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Modulation of limbic circuitry predicts treatment response to antipsychotic medication: a functional imaging study in schizophrenia

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Abstract

The regional neuronal changes taking place in the early and late stages of antipsychotic treatment are still not well characterized in humans. In addition, it is not known whether these regional changes are predictive or correlated with treatment response. Using PET with ^{15}O, we evaluated the time course of regional cerebral blood flow (rCBF) patterns generated by a first (haloperidol) and a second (olanzapine) generation antipsychotic drug (APD) in patients with schizophrenia during a 6 week treatment trial.

Patients were initially scanned after withdrawal of all psychotropic medication (two weeks), and then blindly randomized to treatment with haloperidol (n=12) or olanzapine (n=17) for a period of 6 weeks. Patients were scanned again after 1 and 6 weeks of treatment. All assessments, including scanning sessions, were obtained in a double-blind manner.

As hypothesized, we observed rCBF changes that were common to both drugs, implicating cortico-subcortical and limbic neuronal networks in antipsychotic action. In addition, in these regions, some patterns seen at week 1 and 6 were distinctive, indexing neuronal changes related to an early (ventral striatum, hippocampus) and consolidated [anterior cingulate/medial frontal cortex (ACC/MFC)] stage of drug response. Finally, both after 1 and 6 weeks of treatment, we observe differential patterns of rCBF activation between good and poor responders. After one week of treatment, greater rCBF increase in ventral striatum and greater decrease in hippocampus were associated with good response.

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Disclosure/Conflict of Interest

Adrienne Lahti, Martin Weiler, Henry Holcomb and Karen Cropsey have no financial interests to disclose. Carol Tamminga serves as a consultant and/ or advisor for Acadia Pharmacueticals, Intracellular Therapies, Lilly Pharmaceutical, Alexza Pharmaceuticals, Lundbeck, Inc.

Keywords

Schizophrenia; PET; rCBF; haloperidol; olanzapine

Introduction

Antipsychotic drugs (APDs) act primarily to relieve positive symptoms of schizophrenia (hallucinations, delusions) with little or no effect on primary negative and cognitive symptoms. It has been recently confirmed that, with the exception of clozapine, first- and second generation APDs alleviate positive symptoms to the same extent (Lieberman et al. 2005; McEvoy et al. 2006). However, treatment response to APD in schizophrenia is not homogeneous. Only 5%–10% of patients experience a full recovery in response to treatment and about 30% of patients are “treatment resistant” despite adequate treatment (Harrow et al. 1997). Consequently, clinicians are faced with difficult decisions when managing their patients’ treatment including how long an adequate trial of APD should last, when is the correct dosing achieved, is the patient compliant with treatment, and will the patient experience a relapse if a switch to another APD is initiated. Thus, several weeks may typically elapse before a decision to switch to another APD is made, leaving the patient poorly treated and vulnerable to hospitalization. We lack biomarkers of treatment response to guide dosing and duration of treatment questions.

There has been considerable debate regarding the time course of response to antipsychotic treatment. According to many descriptions (Gelder 2000; Grace 1995; Marder 2000), there is a delay of 2 to 3 weeks prior to APD response, a view that has been strongly challenged by recent meta-analyses of clinical trials. An analysis of 42 published clinical trials found the greatest improvement in positive symptoms in the first and second week of treatment with a cumulative improvement over time thereafter (Agid et al. 2003). Another analysis of 21 trials found a linear response pattern up to 28 days of treatment (van den Oord et al. 2008). The regional neuronal changes taking place across the time course of antipsychotic treatment are still not well characterized. Further, it is not known whether these regional changes are predictive of treatment response. Understanding the mechanisms underlying drug response could enhance the development of more effective and selectively targeted antipsychotic agents.

Using PET with ^{15}O, we evaluated the time course of regional cerebral blood flow (rCBF) patterns generated acutely and subacutely in a 6 week trial using a first (haloperidol) and a second (olanzapine) generation APD in patients with schizophrenia. We hypothesized that regions where the two drugs show similar rCBF changes would more robustly identify regions involved in antipsychotic action, as identified by regions where rCBF and symptom reduction are correlated. Based on our previous work (Lahti et al. 2004; Lahti et al. 2003; Lahti et al. 2006; Lahti et al. 2005), we hypothesized that these regions would include regions in the limbic circuit, such as the ventral striatum, the ACC, and the hippocampus. In addition, based on their known differences in preclinical profiles (Chiodo and Bunney 1983; White and Wang 1983), we hypothesized that the patterns of rCBF activation between the two drugs would be most different in the striatum, where haloperidol would increase rCBF

potently throughout the dorsal and ventral striatum, whereas rCBF increase with olanzapine would be restricted to the ventral striatum. We further hypothesized that some of the patterns seen after acute (1 week) and subacute (6 weeks) treatment would be distinctive, indexing neuronal changes related to an early versus consolidated stage of drug response. Finally we hypothesized that treatment response would correlate with consistent patterns of rCBF changes at acute and subacute treatment.

Methods

Volunteers

Medically healthy persons with schizophrenia were recruited from the Residential Research Unit of the Maryland Psychiatric Research Center (MPRC) in Baltimore, MD, to participate in this study. Thirty-seven agreed to participate and signed consent. Each underwent a Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al. 1987) at hospital admission. Two research psychiatrists reached a consensus diagnosis of schizophrenia based on the clinical interview plus all other sources of data utilizing DSM IV criteria.

Informed consent

Schizophrenia volunteers were fully informed about the nature of the protocol and after being informed, each gave informed consent. Only patients who were competent and clinically judged to be capable of understanding and appreciating the risks involved in this study were selected to participate. Separate people including both the Principal Investigator and non-investigator clinicians presented the nature of the protocol to the volunteers on several occasions and assessed their wiliness to be involved. Family members or caregivers were involved in the information process when available. A patient’s right advocate met with every potential patient upon admission and an ombudsman monitored subjects' understanding of the study and willingness to participate through the study. Prior to signing consent, each patient completed an Evaluation to Sign Consent Form, a form probing the patient’s understanding of some important aspects of the protocol. Subjects remained in-patients for the total length of the study. Patients were closely monitored for increased symptoms and side effects. When clinically necessary, the protocol was interrupted and an individual was restarted on antipsychotic medication. All study personnel completed formal training in the protection of human subjects as required by the University Of Maryland School Of Medicine and the NIH. The University of Maryland IRB approved this project.

Study design

Medication withdrawal and collection of the OFF medication rCBF scans—All schizophrenia volunteers were withdrawn from all psychotropic medications for a period of 2 weeks prior to scanning. All other aspects of inpatient milieu treatment were continued during this project. Clinical monitoring was continuously done and intervention (including study termination) was possible based on clinical judgment of adverse behavioral changes requiring treatment. The two-week medication free period was designed to allow for the disappearance of antipsychotic drugs from central D2 receptors (Tamminga 1993). Symptoms of schizophrenia were assessed at baseline and at the time of each scanning session utilizing the 18-item version of the Brief Psychiatric Rating Scale (BPRS) (1–7

scale) (Overall and Gorham 1962). We evaluated the BPRS Total as well as its Psychosis subscale (items: conceptual disorganization, hallucinatory behavior, and unusual thought content) scores (Hedlund and Vieweg 1980). Of the 37 subjects who signed the consent, 5 dropped out during the withdrawal protocol. Two dropped out because of symptom exacerbation and three because they did not want to continue with the study. These subjects were remedicated and quickly returned to their pre-study status. At the end of the medication withdrawal, thirty-two subjects completed a baseline medication-free scanning session (Baseline or OFF-drug scanning session). We have previously reported on the patterns of correlation between rCBF and symptoms in two independent cohorts of drug free patients with schizophrenia, one of which included the present group of patients (Lahti et al. 2006).

Randomization—Patients who completed the OFF drug scan were blindly randomized to one of four groups: (1) haloperidol fixed dose (10 mg) for 6 days followed by haloperidol optimal dose (range 10–20mg) for 5 weeks (HAL-HAL), (2) olanzapine fixed dose (12.5 mg) for 6 days followed by olanzapine optimal dose (range 12.5 to 25 mg) for 5 weeks (OLZ-OLZ) (3) placebo for 6 days followed by haloperidol (optimal dose) for 5 weeks (PBO-HAL) and (4) placebo for 6 days followed by olanzapine (optimal dose) for 5 weeks (PBO-OLZ). Among the patients randomized to haloperidol (n=14), 10 were randomized to HAL-HAL and 4 to PBO-HAL. Among the patients randomized to olanzapine (n=18), 14 were randomized to OLZ-OLZ and 4 to PBO-OLZ.

The purpose of the one-week PBO lead-in period was to allow for a placebo-controlled evaluation of the ability to predict treatment response using the Week 1 rCBF patterns. Medications were prepared in similar looking capsules by the hospital pharmacist. Medication adjustments were made blindly by the treated psychiatrists in increment of 5 mg for haloperidol and 6 mg for olanzapine. Patients did not receive anticholinergic medication unless their clinical condition required it. A rating of motor symptoms with the MPRC Involuntary Movement Scale (IMS) preceded the use of anticholinergic medication.

rCBF imaging protocol—Patients were scanned at baseline while off-drug, after 6 days (thereafter referred as Week 1 scanning session) and after 6 weeks (Week 6 scanning session) of treatment. Patients were scanned during a rest condition (2 scans) where the subjects were instructed to lie quietly with eyes open. Concurrently with each scanning session, mental status was assessed using the BPRS. All assessments, including those done during the imaging sessions, were obtained in a double-blind manner.

Drop out—In the HAL-HAL group, two subjects dropped out before completing the Week 1 scanning session. One dropped out because of psychosis exacerbation and the other one was a voluntary withdrawal.

In the OLZ-OLZ group, one subject dropped out after completing the Week 1 scanning session as a voluntary withdrawal. Thus, the analyses presented in this paper reflect imaging data on 29 subjects; 12 in the haloperidol group (HAL-HAL n=8, PBO-HAL n=4) and 17 in the olanzapine group (OLZ-OLZ n=13 and PBO-OLZ n=4).

The total schizophrenia volunteer group included 22 male and 7 female persons. Prior to the medication withdrawal, 3 subjects in the haloperidol group had been treated with either a first or a combination of a first and second APD and 8 with a second generation APD. In the olanzapine group, 2 had been treated with a combination of a first and a second generation APD and 10 with a second generation APD. One patient in the haloperidol group and 3 in the olanzapine group had been treated with clozapine prior to drug withdrawal. However, all four had been treated with daily dosage of 300 mg or less. None of the patients were treated with a long-acting APD depot preparation.

PET /^{15}O imaging

Subjects were scanned on the GE Advanced 3 D PET system located at the PET Center of the Johns Hopkins Hospital. The PET acquires 30 parallel slices with a center-to-center separation of 5 mm, an average transaxial resolution of 5.0 mm full width at half maximum (FWHM) and an average resolution of 6.0 mm FWHM, measured in the center of the field-of-view. For each subject, a single 10-minute transmission scan was acquired for attenuation correction using a 10mCi68Ge rotating pin source. The bolus $H_2{}^{15}O$ method (Raichle et al. 1983) was used without arterial blood sampling. Approximately 12 mCi $H_2{}^{15}O$ was administered with each scan. Seven minutes elapsed between scans except where specified. Scan acquisition began 15 seconds after dose delivery. PET data were acquired for 90 seconds. A thermoplastic mask, custom made for each subject, was used to minimize head movement and to align head position for subsequent scanning sessions.

Image analysis

The PET blood flow images were analyzed using the statistical parametric mapping (SPM 2) software (Friston et al. 1996). The scans from each subject were realigned using the first as a reference. Following realignment all images were transformed into the stereotaxic space of the Montreal Neurological Institute (MNI). Prior to generating the SPM $_{(z)}$ map the data were smoothed using a 12-mm Gaussian kernel. Blood flow values were scaled using the ratio adjustment method.

Data analysis

Demographic measures of age, gender, race, and length of illness were compared between the haloperidol and olanzapine drug groups by t-test and chi-square analyses. The BPRS data were analyzed using paired t-test.

The following image analyzes were performed:

1. **Time course analysis** To evaluate the time course of rCBF changes induced by each drug, we contrasted the week 1 scans of patients on active medication (haloperidol: n=8; olanzapine: n=13) with their baseline (off-drug) scans (Week 1 drug effects) and the week 6 scans of all patients with their baseline scans (Week 6 drug effects) using SPM2. Because treatment response has been shown to plateau after 4 weeks (van den Oord et al. 2008), all patients whether or not they had received placebo for 6 days should have reached optimal response by week 6. For hypothesized regions that showed significant rCBF changes, we calculated the

coefficient of correlation between rCBF changes from baseline to week 6 (sampled in the maxima of the identified cluster using a 3×3×3 pixel ROI) and the BPRS Total and Psychosis change scores for the same period.

2. **Conjunction analysis** Similarities of rCBF patterns between the two drugs were assessed between Week 6 and baseline using a conjunction analysis (Price and Friston 1997).

3. **Contrast analysis** We contrasted the rCBF changes between week 6 and baseline between each drug [i.e. Haloperidol (Week 6 minus baseline) vs. olanzapine (Week 6 minus baseline)].

4. **Good vs. poor treatment responders** SPM analysis. To identify patterns of rCBF change related to treatment response using a whole brain approach, we contrasted the rCBF changes between the treatment good (GR) and poor (PR) responders (i.e. haloperidol GR vs. haloperidol PR and olanzapine GR vs. olanzapine PR) for the following epochs: (1) from baseline to week 6 and (2) from baseline to week 1. Good treatment response was defined as a >10% improvement on the BPRS Psychosis score at the final 6-week assessment. While a 15 to 30% reduction in BPRS is traditionally used as an index of good response (Leucht et al. 2005), we used a less stringent threshold because the clinical status of the patients who were taken-off their medications for only 2 weeks was likely different than a relapsed state. The subsequent region of interest analyses were performed using ANOVA.

For the SPM2 analyses, the primary criteria for statistical significance for hypothesized regions was set at p=0.001, uncorrected. For all other brain regions, only clusters of connected voxels above a threshold were tested for significance by means of spatial extent statistic which was set at p=0.05, after correcting for multiple comparisons (Friston et al. 1996).

RESULTS

CLINICAL EFFECTS

There were no differences between the patients in the haloperidol and the olanzapine groups in terms of age (38.3 ± 12.2 vs. 36.1 ± 10.5 years), length of illness (15.3 ± 14.1 vs. 11.3 ± 9.6 years), gender (male/female) (10/2 vs. 12/5) and race ratios (Caucasian/African American) (5/7 vs. 3/14). Overall, patients in the haloperidol group experienced a significantly improvement, as measured on the BPRS Psychosis subscale ($t=2.26$, $p<0.05$) at the final 6 week evaluation (Table 1). Improvement in the olanzapine group was significant at a trend level as measured on the BPRS Total ($t=-2.01$, $p<0.1$) and the BPRS Psychosis subscales ($t=-1.56$, $p<0.2$). Improvement over the first week of treatment did not reach significance for either group. Haloperidol patients were treated with a mean dose of 10.4 ± 3.3 mg/day (range: 5 to 15 mg/day) and the olanzapine patients with a mean dose of 15.9 ± 4.8 mg/day (range: 12.5 to 25 mg/day). Only 2 patients (one treated with haloperidol and one treated with olanzapine) experienced extrapyramidal symptoms and were treated with benztropine 2mg.

TIME COURSE ANALYSIS

Acute APD Effects

Haloperidol: Week1 vs. OFF-drug and OFF-drug vs. Week 1 group average images were contrasted (Table 2 & Figure 1)

Where haloperidol increases rCBF acutely (Figure 1, top panels): there was a significant cluster of rCBF activation encompassing the ventral striatum and the putamen, bilaterally. The left cluster extended into the anterior part of the thalamus. There was a significant cluster in the superior portion of the left sensorimotor cortex.

Where haloperidol decreases rCBF, acutely (Figure 1, bottom panels): There was a significant cluster of rCBF reduction in the right middle temporal cortex. There were significant maxima of rCBF reduction in the right medial temporal cortex, in the ACC, in the midbrain and in the cerebellum, bilaterally.

Olanzapine: Week1 vs. OFF-drug and OFF-drug vs. Week 1 group average images were contrasted (Table 2 & Figure 2)

Where olanzapine increases rCBF, acutely (Figure 2, top panels): there were significant clusters of rCBF activation in the inferior frontal and inferior parietal cortices, both on the right. There was one significant maxima of activation in the left caudate/ventral striatum.

Where olanzapine decreases rCBF, acutely (Figure 2, bottom panels): there was a significant cluster of rCBF deactivation in the left posterior thalamus. In addition, there were significant maxima in the right thalamus, the left medial temporal cortex and the ACC.

Subacute APD Effects

Haloperidol: Week6 vs. OFF-drug and OFF-drug vs. Week 6 (Table 3 and Figure 3) group average images were contrasted. Due to the large size of the clusters and in order to better discriminate the regions showing rCBF changes the data in the tables are reported at a threshold of T>3.75, 45 voxels.

Where haloperidol increases rCBF, subacutely (Figure 3, top panels): There was a significant cluster of rCBF activation encompassing the ventral and dorsal striatum, bilaterally. In addition, significant clusters of activation were also identified in the left thalamus and the left post central cortex and the inferior parietal cortex, bilaterally. Inspection of the data at a lower threshold (t=3.11, p=0.001) indicated that the activation of the thalamus was bilateral.

Where haloperidol decreases rCBF. subacutely (Figure 3, bottom panels): There was a large reduction in rCBF in the ACC/medial frontal cortex embracing 1275 suprathreshold (T=3.11) voxels. In addition, there was a large rCBF reduction encompassing the temporal pole, part of the inferior frontal cortex and the insula, bilaterally. There were significant clusters of deactivation in the inferior and middle temporal cortex, both on the right, the superior frontal cortex on the right, the inferior parietal cortex on the right and in the cerebellum, bilaterally.

Olanzapine: Week 6 vs. OFF-drug and OFF-drug vs. Week 6 group average images were contrasted (Table 4, Figure 4)

Where olanzpaine increases rCBF subacutely (Figure 4, top panels): There were significant clusters of rCBF activation in several cortical regions including a large cluster encompassing most of the inferior parietal cortex, the superior parietal cortex, the middle temporal cortex, all three on the right, the left superior parietal cortex and the left middle/ inferior frontal cortex. In addition there was a significant maxima identified in the ventral striatum, on the right.

Where olanzapine decreases rCBF subacutely (Figure 4, bottom panels): There was a large reduction in rCBF in the ACC/medial frontal cortex embracing 632 suprathreshold (T=3.11) voxels. In addition, there were significant clusters of deactivation in the thalamus and the cerebellum, both on the right. There were significant maximal identified in the thalamus and the midbrain, both on the left.

Correlations between rCBF changes over 6 weeks and clinical improvement (Table 5)—With haloperidol, the rCBF decrease in ACC and the rCBF increase in the thalamus were correlated, albeit at a trend level in the thalamus, with clinical improvement, as measured with the BPRS Total or Psychosis change scores. For olanzapine, the correlation between rCBF decrease in ACC and clinical improvement was medium in size and did not reach significance.

CONJUNCTION ANALYSIS

Overlap of activation between haloperidol and olanzapine (Table 6)—There were overlap of activation between haloperidol and olanzapine in the left pre- and post-central cortex and in the right ventral striatum/ caudate.

Overlap of deactivation between haloperidol and olanzapine (Table 6)—There was overlap of deactivation between haloperidol and olanzapine in the ACC/ medial frontal cortex.

CONTRAST ANALYSIS

Regions more activated with haloperidol vs. olanzapine (Table 6)—Regions that were more activated with haloperidol vs. olanzapine included the putamen and the thalamus, bilaterally, and the left post-central cortex.

Regions more activated with olanzapine vs. haloperidol (Table 6)—Several cortical regions were significantly more activated with olanzapine vs. haloperidol: the right orbitofrontal cortex, the right superior and middle frontal cortex, the inferior frontal cortex, bilaterally, the right superior and inferior parietal cortex and the right superior temporal cortex.

GOOD (GR) VS. POOR (PR) TREATMENT RESPONDERS

GR vs. PR: contrast between pattern of changes from baseline to week 6

Haloperidol: After 6 weeks of treatment, GR had significantly more activation in the right ventral striatum and left thalamus and less activation in the left hippocampus/ parahippocampus compared to the PR (Table 7). Using a less stringent threshold (t=2.41, p=0.01), GR also had significantly less activation in the ACC compared to PR.

Olanzapine: Compared to PR, GR had significantly more activation in the ventral striatum, bilaterally, and in the cerebellum and less activation in several cortical areas, including the sensorimotor, middle and medial frontal, superior parietal cortices as well as the ACC (Table 8).

GR vs. PR: contrast between pattern of changes from baseline to week 1

Haloperidol: After one week of treatment, GR had significantly more activation in the right caudate/ventral striatum and less activation in the left hippocampus compared to PR (Table 7). Olanzapine. In contrast to PR, GR has significantly more activation in the right caudate/ ventral striatum and the ACC and less activation in the left hippocampus and the left inferior frontal cortex (Table 8).

GR vs. PR at Week 1: region of interest analysis in the ventral striatum and hippocampus—RCBF values sampled in the right ventral striatum and left hippocampus at baseline (off meds) and at Week 1 were contrasted between the haloperidol GR and PR, the olanzapine GR and PR and the placebo patients based on their response (GR or PR) to either drug at the end of the study. In the presence of a significant main effect in the overall ANOVA [$F(5, 26)=6.00$; $p<0.002$], pairwise comparisons of mean rCBF within each drug group revealed that compared to PR, GR had a significantly greater increases in rCBF in the ventral striatum (Olanz, $p<0.10$, Hal, $p<0.01$) and a significant decrease in rCBF in the hippocampus (Olanz, $p<0.005$, Hal $p<0.001$) (GR, n= 4 Olanz, n=3 Hal; PR, n=7 Olanz, n=5 Hal) after 1 week of treatment (see Fig. 5). In the placebo group, there were no differences between the patients who experienced a good response to treatment (n=4) once they were treated with haloperidol or olanzapine vs. those who did not (n=4). The functional changes in ventral striatum and hippocampus at Week 1 were inversely correlated ($r=-0.62$, $p<0.01$). Six out of 7 good responders and only 1 out of 12 poor responders had both an increase in ventral striatum and a decrease in hippocampal rCBF at Week 1. Those proportions were significantly different (Yates' chi-square=8.29, df=1; p=0.004).

Discussion

Using PET with ^{15}O, we evaluated the time course of regional cerebral blood flow (rCBF) patterns generated by a first (haloperidol) and a second (olanzapine) generation APD in patients with schizophrenia during a 6 week treatment trial. As hypothesized, we observed rCBF changes that were common to both drugs, implicating cortico-subcortical and limbic neuronal networks in antipsychotic action. In addition, in these regions, some patterns seen at week 1 and 6 were distinctive, indexing neuronal changes related to an early (ventral striatum, hippocampus) and consolidated (ACC/MFC) stage of drug response. Finally, in

these regions, we observe differential patterns of rCBF activation between good and poor responders both at week 1 and 6. At week 1, greater rCBF increase in ventral striatal and greater decrease in hippocampus was associated with good response.

Regions implicated in antipsychotic action

Subcortical regions—With both drugs, rCBF activation was observed in the striatum after 1 and 6 weeks of treatment. However, while haloperidol activated both the ventral and dorsal striatum, olanzapine only activated the ventral part of the striatum and the ventral part of the caudate nucleus. In addition, both at week 1 and 6, good responders in contrast to poor responders in either treatment group showed greater rCBF increase in ventral striatal.

The functional differences seen between the drugs in the activation of the dorsal striatum may account for the well-known clinical difference between the two drugs in the emergence of motor side effects (Sikich et al. 2004). In preclinical studies, olanzapine, in contrast to haloperidol, demonstrates selective electrophysiological action on dopamine neurons, inducing depolarizaion blockade in the mesolimbic (A10) but not nigrostriatal (A9) cells (Chiodo and Bunney 1983; White and Wang 1983). Consistent with this limbic selectivity, olanzapine stimulates immediate early gene (IEG) expression in mesolimbic (ventral striatum, ACC and medial PFC) but not nigrostriatal (dorsal striatum) projections fields (Robertson and Fibiger 1992; Robertson and Fibiger 1996). Thus our finding of selective functional activation of the ventral striatum with olanzapine is consistent with these preclinical data. We have observed the same pattern of ventral, not dorsal, rCBF activation with clozapine, another APD with so-called limbic selectivity (Lahti et al. 2003). A [^{18}F] fallypride PET study comparing the occupancy of striatal D2/D3 dopamine receptors in patients treated with olanzapine or haloperidol fail to find significant differences between the drugs in the degree of receptor occupancy in the dorsal, ventral striatum and medial thalamus (Kessler et al. 2005). Taken together these data suggest that the striatal neuronal response measured by this functional study cannot just be understood in terms of DA D2 receptor binding.

Both drugs had opposite functional effect in the thalamus: increased activation with haloperidol and decreased activation with olanzapine. We have observed similar functional patterns following the administration of a single dose of each of these drugs in subjects with schizophrenia (Lahti et al. 2005). The activation seen with haloperidol in putamen, thalamus and motor cortex is consistent with activation of a circuit postulated to relate to motor function (Alexander et al. 1990). With acute olanzapine administration, decrease thalamic rCBF correlated with sedation, an effect we hypothesized was associated with its histaminergic properties.

Limbic cortex—With each drug, after 6 weeks of treatment, we observed the same pattern of large rCBF decrease in the ACC/medial frontal cortex, a decrease that was correlated with clinical improvement. This stands in contrast to the limited changes observed in the same region after one week on treatment. A decrease in a similar region of the ACC/medial frontal has been reported after risperidone treatment (Ngan et al. 2002) and found to correlate with clinical improvement. Also consistent with these data are the reports of

increased ACC metabolism following a 3 to 4 week antipsychotic medication withdrawal (Holcomb et al. 1996; Miller et al. 1997). Here we found that the ACC/medial frontal neuronal response, while already established during the first week of treatment, grows to encompass a large area of the medial frontal cortex after that. It is thus reasonable to suggest that this ACC/MFC response appears to index a delayed neuronal response to APDs. This region of the ACC/MFC encompasses the anterior region of the rostral ACC (Amodio and Frith 2006). The anterior rostral ACC, located between the orbital MFC and the posterior rostral ACC/MFC, is thus strategically located to foster interactions between the emotional and cognitive functions subserved by these regions (Bush et al. 2000; Greicius et al. 2003).

Our previous imaging studies have reported rCBF decrease in the hippocampus in association with either haloperidol or clozapine treatment (Lahti et al. 2003). In addition, we have reported that, compared to normal volunteers, drug-free schizophrenia patients show increased rCBF in the hippocampus, a difference that “normalize” after haloperidol treatment (Medoff et al. 2001). Liddle (Liddle et al. 2000) reported that the magnitude of metabolism decrease in left hippocampus after a single dose of risperidone predicted subsequent reduction in delusions and hallucinations.

In this study, with each drug, we observed a significant rCBF decrease in the medial temporal cortex after 1 week of treatment. At week 6, a significant hippocampal rCBF decrease was observed in the haloperidol group while in the olanzapine group, the decrease was only observed at a liberal threshold ($p<0.05$). In addition, at week 1, good responders in contrast to poor responders in either treatment group showed greater rCBF decrease in the hippocampus. Thus, consistent with Liddle’s study (Liddle et al. 2000), we found that the response in the hippocampus seems to index an early neuronal response to APDs.

Neocortex—With haloperidol the major pattern of functional changes seen in the cortex was that of rCBF deactivation. On the other hand, the pattern seen with olanzapine was that of cortical activation. These opposite cortical patterns were observed in another group of drug free patients scanned following single dose administration of either haloperidol or olanzapine (Lahti et al. 2005). One might speculate about the therapeutic implication and the mechanism(s) by which such a cortical activation could be achieved with olanzapine. While the effect of olanzapine in treating positive symptoms is qualitatively similar to that of first generation drugs, its spectrum of effects may be broader (Davis and Chen 2001). In the CATIE study, olanzapine treatment was associated with the lowest discontinuation rates in comparison to several 2nd generation APD and fluphenazine. In addition, in a group of first episode patients, olanzapine treatment (Keefe et al. 2004) was asociated with a greater improvement on task of information processing and speed compared to low dose haloperidol.

It is possible that olanzapine action on other neurotransmitter systems is responsible for its functional effect on cortical regions. Olanzapine induces immediate early gene expression in the medial prefrontal cortex, an effect not seen with haloperidol. Several laboratories have shown that olanzapine increases dopamine release in the prefrontal cortex, an action possibly related to its serotonin and/or noradrenergic receptor affinity (Moghaddam and Bunney 1999; Pehek 1996; Rollema et al. 1997; Youngren et al. 1999). In addition,

olanzapine can antagonize the effects of NMDA antagonists in a variety of experimental designs, including the reversal of PCP-induced deficits in prepulse inhibition (Bakshi and Geyer 1995). 6-hydroxydopamine lesions of the VTA that caused dystrophic changes in cortical projection neurons are reversed with olanzapine, but not haloperidol (Wang and Deutch 2008), suggesting that olanzapine can exert a trophic effect on lesioned cortical neurons. Speculatively, the functional activation seen in cortical regions might suggest a mechanism by which olanzapine, but not haloperidol, prevents progressive cortical contraction in first-episode schizophrenia (Lieberman et al. 2005). In that study, less improvement in cognitive function after 12 weeks of haloperidol treatment was associated with greater decrease in gray matter volumes, an effect not seen with olanzapine. In our study, good response in the olanzapine group was associated with less cortical activation during a resting state. We have reported that, during cognitive task, in the olanzapine, but not in the haloperidol group, rCBF in the ACC/medial frontal cortex was significantly and positively correlated with improvement in processing speed (Lahti 2005).

Week 1 rCBF patterns in GR vs. PR

These preliminary data point to important drug-induced regional modulation differences in the ventral striatum and hippocampus between PR and GR. Because these patterns were not seen in the placebo group, they cannot be explained by subjective reaction to treatment. These patterns of rCBF changes may represent important biomarkers of treatment response. These data are in agreement with those of Buchsbaum (Buchsbaum et al. 2007; Buchsbaum et al. 1992) who found that lower pretreatment and greater increase in striatal metabolic rate with treatment were linked to better clinical response to APDs. Likewise, Cohen (Cohen et al. 1998) found that high pretreatment basal ganglia rates predicted poor treatment response to APDs. Treatment resistant subjects who became responders to clozapine showed higher basal ganglia perfusion compared to those who did not (Rodriguez et al. 1997). As previously discussed, Liddle (Liddle, et al., 2000) reported that the metabolism decrease in hippocampus after a single dose of risperidone predicted subsequent reduction in delusions and hallucinations.

Implication for antipsychotic action

These data point to an important role of the ventral striatum in antipsychotic action: increased ventral striatum activity in the early stage of treatment is predictive of treatment response. Imaging studies have shown that, compared to normal volunteers, drug-free patients with schizophrenia have excessive amphetamine-induced release of striatal dopamine DA (Laruelle et al. 1996). In addition, this elevated evoked release of striatal DA in drug-free schizophrenia patients was found to be predictive of treatment response (Abi-Dargham et al. 2000).

The ventral striatum receives glutamatergic-inputs from multiple regions of the PFC, the hippocampus, the amgydala and the thalamus and DA-inputs originating mainly from the VTA. These inputs synapse on the dendritic spines and shafts of medium-sized GABA-ergic projection neurons (Kotter 1994; Starr 1995). The convergence of DA and GLU on the spiny neurons provides a potent modulatory interaction between these neurotransmitters. Because, DA is known to exert a potent inhibitory effect on glutamatergic (GLU) neurotransmission

(Morari et al. 1998), it is possible that, in good treatment responders, D2 blockade restores GLU transmission that was inhibited through elevated DA. Improved GLU transmission in the VS might result in improved neuronal transmission in projected areas. We have hypothesized that the early physiological processes that lead to therapeutic benefit are related to changes in GLU transmission within the VS and in GLU-mediated projections to limbic regions (Figure 6). Putatively, changes in ventral striatum and hippocampus rCBF might index neuronal events related to the early stages of drug response while rCBF changes in ACC/medial frontal cortex might relate to a more “consolidated” drug response.

Clinical implication

Clinicians face difficult decisions when managing their patients’ antipsychotic medications: how long should an adequate trial of APD last, when is the correct dosing achieved, will the patient experience a relapse if a switch from one APD to another one is initiated. In addition, patients who are non responsive to at least two APD should be considered for a clozapine trial, a difficult decision considering the risks of agranulocytosis, seizure, and metabolic syndrome. The availability of biomarkers of treatment response could help guide dosing and duration of treatment questions. Early detection of drug response could yield specific treatment strategies that are tailored to the individual, thus improving the quality of life of patients and drastically reducing the cost associated with treatment strategies that may not work. In addition, understanding the mechanisms underlying drug response could enhance the development of more effective and selectively targeted antipsychotic agents.

Limitations of the study—A 2 week withdrawal is likely not enough to allow medication-induced brain changes to fully revert to a baseline condition. However the potent rCBF increase observed in the dorsal and ventral striatum with haloperidol strongly suggest that DA receptors were not blocked by residual medication. Because schizophrenia volunteers were taken-off their medication for only 2 weeks prior to the treatment phase of the study, their clinical status was likely different than a relapsed state. This might limit the generalization of these data. Another important limitation of this study is the limited number of volunteers at each time point, especially in the GR vs PR analysis. In addition, one has to keep in mind that increases in CBF does not necessarily mean there is overall neuronal activation (excitation), but that the CBF reflects the metabolic substrate of many neurons that are activated and deactivated by excitatory and inhibitory processes.

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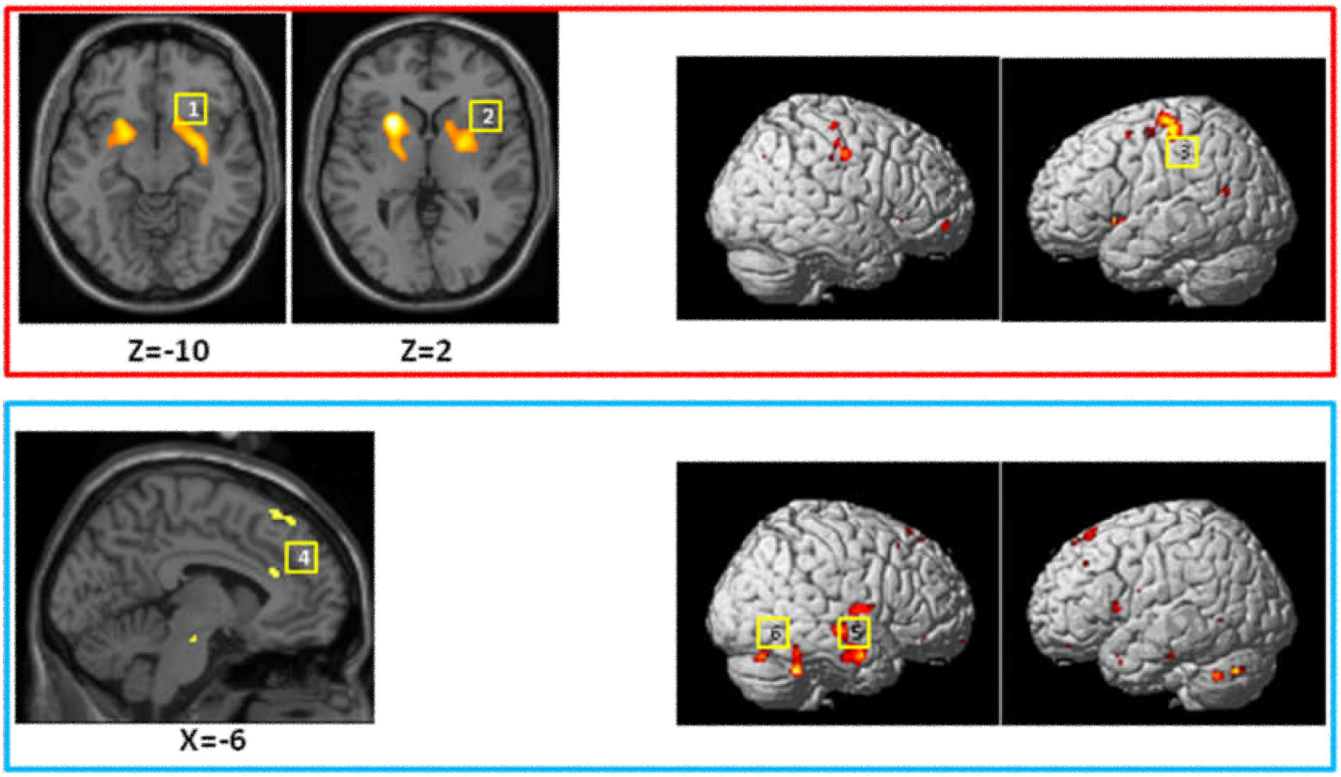

Figure 1.

rCBF changes with haloperidol after one week of treatment. rCBF increases are shown on top panels, rCBF decreases on bottom panels. There were significant activations in the ventral striatum (1), the dorsal striatum (2), and the left sensorimotor cortex (3). There were significant deactivations in the ACC (4), the right middle temporal cortex (5) and the cerebellum (6). The display threshold for voxel was set at T=3.11, $p<0.001$.

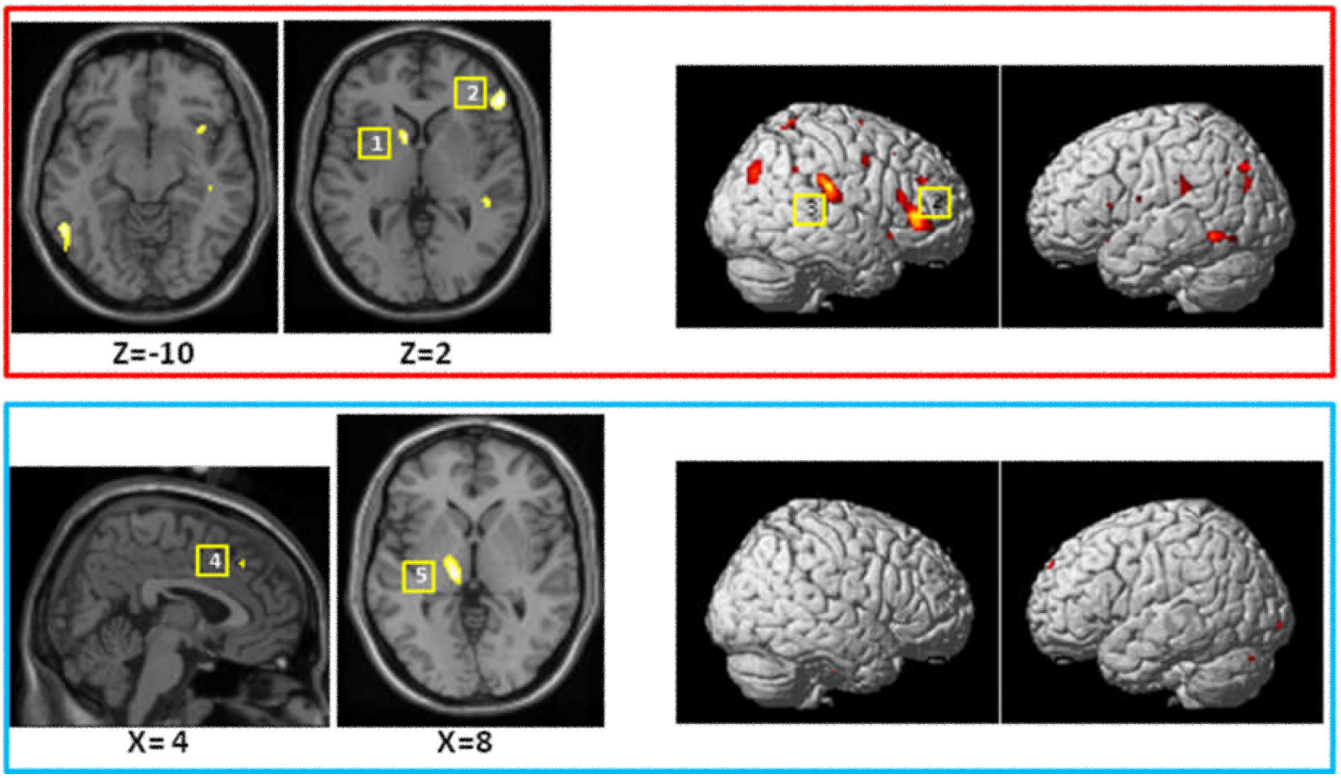

Figure 2.

rCBF changes with olanzapine after one week of treatment. rCBF increases are shown on top panels, rCBF decreases on bottom panels. There were significant activations in the caudate/ventral striatum (1) and the inferior frontal (2) and inferior parietal (3) cortex, both on the right, and significant deactivation in the ACC (4) and the left posterior thalamus (5). The display threshold for voxel was set at T=3.11, $p<0.001$.

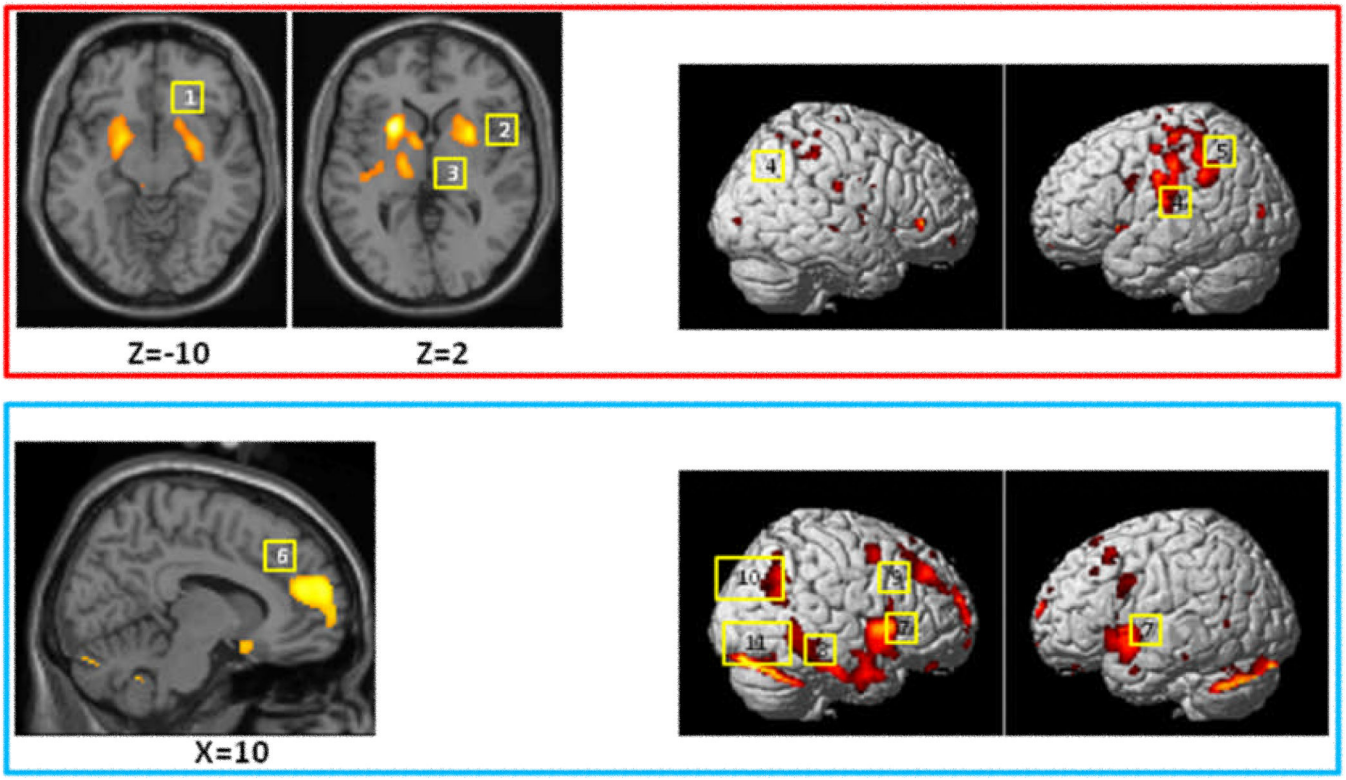

Figure 3.

rCBF changes with haloperidol after 6 weeks of treatment. rCBF increases are shown on top panels, rCBF decreases on bottom panels. There were significant activations in the ventral striatum (1), the dorsal striatum (2), the thalamus (3), the left post central cortex (4) and the left inferior parietal cortex (5). There were significant deactivations in the ACC/medial frontal cortex (6), in a large cluster encompassing the temporal pole, part of the inferior frontal cortex and the insula (7), bilaterally, the inferior and middle temporal cortex (8), the superior frontal cortex (9), the inferior parietal cortex (10) and the cerebellum (11). The display threshold for voxel was set at T=3.11, p<0.001.

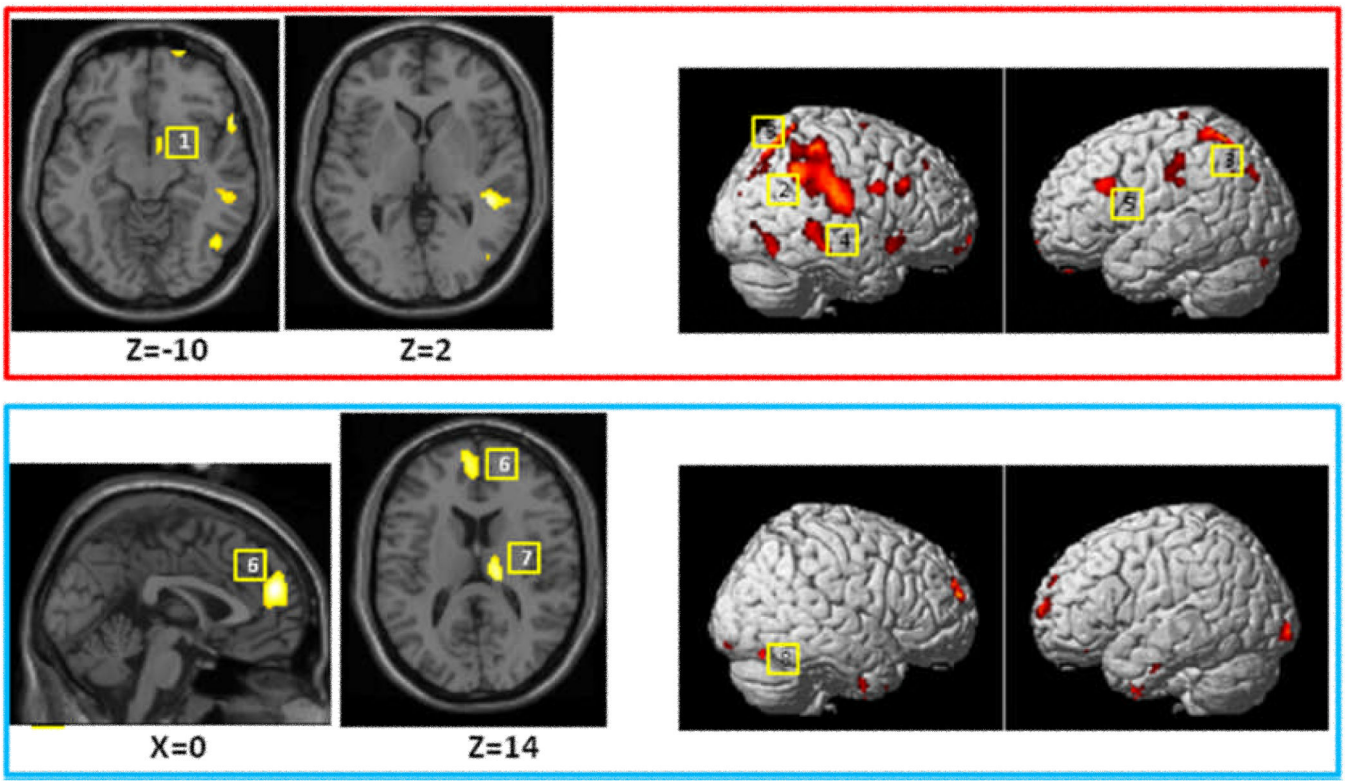

Figure 4.

rCBF decreases with olanzapine after 6 weeks of treatment. rCBF increases are shown on top panels, rCBF decreases on bottom panels. There were significant activations in the right ventral striatum (1), a large cluster encompassing most of the right inferior parietal cortex (2), the superior parietal cortex (3), bilaterally, the right middle temporal cortex (4), the left middle/inferior frontal cortex (5). There were significant deactivations in the ACC/medial frontal cortex (6), the thalamus (7) and the cerebellum (8). The display threshold for voxel was set at T=3.11, $p<0.001$.

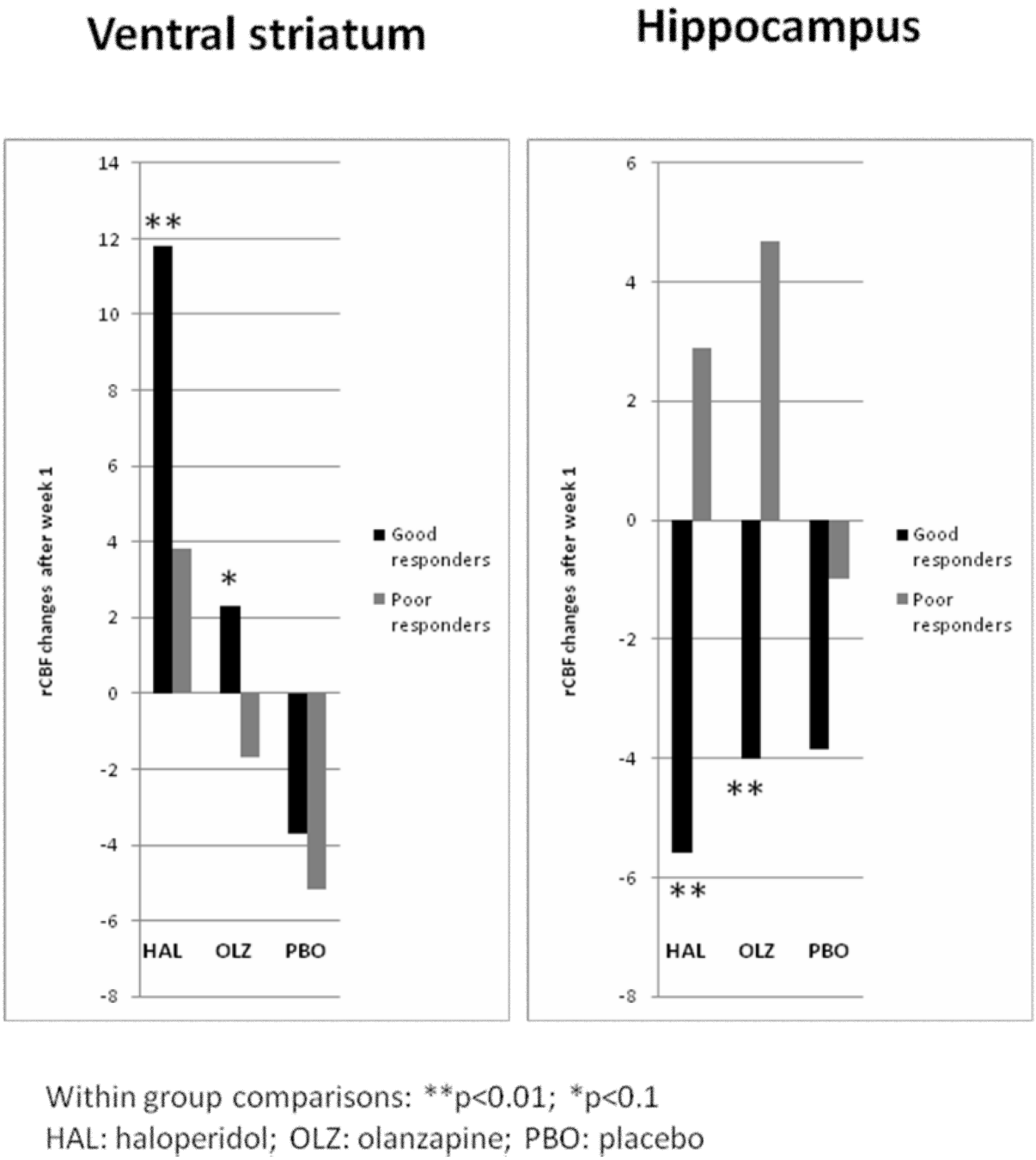

Figure 5.

RCBF values sampled in the right ventral striatum and left hippocampus at baseline (off meds) and at Week 1 were contrasted between the haloperidol GR and PR, the olanzapine GR and PR and the placebo patients based on their response (GR or PR) to either drug at the end of the study. Compared to PR, GR had a significantly greater increases in rCBF in the ventral striatum (Olanz, $p<0.10$, Hal, $p<0.01$) and a significant decrease in rCBF in the hippocampus (Olanz, $p<0.005$, Hal $p<0.001$) (GR, n= 4 Olanz, n=3 Hal; PR, n=7 Olanz, n=5 Hal) after 1 week of treatment. In the placebo group, there were no differences between the

patients who experienced a good response to treatment (n=4) after treatment with haloperidol or olanzapine vs. those who did not (n=4).

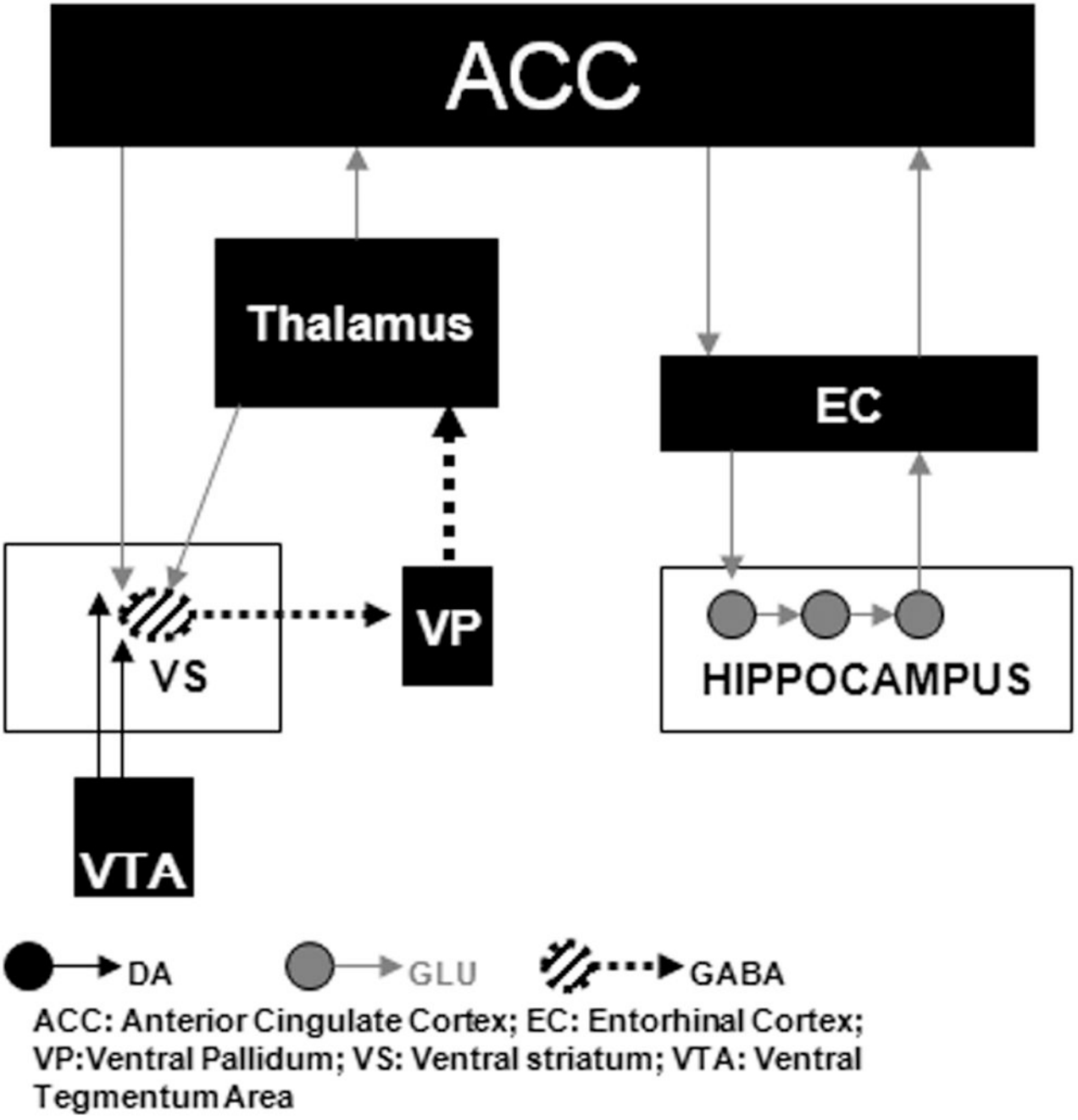

Figure 6.

APD action likely occurs first in the DA D2-receptor rich ventral striatum (VS) where DA afferents from the ventral tegmental area (VTA) and glutamatergic (Glu) afferents from the PFC converge on the same spiny neurons which, in turn, project to the ventral pallidum (VP). The GABA-ergic efferents of the VP project to the thalamus where they synapse on Glu neurons projecting to the PFC. In good treatment responders, D2 blockade restores Glu transmission that was inhibited through elevated DA, leading to restored neurotransmission in the VS and projections areas, including the hippocampus and the anterior cingulate cortex

(ACC). In poor responders (PR), these processes are impaired and the restoration of Glu transmission is not achieved.

Table 1

BPRS Total and Psychosis scores after 1 and 6 weeks of treatment

	Haloperidol		Olanzapine	
	BPRS Total (n=8)	**BPRS Psychosis (n=8)**	**BPRS Total (n=13)**	**BPRS Psychosis (n=13)**
Off-drug	32.9+6.6	5.5+2.3	38.5+9.3	8.1+3.1
Week 1	31.8+4.8	5.0+1.7	36.7+10.1	7.7+2.9
	BPRS Total (n=12)	**BPRS Psychosis (n=12)**	**BPRS Total (n=17)**	**BPRS Psychosis (n=17)**
Off drug	34.4+7.6	6.1+2.4	37.3+8.9	7.0+2.9
Week 6	33.2+8.1	4.8+1.8**	33.8+6.9*	5.9+2.5

Within group comparisons

** P<0.05

* p<0.1

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Table 2

Regional cerebral blood flow (rCBF) changes from baseline (off-medication) to week 1 of treatment with haloperidol and olanzapine

x, y, z[a]	T	p[u]	Cluster size	p[c]	Region (BA)
	Haloperidol: rCBF increases from baseline to week 1 of treatment				
−22, 14, 2	**7.76**		**907**	**0.0001**	**L. Putamen/ventral striatum**
24, −2, −2	**6.60**		**939**	**0.0001**	**R. Putamen**
16, 12, −6	5.01				**R. Ventral Striatum**
34, −4, −12	4.58				
−28, −22, 64	**4.97**		**411**	**0.001**	**L. Post Central/ Pre Central C.**
−36, −24, 56	4.93				**(BA 3/4)**
18, −16, 58	3.69				
	Haloperidol: rCBF decreases from baseline to week 1 of treatment				
16, −6, −16	**4.43**	**0.0001**	**104**		**R. Medial Temporal (BA 34)**
56, −4, −24	**4.25**		**211**	**0.034**	**R. Middle Temporal (BA 21)**
60, −18, − 6	4.20				
58, −12, −26	3.67				
−10, −18, −24	***3.87***	***0.0001***	***45***		***Midbrain***
46, −70, −24	***3.77***	***0.0001***	***47***		***R. Cerebellum***
−6, 30, 22	***3.60***	***0.0001***	***14***		***ACC (BA 32)***
2, 18, 34	***3.56***	***0.0001***	***30***		***ACC (BA 32)***
−46, −68, −36	***3.46***	***0.0001***	***35***		***L. Cerebellum***
	Olanzapine: rCBF increases from baseline to week 1 of treatment				
56, 36, 2	**4.35**		**227**	**0.025**	**R. Inf. Frontal (BA 45/46)**
60, 30, 10	3.67				
58, 24, 18	3.63				
68, −24, 20	**4.22**		**183**	**0.056**	**R. Inf. Parietal (BA 40)**
58, −28, 30	4.13				
− 8, 10, 0	***4.05***	***0.0001***	***60***		***Caudate/ventral striatum***

x, y, z[a]	T	p[u]	Cluster size	p[c]	Region (BA)
	Haloperidol: rCBF increases from baseline to week 1 of treatment				
	Olanzapine: rCBF decreases from baseline to week 1 of treatment				
−12, − 20, 2	**4.92**		**234**	**0.023**	**L. Thalamus**
−8, −12, −8	3.85				
14, − 20, 8	***3.67***	***0.0001***	***47***		***R. Thalamus***
−18, − 6, −22	***3.56***	***0.0001***	***32***		***L. Medial temporal (BA 34)***
4, 32, 42	***3.22***	***0.001***	**6**		***ACC (BA 32)***

x, y, z[a]: Montreal Neurological Institute (MNI) anatomical coordinates

BA Brodmann area; R, right; L, left

p[u] (uncorrected p value):T: 3.11 (p<0.001)

p[c](corrected P value): p< 0.05

Table 3

Regional cerebral blood flow (rCBF) changes from baseline (off-medication) to week 6 of treatment with haloperidol

x, y, z[a]	T	p[u]	Cluster size	p[c]	Region (BA)
Haloperidol: rCBF increases from baseline to week 6 of treatment					
−22, 12, 6	**8.03**		**581**	**0.000**	**L. Putamen**
−20, 4, −10	4.87				**Ventral Striatum**
34, −40, 44	**6.58**		**110**	**0.008**	**R. Inf. Parietal (BA 40)**
34, −34, 50	5.12				
28, 8, 6	**5.66**		**444**	**0.000**	**R. Putamen**
18, 16, −6	4.59				**Ventral Striatum**
28, 0, −10	4.45				
−44, −14, 30	**5.64**		**244**	**0.000**	**L. Post Central C.**
−38, −18, 18	4.62				
−16, −14, 0	**4.64**		**80**	**0.021**	**L. Thalamus**
−6, 6, −4	**4.62**		**70**	**0.031**	**L. Caudate**
−8, 2, 4	4.35				
−18, −24, 58	**4.58**		**64**	**0.039**	**L. Post Central C.**
−48, −44, 32	**4.36**		**114**	**0.007**	**L. Inf. Parietal (BA 40)**
−42, −40, 44	3.93				
Haloperidol: rCBF decreases from baseline to week 6 of treatment					
34, −78, −26	**6.37**		**566**	**0.0001**	**R. Cerebellum**
48, −48, −38	5.36				
22, −76, −28	5.32				
50, 6, −2	**5.82**		**423**	**0.0001**	**R. Insula/Sup. Temporal/Inf.**
40, 14, −14	3.95				**Frontal**
−46, −66, −36	**5.65**		**473**	**0.0001**	**L. Cerebellum**
−14,−74, −32	5.08				
−14, −84, −28	4.88				
−46, 6, −8	**5.51**		**253**	**0.0001**	**L. Sup. Temporal**

x, y, z[a]	T	p[u]	Cluster size	p[c]	Region (BA)
Haloperidol: rCBF increases from baseline to week 6 of treatment					
28, 38, 38	**5.39**		**116**	**0.006**	**R. Sup. Frontal (BA 9)**
60, −22, −28	**4.85**		**133**	**0.004**	**R. Inf. Temporal (BA 20)**
10, 58, 18	**4.79**		**419**	**0.0001**	**ACC/Medial Frontal C.**
10, 48, 18	4.67				
4, 60, 0	4.40				
−34, 12, 10	**4.74**		**55**	**0.055**	**L. Insula/Sup. Temporal/Inf. Frontal**
54, −60, 38	**4.70**		**85**	**0.018**	**R. Inf. Parietal/Gyrus angularis**
58, −60, 24	4.18				**(BA 39/40)**
64, −50, −6	**4.54**			**0.010**	**R. Middle Temporal (BA 21)**
64, −42, −14	4.54				
58, −2, −30	**4.52**			**0.004**	**R. Middle Temporal (BA 21)**
		p*			
24, −24, −12	**3.49***	**0.0001**	**11**		**R. Parahippocampus C.**
−8, −14, −18	**3.36***	**0.0001**	**4**		**Midbrain**

x, y, z[a]: Montreal Neurological Institute (MNI) anatomical coordinates

BA: Brodmann area; R, right; L, left

p[u]:T: 3.75 (p<0.0001), 45 voxels

p[c] (corrected p value): p< 0.05

p* (uncorrected p value) T:3.11 (p<0.001)

Table 4

Regional cerebral blood flow (rCBF) changes from baseline (off-medication) to week 6 of treatment with olanzapine

x, y, z[a]	T	p[u]	Cluster size	p[c]	Region (BA)
Olanzapine: rCBF increases from baseline to week 6 of treatment					
66, −14, 16	**5.46**		**1627**	**0.0001**	**R. Post Central C.**
58, −46, 38	5.11				**R. Inf. Parietal (BA 40)**
60, − 30, 36	5.02				**R. Inf. Parietal (BA 40)**
16, −56, 66	**5.36**		**443**	**0.001**	**R. Sup. Parietal /Sup. Occipital**
30, −62, 60	4.89				**C.**
24, −72, 46	4.89				
50, −36, −2	**5.28**		**310**	**0.006**	**R. Middle Temporal (BA 21)**
58, −32, −12	3.62				
−28, −54, 64	**5.06**		**239**	**0.021**	**L. Sup. Parietal C.**
−22, −60, 60	4.57				
−42, 22, 28	**4.73**		**226**	**0.026**	**L. Middle/Inf. Frontal (BA 9/44)**
8, 4, −10	***3.62***	***0.0001***	***34***		***R. Ventral Striatum***
Olanzapine: rCBF decreases from baseline to week 6 of treatment					
0, 52, 22	**5.33**		**632**	**0.0001**	**ACC/Medial Frontal**
14, −18, 12	**4.73**		**79**	**0.0001**	**R. Thalamus**
20, −20, 2	3.38				
10, −78, −22	**4.44**		**195**	**0.045**	**Cerebellum**
14, −92, −14	3.54				
12, −66, −18	3.48				
−10, −12, −14	***3.83***	***0.0001***	***98***		***Midbrain***
−12, −26, 2	***4.12***	***0.0001***	***81***		***L. Thalamus***

x, y, z[a]: Montreal Neurological Institute (MNI) anatomical coordinates

BA: Brodmann area; R, right; L, left

p[u] (uncorrected p value):T: 3.11 (p<0.001)

p[C] (corrected P value): p< 0.05

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Table 5

Correlations between rCBF changes from baseline (off-medication) to week 6 and BPRS changes from baseline to week 6 in pre-hypothesized regions

	Δ BPRS Psy W6 – Off (r/p)	Δ BPRS Tot W6 – Off (r/p)
	Haloperidol (n=12)	
L. V.Striatum (−20, 4, −10)	**−0.44/0.3**	**−0.35/0.4**
R. V. Striatum (18, 16, −6)	**−0.33/0.4**	**−0.35/0.4**
L. Thalamus (−16, −14, 0)	**−0.68/0.06**	**−0.37/0.4**
ACC (10, 58, 18)	**0.46/0.2**	**0.59/0.1**
ACC (10, 48, 18)	**0.55/0.2**	**0.75/0.03**
	Olanzapine (n=15)	
R. V. Striatum (8, 4, −10)	**−0.0/ns**	**−0.08/ns**
ACC (0, 52, 22)	**0.35/0.2**	**0.24/0.4**
R. Thalamus (14, −18, 12)	**−0.28/0.3**	**−0.19/0.5**

Δ: change; BPRS Psy: Psychosis subscale score; BPRS Tot: BPRS Total score; r: coefficient of correlation; p: P value.

Table 6

Conjunction and contrast analyses

x, y, z[a]	T	p[u]	Cluster size	p[c]	Region (BA)
Conjunction analysis: Overlap of activation between haloperidol and olanzapine from baseline to week 6					
−18, −24, 58	**4.58**		**236**	**0.022**	**L. Pre Central (BA 4)**
−28, −20, 64	3.68				
−6, −26, 62	3.33				
−66, −22, 26	**4.42**		**192**	**0.047**	**L. Post Central (BA 3)**
−60, −22, 42	4.32				
−58, −30, 52	3.46				
22, 18, 0	**4.23**	***0.000***	**32**		**Ventral Striatum/Caudate**
26, 12, 10	4.12				
Conjunction analysis: Overlap of deactivation between haloperidol and olanzapine from baseline to week 6					
−16, 68, 14	5.60		**799**	**0.000**	**ACC/Medial Frontal**
10, 58, 18	4.79				
10, 48, 20	4.64				
Contrast analysis: More activation with haloperidol vs. olanzapine from baseline to week 6					
−22, 10, 6	**6.12**		**924**	**0.000**	**L. Putamen**
−18, −12, 0	5.32				
−12, −22, 0	5.21				**L. Thalamus**
−44, −14, 30	**4.81**		**209**	**0.035**	**L. Post Central**
−36, −24, 22	4.18				
30, 6, 6	**4.61**		**427**	**0.001**	**R. Putamen**
26, 2, −10	4.48				
18, 16, −6	3.36				
10, −18, 0	**4.32**		**213**	**0.032**	**R. Thalamus**
14, −6, 14	3.98				
Contrast analysis: More activation with olanzapine vs. haloperidol from baseline to week 6					

x, y, z[a]	T	p[u]	Cluster size	p[c]	Region (BA)
20, 70, −8	**5.19**		**211**	**0.034**	**R. Sup. Frontal (BA 10**
26, 60, −14	4.17				
6, 64, 0	3.35				
32, −64, 58	**4.85**		**280**	**0.010**	**R. Sup. Parietal (BA 7)**
42, −70, 40	3.88				
54, 6, 2	**4.65**		**394**	**0.002**	**R. Sup. Temporal (BA 22)**
56, 20, −12	3.81				
10, 46, −30	**4.64**		**188**	**0.051**	**R. Orbito−frontal (BA 11)**
52, −60, 40	**4.42**		**447**	**0.001**	**R. Inf. Parietal (BA 40)**
60, −50, 36	4.27				
56, −60, 24	3.95				
−46, 14, 24	**4.33**		**217**	**0.030**	**L. Inf. Frontal (BA 44)**
−48, 12, 36	3.54				
40, 2, 48	**3.96**		**267**	**0.013**	**R. Middle Frontal (BA 8)**
42, 18, 24	**3.93**		**198**	**0.043**	**R. Inf. Frontal (BA 44)**
56, 14, 22	3.84				

x, y, z[a]: Montreal Neurological Institute (MNI) anatomical coordinates

BA: Brodmann area; R, right; L, left

p[u] (uncorrected p value):T: 3.11 (p<0.001)

p[c] (corrected P value): p< 0.05

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Table 7

Haloperidol : Contrasts between rCBF changes from baseline to week 6 in good responders (n=5) versus poor responders (n=7)

	x, y, z[a]	T	p[u]	p[c]	Region (BA)
Contrasts between rCBF changes from baseline to week 6 in GR vs. PR (n=12)					
More activation in GR	**24, 2, −6**	**5.86**		**0.005**	**R. Ventral striatum**
	−18, −28, 8	***4.9***	***0.0001***		***L. Thalamus***
Less activation in GR	***−26, −26, −24***	***3.54***	***0.0001***		***L. Hippocampus***
Contrasts between rCBF changes from baseline to week 1 in GR vs. PR (n=8)					
More activation in GR	***14, 12, 6***	***4.05***	***0.0001***		***R. Caudate/ventral striatum***
Less activation in GR	***−22, −24, −24***	***3.70***	***0.0001***		***L. Hippocampus***

x, y, z[a]: Montreal Neurological Institute (MNI) anatomical coordinates

BA: Brodmann area; R, right; L, left

p[u] (uncorrected p value):T: 3.27 (p<0.001)

p[c] (corrected p value): p<0.05

Table 8

Olanzapine: rCBF changes from baseline to week 6 in good responders (n=8) versus poor responders (n=9)

	x, y, z[a]	T	p[u]	p[c]	Region (BA)
Contrasts between rCBF changes from baseline to week 6 in GR vs. PR (n=17)					
More activation in GR	**−14, −46, −32**	**4.92**		**0.012**	**Cerebellum**
	30, 10, −10	**4.78**		**0.001**	**R. Ventral putamen**
	−4, 8, −12	***3.57***	***0.0001***		***L.Ventral striatum***
Less activation in GR	**−52, 0, 28**	**6.21**		**0.000**	**L. Sensorimotor (6)**
	−30, 44, 16	**4.88**		**0.003**	**L. Middle Frontal (46)**
	−16, −28, 52	**4.71**		**0.002**	**L. Sup Parietal (5)**
	−26, −12, 58	**4.48**		**0.000**	**L. Middle Frontal (6)**
	8, −12, 56	**4.19**		**0.001**	**Medial Frontal (6)**
	−4, 10, 34	***3.65***	***0.0001***		***ACC***
Contrasts between rCBF changes from baseline to week 1 in GR vs. PR (n=11)					
More activation in GR	***10, 2, 8***	***5.12***	***0.0001***		***R. Caudate/ventral striatum***
	10, 34, 12	***3.86***	***0.0001***		***ACC***
Less activation in GR	**−60, 16, 24**	**5.52**		**0.028**	**L. Inf. Frontal(45)**
	−24, −22, −22	***4.07***	***0.0001***		***L. Hippocampus***

x, y, z[a]: Montreal Neurological Institute (MNI) anatomical coordinates

BA: Brodmann area; R, right; L, left

p[u] (uncorrected p value):T: 3.12 (p<0.001)

p[c] (corrected p value): p<0.05