pharmacol Exp Ther. 1996; 277(1):40–47. [PubMed: 8613947]

25. Ichikawa J, Ishii H, Bonaccorso S, Fowler WL, O'Laughlin IA, Meltzer HY. 5-HT$_{2A}$ and D$_2$ receptor blockade increases cortical DA release via 5-HT$_{1A}$ receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem. 2001; 76(5):1521–1531. [PubMed: 11238736]

26. Meisenzahl EM, Scheuerecker J, Zipse M, et al. Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation. Eur Arch Psychiatry Clin Neurosci. 2006; 256(8):522–531. [PubMed: 17151834]

27. Honey GD, Bullmore ET, Soni W, Varatheesan M, Williams SC, Sharma T. Differences in frontal cortical activation by a working memory task after substitution of risperidone for typical antipsychotic drugs in patients with schizophrenia. Proc Natl Acad Sci U S A. 1999; 96(23): 13432–13437. [PubMed: 10557338]

28. Jones HM, Brammer MJ, O'Toole M, et al. Cortical effects of quetiapine in first-episode schizophrenia: a preliminary functional magnetic resonance imaging study. Biol Psychiatry. 2004; 56(12):938–942. [PubMed: 15601603]

29. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979; 6(2):65–70.

30. Greenhouse SW, Geisser S. On methods in the analysis of profile data. Psychometrika. 1959; 24:95–112.

31. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis, I: segmentation and surface reconstruction. Neuroimage. 1999; 9(2):179–194. [PubMed: 9931268]

32. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis, II: inflation, flattening, and a surface-based coordinate system. Neuroimage. 1999; 9(2):195–207. [PubMed: 9931269]

33. Hall RC. Global assessment of functioning: a modified scale. Psychosomatics. 1995; 36(3):267–275. [PubMed: 7638314]

34. Lukoff D, Liberman RP, Nuechterlein KH. Symptom monitoring in the rehabilitation of schizophrenic patients. Schizophr Bull. 1986; 12(4):578–602. [PubMed: 3810065]

35. Andreasen, N., et al. The Scale for the Assessment of Negative Symptoms (SANS). Iowa City: University of Iowa; 1983.

36. Andreasen, N. The Scale for the Assessment of Positive Symptoms (SAPS). Iowa City: University of Iowa; 1984.

37. 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(8): 811–822. [PubMed: 19652121]

38. Lesh TA, Niendam TA, Minzenberg MJ, Carter CS. Cognitive control deficits in schizophrenia: mechanisms and meaning. Neuropsychopharmacology. 2011; 36(1):316–338. [PubMed: 20844478]

39. Garver DL, Holcomb JA, Christensen JD. Cerebral cortical gray expansion associated with two second-generation antipsychotics. Biol Psychiatry. 2005; 58(1):62–66. [PubMed: 15992524]

40. Goghari VM, Smith GN, Honer WG, et al. Effects of eight weeks of atypical antipsychotic treatment on middle frontal thickness in drug-naive first-episode psychosis patients. Schizophr Res. 2013; 149(1–3):149–155. [PubMed: 23830856]

41. Dorph-Petersen KA, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a

comparison of haloperidol and olanzapine in macaque monkeys. Neuropsychopharmacology. 2005; 30(9):1649–1661. [PubMed: 15756305]

42. Vernon AC, Natesan S, Crum WR, et al. Contrasting effects of haloperidol and lithium on rodent brain structure: a magnetic resonance imaging study with postmortem confirmation. Biol Psychiatry. 2012; 71(10):855–863. [PubMed: 22244831]

43. Konopaske GT, Dorph-Petersen KA, Pierri JN, Wu Q, Sampson AR, Lewis DA. Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. Neuropsychopharmacology. 2007; 32(6):1216–1223. [PubMed: 17063154]

44. Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. Biol Psychiatry. 1999; 45(1):17–25. [PubMed: 9894571]

45. Miller DD, Andreasen NC, O'Leary DS, et al. Effect of antipsychotics on regional cerebral blood flow measured with positron emission tomography. Neuropsychopharmacology. 1997; 17(4):230–240. [PubMed: 9326747]

46. Carter CS, Bullmore ET, Harrison P. Is there a flame in the brain in psychosis? Biol Psychiatry. 2014; 75(4):258–259. [PubMed: 24439553]

47. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011; 70(7):663–671. [PubMed: 21641581]

48. van Berckel BN, Bossong MG, Boellaard R, et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biol Psychiatry. 2008; 64(9):820–822. [PubMed: 18534557]

49. Pasternak O, Westin CF, Bouix S, et al. Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. J Neurosci. 2012; 32(48):17365–17372. [PubMed: 23197727]

50. Tourjman V, Kouassi É, Koué ME, et al. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. Schizophr Res. 2013; 151(1–3):43–47. [PubMed: 24200418]

51. Meisenzahl EM, Schmitt GJ, Scheuerecker J, Möller HJ. The role of dopamine for the pathophysiology of schizophrenia. Int Rev Psychiatry. 2007; 19(4):337–345. [PubMed: 17671867]

52. Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr Opin Pharmacol. 2011; 11(1):59–67. [PubMed: 21420906]
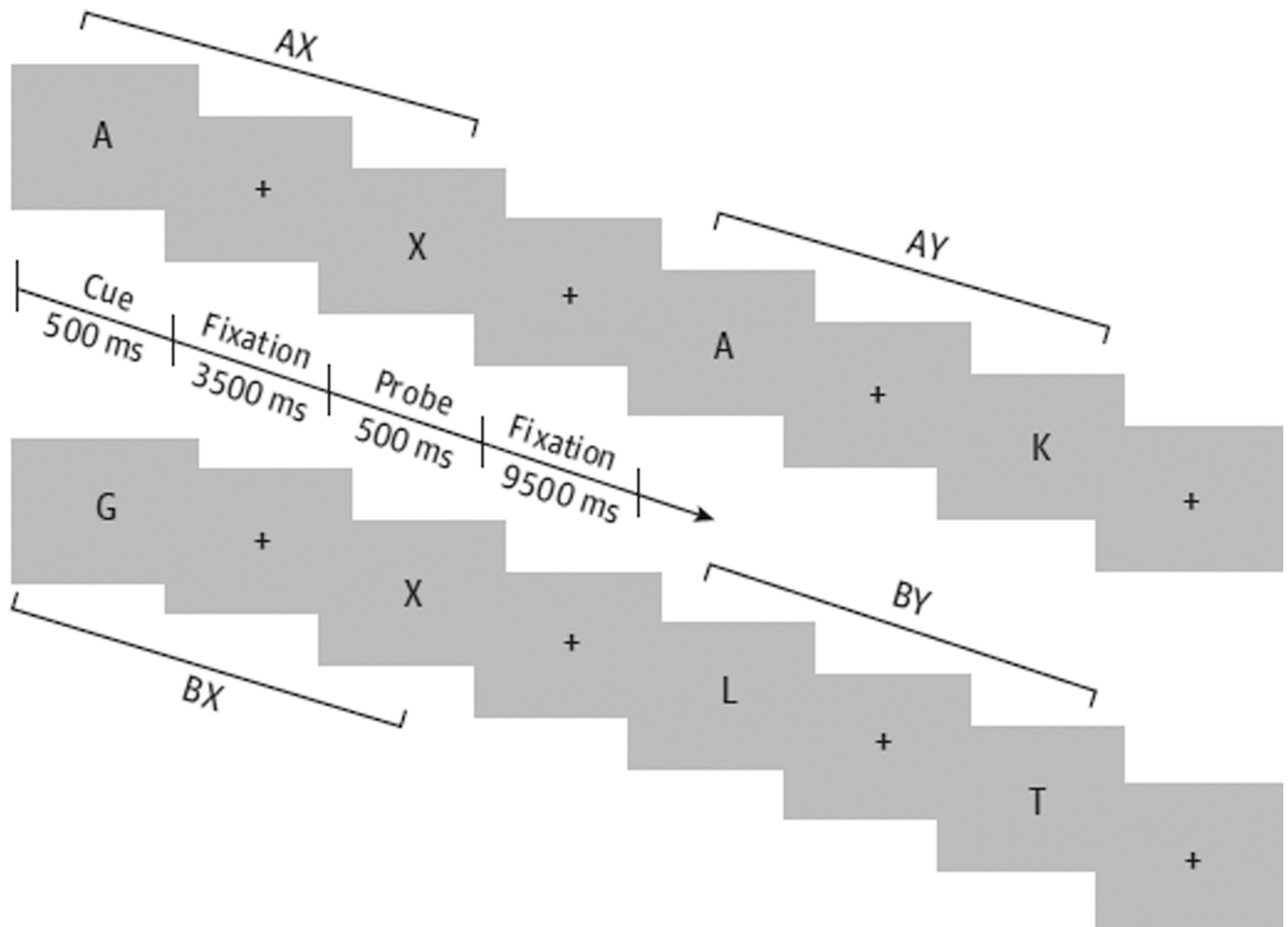
Figure 1. Task Parameters and Timing for the AX Version of the Continuous Performance Task (AX-CPT)

The task was presented using E-prime software (http://www.pstnet.com/eprime.cfm). Presentation of stimuli was pseudorandom, and the first 2 stimuli for each participant were target (*AX*) trials. Correct responses reflect an index-finger button press to an *X* probe following an *A* cue (AX trial). All other cues and probes should be correctly identified as nontargets and be given a middle-finger button press. Target (*AX*) sequence trials are frequent (70.0% of trials) and set up a prepotent tendency to make a target response when the probe letter *X* occurs. Consequently, trials in which the probe *X* is preceded by a non-*A* cue (eg, *BX* trials) are the most difficult (12.5% of trials). *AY* and *BY* trials offer additional control conditions and represent 10.0% and 7.5% of the trials, respectively. The task consisted of 4 runs of 40 trials for a total of 160 trials and a total time of 37 minutes 20 seconds.
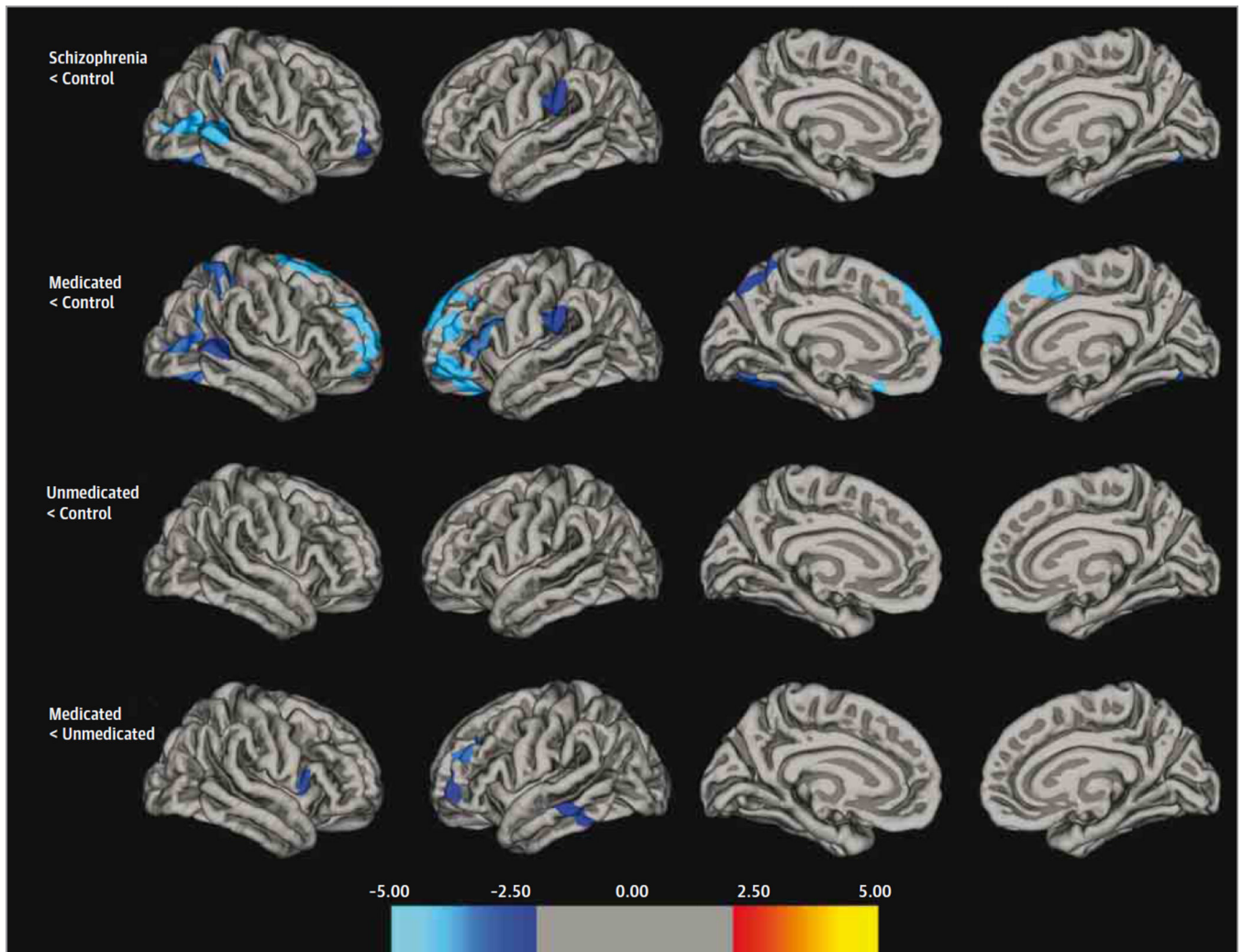
Figure 2. Between-Group Results for Cortical Thickness Analyses Representing Regions That Survived Clusterwise Correction ($P < .05$)

Row 1, Patients with first-episode schizophrenia (schizophrenia) compared with control participants (control). Row 2, Patients who received atypical antipsychotics (medicated) compared with control group. Row 3, Patients who did not receive antipsychotics (unmedicated) compared with control group. Row 4, Medicated compared with unmedicated patient groups. The significance scale reflects the transformation $-\log_{10}$ (P value).
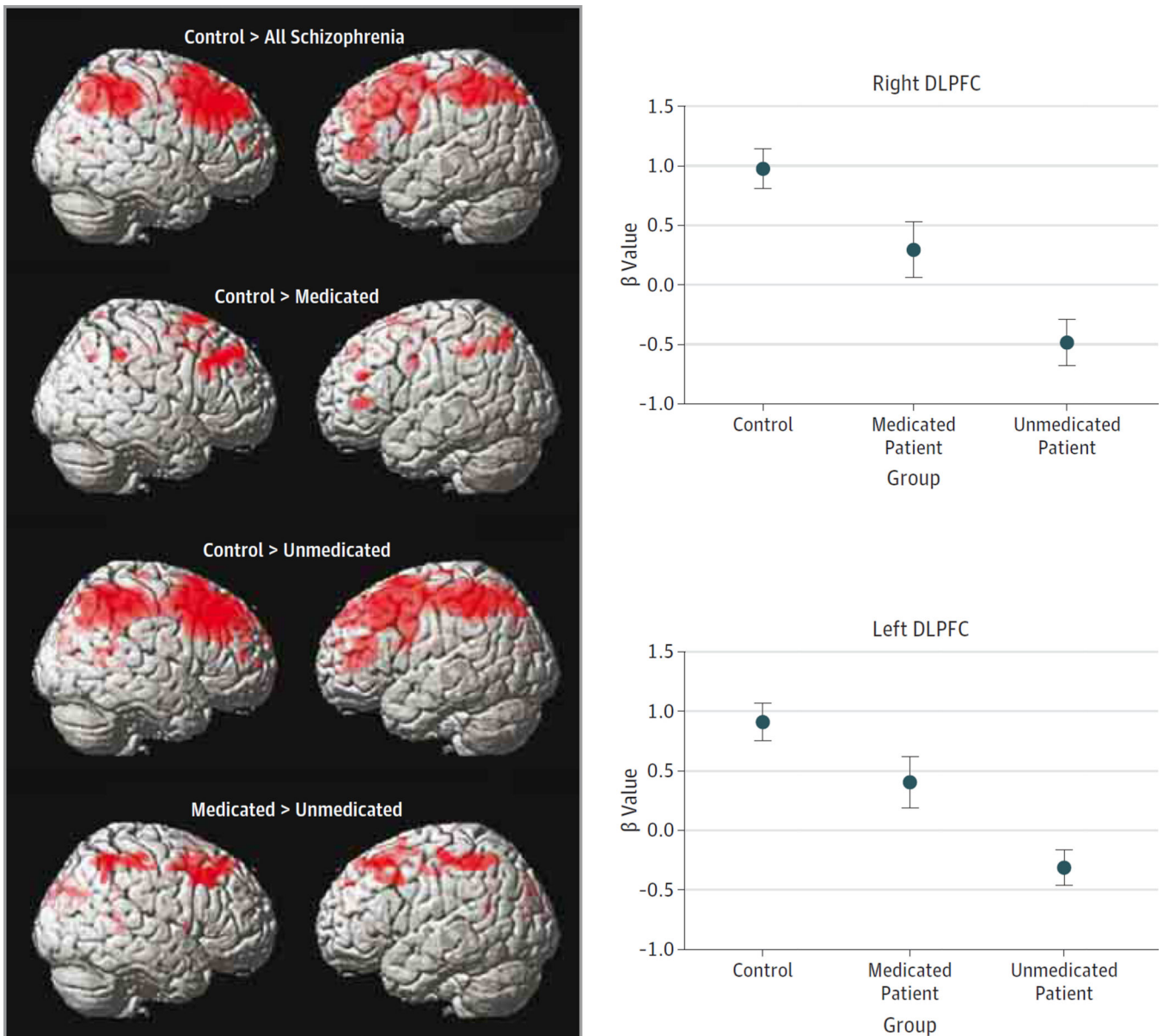
Figure 3. Between-Group Results for the AX Version of the Continuous Performance Task (AX-CPT) Cue *B*−Cue *A* Contrast at an Uncorrected Threshold of *P* < .01 (for Display Purposes) in Healthy Control Participants and Patients With Schizophrenia

Graphs reflect β values (AX-CPT cue *B* − cue *A* contrast) from a priori left and right dorsolateral prefrontal cortex (DLPFC) regions of interest. Error bars reflect SE. Medicated indicates individuals with first-episode schizophrenia who had been treated for a number of weeks with atypical antipsychotics; unmedicated indicates individuals with first-episode schizophrenia who were not treated with antipsychotics.

Table 1

Demographic, Clinical, and Behavioral Data

Measure	Control (n = 37)	Medicated (n = 23)	Unmedicated (n = 22)
	Study Group[a]	Patient Group[b]	
Demographic and clinical data			
Age, y	19.7 (2.6)	20.4 (2.9)	20.2 (3.3)
Male sex, %	73	78	86
Right-handedness, %	89	96	100
Educational level, y			
Participant	13.6 (2.2)	12.7 (1.7)	12.4 (2.2)
Parental	14.5 (2.4)	15.1 (2.1)	14.9 (2.3)
IQ (WASI)	112.6 (11.1)	101.4 (13.5)	102.6 (14.3)
Duration of illness, mean (SD) [IQR], d[c]	NA	153 (86) [147]	210 (127) [215]
SANS score	NA	8.5 (3.3)	8.6 (4.9)
SAPS score	NA	5.9 (3.0)	7.5 (3.5)
BPRS score	NA	42.0 (8.7)	43.1 (11.9)
GAF score	NA	45.7 (9.8)	43.5 (9.0)
Antipsychotic use			
Duration, d	NA	99 (77)	NA
Dose, CPZ, mg	NA	190 (121)	NA
Antipsychotic type at MRI scan, No. of participants			
Risperidone	NA	11	NA
Aripiprazole	NA	4	NA
Olanzapine	NA	5	NA
Quetiapine fumarate	NA	3	NA
History of antipsychotic use in the unmedicated patient group[d]			
Duration, d	NA	NA	32 (26)
Dose, CPZ, mg	NA	NA	156 (88)
Days without medication, No.	NA	NA	66 (54)
Antipsychotic type used in unmedicated patient group, No. of participants[d]			
Risperidone	NA	NA	4
Aripiprazole	NA	NA	1
Behavioral data			
d′-Context score	3.78 (0.66)	3.26 (1.02)	2.58 (0.97)
AX-CPT accuracy, % correct[e]			
AX	0.98 (0.02)	0.96 (0.05)	0.93 (0.09)
AY	0.83 (0.18)	0.79 (0.19)	0.79 (0.25)

Measure	Study Group[a]		
		Patient Group[b]	
	Control (n = 37)	Medicated (n = 23)	Unmedicated (n = 22)
BX	0.93 (0.10)	0.86 (0.13)	0.79 (0.20)
BY	0.99 (0.03)	0.98 (0.04)	0.96 (0.07)
AX-CPT reaction time, ms			
AX	552 (116)	616 (204)	584 (148)
AY	718 (144)	785 (152)	778 (175)
BX	600 (189)	723 (286)	755 (282)
BY	561 (139)	626 (203)	641 (179)

Abbreviations: AX-CPT, AX version of the Continuous Performance Task; BPRS, Brief Psychiatric Rating Scale; CPZ, chlorpromazine equivalent value; GAF, Global Assessment of Functioning Scale; IQR, interquartile range; MRI, magnetic resonance imaging; NA, not applicable; SANS, Schedule for the Assessment of Negative Symptoms; SAPS, Schedule for the Assessment of Positive Symptoms; WASI, Wechsler Abbreviated Scale of Intelligence.

[a] Unless otherwise indicated, data are expressed as mean (SD).

[b] Medicated indicates individuals with first-episode schizophrenia who had been treated for a number of weeks with atypical antipsychotics; unmedicated indicates individuals with first-episode schizophrenia who were not treated with antipsychotics.

[c] Defined as the number of days from the first-threshold psychotic symptom presentation, which was based on all available information (ie, parent/participant report, medical records), to the MRI scan.

[d] Represents antipsychotic treatment history for 5 participants in the unmedicated patient group who discontinued treatment a minimum of 1 month before the MRI scan. The other 17 patients in the unmedicated group were antipsychotic naive.

[e] Arcsine transformed error rates were computed for statistical tests to compensate for data nonnormality.

Table 2

Regions of Significant Cortical Thinning

Region[a]	Maximum Vertex Difference, $-\log_{10}(P$ Value$)$	Size, mm²	P Value for CWP
Both Patient Groups < Control Group			
Right middle temporal	−4.517	1417.65	<.001
Right superior parietal	−4.234	831.49	.001
Right lateral occipital	−4.935	786.23	.002
Left supramarginal	−4.423	492.09	.03
Right rostral middle frontal	−3.962	494.08	.03
Medicated Patient Group < Control Group			
Left rostral middle frontal	−6.097	2237.49	<.001
Right superior frontal	−4.248	1313.58	<.001
Right rostral middle frontal	−4.137	2492.14	<.001
Left lateral orbitofrontal	−4.116	1475.42	<.001
Left pars opercularis	−3.703	812.06	<.001
Right lateral occipital	−3.284	860.03	.001
Right lateral occipital	−5.428	811.66	.002
Right superior parietal	−4.453	802.03	.002
Left fusiform	−3.394	670.54	.004
Right superior temporal	−5.856	543.02	.02
Left supramarginal	−3.296	442.47	.047
Left precuneus	−2.781	442.29	.047
Medicated Patient Group < Unmedicated Patient Group			
Left rostral middle frontal	−4.009	508.31	.02
Left rostral middle frontal	−3.793	788.92	.001
Left middle temporal	−3.738	443.82	.047
Right pars opercularis	−3.07	511.29	.03

Abbreviation: CWP, clusterwise probability.

[a]Indicates CWP of $P < .05$. No significant clusters were observed for the control group compared with both patient groups, the control group compared with the medicated patient group (individuals with first-episode schizophrenia who had been treated for a number of weeks with atypical antipsychotics), the unmedicated patient group (individuals with first-episode schizophrenia who were not treated with antipsychotics) compared with the control group, the control group compared with the unmedicated patient group, or the unmedicated compared with the medicated patient groups.