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Antipsychotic Dose and Diminished Neural Modulation: A Multi-Site fMRI Study

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Abstract

Background—The effect of antipsychotics on the blood oxygen level dependent signal in schizophrenia is poorly understood. The purpose of the present investigation is to examine the effect of type (typical or atypical) and dose of antipsychotic medication on independent neural networks during a motor task in a large, multi-site functional magnetic resonance imaging investigation.

Methods—Seventy-nine medicated patients with schizophrenia and 114 comparison subjects from the Mind Clinical Imaging Consortium database completed a paced, auditory motor task during functional magnetic resonance imaging (fMRI). Independent component analysis identified temporally cohesive but spatially distributed neural networks. The independent component analysis time course was regressed with a model time course of the experimental design. The resulting beta weights were evaluated for group comparisons and correlations with chlorpromazine equivalents.

Results—Group differences between patients and comparison subjects were evident in the cortical and subcortical motor networks, default mode networks, and attentional networks. The chlorpromazine equivalents correlated with the unimotor/bitemporal ($\rho = -0.32$, $P = 0.0039$), motor/caudate ($\rho = -0.22$, $P = 0.046$), posterior default mode ($\rho = 0.26$, $P = 0.020$), and anterior default mode networks ($\rho = 0.24$, $P = 0.03$). Patients on typical antipsychotics also had

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Disclosures

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less positive modulation of the motor/caudate network relative to patients on atypical antipsychotics ($t_{77} = 2.01$, $P = 0.048$).

Conclusion—The results indicate that antipsychotic dose diminishes neural activation in motor (cortical and subcortical) and default mode networks in patients with schizophrenia. The higher potency, typical antipsychotics also diminish positive modulation in subcortical motor networks. Antipsychotics may be a potential confound limiting interpretation of fMRI studies on the disease process in medicated patients with schizophrenia.

Keywords

fMRI; independent component analysis; motor cortex; default mode network; antipsychotic

1. Introduction

Antipsychotic medications ameliorate the perceptual disturbances and delusions in patients with schizophrenia (Keefe *et al.*, 1999; van Os and Kapur, 2009). However, these medications are associated with disabling and problematic movement-related side effects. Parkinsonism, akathisia and tardive dyskinesia are related to the dose and type of antipsychotic with higher potency medications and higher dosages producing more problematic side effects over time (Wirshing, 2001). Despite the therapeutic benefit and the potential side effects of antipsychotics, functional magnetic resonance imaging investigations aiming to make conclusions on the disease process of schizophrenia are typically conducted on medicated patients. At this time, the effect of antipsychotics on the blood oxygen level dependent signal (BOLD) in schizophrenia is poorly understood.

Functional magnetic resonance imaging (fMRI) utilizing motor paradigms (finger-tapping, oppositional finger movements) have shown the most consistent antipsychotic-related effects on cortical and subcortical motor networks (Wenz *et al.*, 1994; Schroder *et al.*, 1995; Braus *et al.*, 1999; Schroder *et al.*, 1999; Muller *et al.*, 2002; Muller *et al.*, 2003; Rogowska *et al.*, 2004). Functional imaging studies in antipsychotic naïve patients do not show diminished motor activation patterns (Braus *et al.*, 1999; Braus *et al.*, 2000; Muller *et al.*, 2002), but a single dose of an antipsychotic reduces neuronal activation in the striatum in healthy volunteers (Tost *et al.*, 2006). Patients with schizophrenia treated with antipsychotics have diminished neuronal activation in the sensorimotor cortices, supplemental motor areas, basal ganglia, and cerebellum (Wenz *et al.*, 1994; Schroder *et al.*, 1995; Braus *et al.*, 1999; Schroder *et al.*, 1999; Muller *et al.*, 2002; Muller *et al.*, 2003; Rogowska *et al.*, 2004). Although the sample sizes have been very small, the type of antipsychotic appears to affect neuronal activation in the motor networks (Braus *et al.*, 1999; Muller *et al.*, 2002; Muller *et al.*, 2003; Bertolino *et al.*, 2004). The high potency, typical antipsychotics such as haloperidol and fluphenazine are associated with diminished BOLD signal relative to the lower potency atypical antipsychotics such as clozapine and olanzapine. The relationship of antipsychotic dose and BOLD signal during a motor paradigm has yet to be investigated.

Resting state and attentionally mediated functional imaging paradigms (working memory, continuous performance task) have also shown medication-related changes in patients with schizophrenia. Healthy volunteers and patients with schizophrenia who received a single dose of haloperidol had lower neuronal activity at rest in the frontal cortex and increased activity in the striatum (Bartlett *et al.*, 1994; Lahti *et al.*, 2003; Lahti *et al.*, 2005). In patients, clozapine had relatively more activation at rest in the anterior cingulate and dorsolateral frontal cortex with respect to haloperidol (Lahti *et al.*, 2003). Patients and healthy volunteers completing a continuous performance task had reduced activation in the

frontal cortex after a single dose of risperidone (Cohen *et al.*, 1997; Liddle *et al.*, 2000; Ngan *et al.*, 2002; Lane *et al.*, 2004). Two functional imaging studies with working memory have investigated the functional activation patterns as patients are switched from typical to atypical antipsychotics (Honey *et al.*, 1999; Buchsbaum *et al.*, 2009). Patients switched to atypical antipsychotics had increased functional activation in the dorsolateral prefrontal cortex and more normalization (approached healthy comparison subjects) in the medial frontal, orbital and the anterior cingulate (Buchsbaum *et al.*, 2009). Other cognitive tasks such as forced choice auditory discrimination and preparing to overcome prepotency task have also shown that the antipsychotic effects may increase anterior cingulate activation in patients with schizophrenia (Lahti *et al.*, 2004; Snitz *et al.*, 2005). The anterior cingulate is part of the default mode network. The default mode network is associated with task-induced deactivations and may be implicated in the pathophysiology of schizophrenia (Raichle *et al.*, 2001; Garrity *et al.*, 2007). The effect of antipsychotic dose on the default mode network is not known at this time.

The purpose of the present investigation is to examine the effect of dose of antipsychotic medication (as measured by chlorpromazine equivalents) and type (typical or atypical) on different neural networks during a motor response to auditory stimuli. This block design task requires both attentional and motor demands on the subjects. We hypothesized that the increased dose of antipsychotic would be associated with diminished positive modulation of motor and attentional networks in patients with schizophrenia. Given the effect of atypical antipsychotics on the anterior cingulate network and medial prefrontal cortex, we hypothesized that the increased dose would be associated with less negative modulation of the default mode network. We also hypothesized that the higher potency, typical antipsychotics would have less positive modulation on the motor networks and less negative modulation of the default mode networks relative to patients treated with the lower potency, atypical antipsychotics.

2. Methods

2.1 Participants

The Mind Clinical Imaging Consortium (MCIC) is a multisite, collaborative effort of four investigative teams from New Mexico (UNM), Boston (MGH), Iowa (IOWA), and Minnesota (MINN). The institutional review board at each site approved this study, and all participants provided written informed consent. All healthy comparison subjects were screened to rule out any medical, neurological, or psychiatric illnesses, including any history of substance abuse. Inclusion criteria for the patient group consisted of diagnosis of schizophreniform, schizophrenia, or schizoaffective disorder confirmed by Structured Clinical Interview for DSM-IV-TR Disorders (First *et al.*, 1997) or the Comprehensive Assessment of Symptoms and History (Andreasen *et al.*, 1992). Patients with schizophrenia ranged in age from 18 to 60 years of age. To better assess differences in type of antipsychotic, we excluded patients on both typical and atypical antipsychotics (e.g. clozapine and haloperidol). To control for task performance, we included subjects who performed within ± 1 standard deviation of the average hit rate for both experimental runs.

2.2 Clinical Assessment

Clinicians and trained raters measured positive and negative symptoms with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Clinicians assessed antipsychotic related movement disorders with the Simpson Angus Scale (parkinsonism) (Simpson and Angus, 1970), Barnes Akathisia Scale (Barnes, 1989), and the Abnormal Involuntary Movement Scale (tardive dyskinesia) (Guy, 1976). Each subject also completed

a detailed medication history of current and past medications. Current dosages of antipsychotics were converted to chlorpromazine equivalents based on expert consensus guidelines (Kane *et al.*, 2003). The following formula calculated dose years of antipsychotics: $[(\text{dose (mg)} * 100 \text{ CPZ}) / \text{drug equivalent}] * [\text{days on dose} / 365.25] * [1 \text{ year} / (100 \text{ CPZ} * 1 \text{ year})]$.

2.3 Task

This task was a block-design, motor response to auditory stimulation. Auditory stimuli were presented to each participant over the course of two runs while undergoing the fMRI scan. Each run included 15 blocks, each with duration of 16s on and 16s off. For the duration of the on-block, 200 msec tones were presented with a 500 msec SOA (stimulus onset asynchrony). During a test scan, the volume was individually calibrated to ensure that all test subjects were able to hear the tones comfortably over the background noise of the scanner. The auditory scale consisted of 16 different tones, ranging in frequency from 236 Hz to 1318 Hz. The first tone presented within a given block was set at the lowest pitch. Each tone that followed was at a higher pitch than the previous, creating a stair-step pattern of tones, which rose to a peak, followed by a symmetric descent. The participant was instructed to press the right thumb of the MIND input device (<http://www.mrn.org/facilities/mind-input-device>) each time after hearing each individual tone. This pattern of ascending and descending scales continued for the duration of the 16 sec block. The total duration of each run was 240 seconds.

2.4 Imaging Parameters

Functional data were acquired at all four sites with echo-planar imaging (EPI) sequences. IOWA, MINN, and MGH used a Siemens 3 Tesla Trio Scanner. UNM used a Siemens 1.5 Tesla Sonata. Different scanner manufactures and field strengths result in relatively small variability compared to subject differences (Yendiki *et al.*, 2010). The imaging sequence parameters for these functional scans are as follows: pulse sequence = PACE-enabled, single shot, single echo EPI, scan plane = oblique axial, parallel to the anterior-posterior commissure plane, field of view = 22 cm, 27 slices, slice thickness = 4mm, 1 mm skip, repetition time (TR) = 2000 ms, echo time (TE) = 30ms (3.0T); 40ms (1.5T), flip angle (FA) = 90 degrees, band width (BW) = $\pm 100 \text{ kHz} = 3126 \text{ Hz/Px}$, 64x64 matrix, 1 shot.

2.5 Preprocessing

The fMRI data was preprocessed with SPM5 (www.fil.ion.ucl.ac.uk/spm). Images were motion-corrected using INRIalign – an algorithm unbiased by local signal changes (Freire and Mangin, 2001; Freire *et al.*, 2002). Data were spatially normalized into the standard Montreal Neurological Institute space (Friston, 1995) and slightly sub-sampled to $3 \times 3 \times 3 \text{ mm}$, resulting in $53 \times 63 \times 46$ voxels. Next, the data were spatially smoothed with a $10 \times 10 \times 10 \text{ mm}$ full width at half-maximum Gaussian kernel. The resulting coordinates were converted to the Talairach and Tournoux standard space for anatomical mapping (Talairach and Tournoux, 1988).

2.6 Independent Component Analysis

The group independent component analysis of fMRI toolbox (GIFT) version 1.3c (<http://icatb.sourceforge.net>) was used to analyze the preprocessed data (Calhoun *et al.*, 2001b). Independent component analysis (ICA) is a data-driven multivariate analysis method that identifies distinct groups of brain regions with the same temporal pattern of hemodynamic signal change. FMRI time series data for all participants were first compressed through principal component analysis (PCA). Three PCA data reduction stages reduce the impact of noise and make the estimation computationally tractable (Calhoun *et*

al., 2001a; Schmithorst and Holland, 2004; Calhoun *et al.*, 2009). The final dimensionality of the data were estimated to be twenty maximally-independent components using the modified minimum description length (MDL) criteria tool built into GIFT (Li *et al.*, 2007). Group spatial ICA was performed on the participants' aggregate data, resulting in the final estimation of our independent components. The algorithm used in this process was the infomax algorithm, which minimizes the mutual information of network outputs (Bell and Sejnowski, 1995). From the group spatial ICA, we reconstructed spatial maps and their corresponding ICA time courses that represented both the spatial and temporal characteristics of each component, subject, and session. These characteristics are able to depict component and subject group variability existent in the data. In all, this resulted in 9,200 independent component spatial maps (230 subjects $\times$ 2 scans $\times$ 20 independent components), each with an associated ICA time course of the data. These maps and time courses were then subjected to a second-level analysis to determine whether the resultant components were task-related or simply noise and/or artifacts.

2.7 Statistical Analysis of ICA Time Courses

We performed a temporal sorting of the ICA time courses using an SPM5 design matrix containing one regressor corresponding to the block design with the auditory sensorimotor stimuli. Temporal sorting regresses the model time course (design matrix) with the ICA time course. Using a multiple linear regression sorting criteria, the concatenated ICA time courses were fit to the model time course. Upon completion of this step, components were then sorted according to the R-square statistic. This resulted in a set of beta weights for each regressor associated with a particular subject and independent component. The value of the resulting beta weight directly indicated the degree to which the component was modulated by the task. The beta weights for each subject were used for group comparisons.

2.8 Component Selection

We were primarily interested in identifying the components from the cortical and subcortical motor networks, attentional networks, and the default mode networks. After discarding the components that were related to artifact, we used the methods from Stevens *et al.* to select the components of interest (Stevens *et al.*, 2007). We compared each component spatial map with *a priori* maps of white matter and cerebral spinal fluid. Components that had a higher correlation with these maps were not considered to be meaningful activations and were discarded.

2.9 Statistical Analyses

Group differences in demographics were assessed with either a *t*-test or Chi-square. We performed a two-sample *t*-test for the selected component beta weights. We then compared the correlations of chlorpromazine equivalents and dose-years of antipsychotics with the beta weights for each selected component in the patients with schizophrenia. The chlorpromazine equivalents and dose-years of antipsychotics required the use of nonparametric statistics because of their non-gaussian, skewed distribution. We also compared beta weights with patients on typical and atypical antipsychotics with a two-sample *t*-test. To assess the impact of symptom severity, we performed pairwise correlations on the betas of selected components with reality distortion (summation of global ratings from the delusions and hallucinations subscales from the SAPS), negative (summation of global ratings from the affect, alogia, avolition, anhedonia subscales from the SANS), and disorganized symptoms (summation of global ratings from the bizarre behavior and positive formal thought disorder subscales from the SAPS). We also performed pairwise correlations on the betas with movement ratings from the Abnormal Involuntary Movement Scale, the Barnes Akathisia Scale, and the Simpson Angus Scale. Finally, we performed an ANOVA for the top two components from the ICA temporal sort to assess for site differences.

3. Results

3.1 Clinical Data and Behavioral Results

We initially identified 108 patients and 122 comparison subjects with complete imaging, demographic, and medication information. Behavioral response as measured by the number of button presses for each run was recorded for each subject. The average behavioral response for patients and comparison subjects was 0.92 (ratio of total button presses/total number of tones). The response rate was normally distributed reflecting errors of omission and commission. To ensure that subjects had similar behavioral response and similar performance for each run, we only included subjects who completed the behavioral response (i.e., button press total) within one standard deviation (± 0.17) of the average. This reduced our sample to 79 patients and 114 comparison subjects. Each site lost participants with this behavioral criterion.

The demographic information and clinical variables are presented in Table 1. Subjects were represented from all four sites (patients, comparison subjects): IOWA (21, 45), MGH (14, 15), MINN (21, 24), and UNM (23, 30). Patients differed from comparison subjects in relation to IQ as measured by the Wide Range Achievement Test Third Edition (Reading subtest) (WRAT3) ($t_{188} = -4.19$, $P < 0.01$), but maternal and paternal education were not significantly different between groups ($P = 0.17$, $P = 0.32$, respectively).

All patients included in this sample were taking antipsychotics at the time of the scan. The medication information and chlorpromazine equivalents are presented in Table 2. Seven patients were taking typical antipsychotics. Five of these seven patients were prescribed benztropine. Seventy-two patients were taking atypical antipsychotics. Three of the 72 patients were prescribed benztropine, and one patient was prescribed amantadine. Patients taking typical and atypical antipsychotics were not significantly different with the Simpson Angus Scale ($P = 0.38$), Barnes Akathisia Scale ($P = 0.25$), and the Abnormal Involuntary Movement Scale ($P = 0.59$). The chlorpromazine equivalents approached statistical significance between the typical and atypical groups ($P = 0.07$).

3.2 Component Selection

ICA identified 20 temporally cohesive but spatially distributed components. Visual inspection determined that three components were related to artifact. Six components correlated with spatial maps for cerebral spinal fluid and white matter. The remaining eleven components represented motor (cortical and subcortical), attention (fronto-parietal and inferior frontal), default mode, and visual (occipital lobe) functions. The two basal ganglia/motor networks had similar activation patterns in the caudate, lentiform nucleus, thalamus and cerebellum. To facilitate discussion, we have labeled these components based on their site of maximal activation: motor/caudate and motor/posterior cingulate. The attention networks included the right and left fronto-parietal networks as well as the inferior frontal frontal networks. The default mode networks were divided into two anterior components and one posterior component. The two anterior default mode networks are also labeled after their site of maximal activation: the anterior default mode network/medial frontal and the anterior default mode network/caudate. The axial views of the selected components are shown in Figure 1 and the top five brain regions within each component based on a random effects one-sample t test are presented in Table 3.

The mean time course of each component was regressed with the SPM5 design matrix for a temporal sort. Consistent with the experimental motor demands of the experimental paradigm, the unimotor/bitemporal component had the highest correlation with the experimental design ($r^2 = 0.47$). The posterior default mode network had the next highest correlation ($r^2 = 0.14$). The regression values for each component are presented in Table 4.

3.3 Group Differences

We assessed group differences in beta weights with a two-sample *t*-test. Eight of the eleven selected components had significant differences between patients with schizophrenia and healthy comparison subjects. These components included the unimotor/bitemporal ($t_{191} = 2.07$, $P = 0.04$), posterior default mode ($t_{191} = 2.89$, $P < 0.01$), motor/posterior cingulate ($t_{191} = 2.41$, $P = 0.017$), anterior default mode/medial frontal ($t_{191} = 2.39$, $P = 0.018$), motor caudate ($t_{191} = -2.65$, $P < 0.01$), anterior default mode/caudate ($t_{191} = 2.06$, $P = 0.04$), right fronto-parietal ($t_{191} = -4.05$, $P < 0.01$), and bimotor ($t_{191} = 5.06$, $P < 0.01$) components. These results are presented in Figure 2 and Table 4. The patients had positive modulation of the bimotor component while the comparisons had negative modulation of this same component. The different activation patterns may be related to the motor and default mode (cingulate, inferior parietal lobule) anatomy of this particular component.

3.4 Antipsychotic Dose

We assessed the correlations between the chlorpromazine equivalents and beta weights for the eleven selected components. These results are shown in Table 4 and Figure 3. The Spearman's rank correlations within the patient group (79 observations) revealed significant correlations with the unimotor/bitemporal ($\rho = -0.32$, $P = 0.0039$), motor/caudate ($\rho = -0.22$, $P = 0.046$), posterior default mode network ($\rho = 0.26$, $P = 0.020$), and anterior default mode network ($\rho = 0.24$, $P = 0.030$). The unimotor/bitemporal component was significant after Bonferroni correction for multiple comparisons ($P < 0.0045$). The Spearman's rank correlations were also significant within these networks with cumulative dose years for antipsychotics for the unimotor/bitemporal ($\rho = -0.34$, $P = 0.0025$), motor/caudate ($\rho = -0.22$, $P = 0.046$), and the posterior default mode network ($\rho = 0.23$, $P = 0.044$). The anterior default mode network was not significant with dose years of antipsychotics ($P = 0.59$).

3.5 Antipsychotic Type

We assessed differences between patients on typical and atypical antipsychotics with a two-sample *t*-test in the betas from the four components that had significant correlations with the chlorpromazine equivalents. Patients on typical antipsychotics had significantly less positive modulation in the motor/caudate network relative to the patients on atypicals ($t_{77} = 2.01$, $P = 0.048$). Patients on typical antipsychotics had a trend towards less negative modulation in the anterior default mode network/caudate network relative to patients on atypical antipsychotics ($t_{77} = -1.92$, $P = 0.058$). These results are shown in Figure 4. The betas from the unimotor and posterior default mode network did not have any significant between patients on typical and atypical antipsychotics ($P = 0.16$, $P = 0.85$, respectively).

3.5 Symptom and Movement Ratings

We performed pairwise correlations with symptom ratings and the top two components from the ICA temporal sort: the unimotor/bitemporal network and the posterior default mode network. We did not find a significant relationship with the unimotor/bitemporal network and positive ($P = 0.57$), negative ($P = 0.084$), and disorganized symptoms ($P = 0.40$). We also did not find a significant relationship with the posterior default mode network and positive ($P = 0.62$), negative ($P = 0.21$), and disorganized symptoms ($P = 0.91$). We did not find any significant relationships with pairwise correlations between the betas for the unimotor/bitemporal and posterior default mode network and the Abnormal Involuntary Movement, Simpson Angus Scale, and the Barnes Akathisia Scale ($P > 0.22$).

3.6 Site Differences

We performed a one-way ANOVA with site to assess for site differences in the top two components from the ICA temporal sort, the unimotor/bitemporal and posterior default mode networks. We also used a one-way ANOVA to assess for site differences on demographic variables such as age, IQ, duration of illness and chlorpromazine equivalents. Site had a significant effect on the unimotor/bitemporal network ($F_{3, 189} = 54.25, P < 0.001$) and the posterior default mode network ($F_{3, 189} = 8.29, P < 0.001$). Subjects at MGH had less positive and negative modulation. Site differences were not significant for age ($F_{3, 189} = 2.38, P = 0.071$), IQ as measured by the WRAT-3 ($F_{3, 186} = 0.39, P = 0.76$), duration of illness ($F_{3, 72} = 0.51, P = 0.68$), and chlorpromazine equivalents ($F_{3, 75} = 1.03, P = 0.38$). We repeated the correlations between the betas for the unimotor/bitemporal networks and chlorpromazine equivalents without MGH. The correlations between the betas for the unimotor/bitemporal and chlorpromazine equivalents remained significant ($\rho = -0.43, P < 0.001, 65$ observations).

4. Discussion

We used the motor response to an auditory stimulus and independent component analysis to probe the relationship of antipsychotics on the fMRI BOLD signal in patients with schizophrenia. The unimotor/bitemporal network was strongly task correlated in patients and comparison subjects. Patients with schizophrenia had decreased positive modulation of the unimotor/bitemporal network and motor/posterior cingulate relative to the healthy comparison subjects. In patients with schizophrenia, the neuronal activation of the unimotor/bitemporal and motor/caudate networks was inversely correlated with antipsychotic dose. Patients receiving a higher antipsychotic dose had diminished positive neural activation in these motor networks. The results indicate that antipsychotics affect motor networks, consistent with earlier work showing antipsychotic-related effects on the BOLD signal on cortical and subcortical motor networks (Braus et al., 1999; Muller et al., 2002; Tost et al., 2006). We have extended these findings by showing dose-related effects on the BOLD signal.

The unimotor/bitemporal and motor/caudate networks are part of the cortico-striatal-thalamo-cortical (CSTC) motor circuit (Alexander *et al.*, 1986). Dopamine “dysbalanced” states such as Parkinson’s disease interrupt this motor feedback loop at the striatum (Sabatini *et al.*, 2000; Mehler-Wex *et al.*, 2006; Tost *et al.*, 2006). Similarly, antipsychotics may create a similar state of dopamine dysbalance. Antipsychotics share the common feature of dopamine antagonism at the D2 receptor (Seeman *et al.*, 1976). Antipsychotic response is also related to affinity for the D2 receptor as well as D2 occupancy in the striatum (Kapur *et al.*, 2000). Striatal dopamine antagonism with antipsychotics may interrupt the CTSC circuit resulting in somatomotor hypoactivation. Consistent with our results, the degree of interruption of this motor feedback loop and subsequent reduced cortical motor activity may be related to the dose and type of antipsychotic.

Patients with schizophrenia also had decreased negative modulation of the posterior default mode and anterior default mode/caudate networks relative to healthy comparison subjects. The increased antipsychotic dose also resulted in less negative modulation of these networks. This is the first study to show a possible antipsychotic-related effect on the default mode network. The relationship with dose-years of chlorpromazine equivalents was also present in the posterior default mode network. The default mode network is purported to have an effect on attentional circuits such as the fronto-parietal networks (Raichle *et al.*, 2001; Demirci *et al.*, 2009). Diminished task-induced deactivations may be associated with cognitive impairment (Fox et al., 2005). The anterior default mode network includes the anterior cingulate, an anatomic area associated with sensitivity to antipsychotic medications

(Lahti *et al.*, 2003; Lahti *et al.*, 2004; Lahti *et al.*, 2005; Snitz *et al.*, 2005). Longitudinal studies with neuroleptic naïve patients or patients on typical antipsychotics have shown that the atypical antipsychotic treatment “normalizes” anterior cingulate activity in patients with schizophrenia (Snitz *et al.*, 2005; Schlagenhauf *et al.*, 2010). Our results are consistent with these studies on antipsychotic-related effects on the anterior cingulate. We have extended these findings to include dose-related antipsychotic effects on the anterior and posterior default mode networks.

The type of antipsychotic (typical or atypical) also affects the activation patterns of the motor/caudate network networks and had a non-significant trend on the anterior default mode/caudate network. Two issues should be considered when interpreting these results. First, the two groups had markedly dissimilar sizes ($n = 7$, $n = 72$). Second, the typical antipsychotics included the high potency antipsychotics haloperidol, fluphenazine, and thiothixene that have high D2 binding affinities (Richelson and Nelson, 1984; Richelson, 1999). Mid- and low-potency typical antipsychotics with weaker D2 binding affinities were not included in this sample. The atypical group included the high D2 binding affinity of risperidone but also included many patients taking atypical medications with relatively weak D2 binding including clozapine. The diminished neural activation of the patients prescribed typical antipsychotics in the motor caudate and anterior default mode/caudate networks may be more indicative of the high D2 binding affinities of the typical antipsychotics included in this sample as opposed to the typical/atypical antipsychotic distinction.

This investigation has several limitations. First, reaction time was not recorded due to a software malfunction. We were therefore unable to assess the effect of reaction time on neural activation and antipsychotic dose. However, the total number of button presses was recorded for each experimental run. To control for task performance, we only included subjects who were within one standard deviation of the average response rate. Second, MGH had significant differences in neural activation of the unimotor/bitemporal and default mode networks. The subjects at MGH did not differ on key demographic variables or chlorpromazine equivalents. We repeated the Spearman’s rank correlations for the unimotor/bitemporal networks without MGH and were encouraged to find a stronger relationship between chlorpromazine equivalents and neural activation. Third, the chlorpromazine equivalents facilitate dose-related comparisons of different types of antipsychotics but are at best an approximation. Fourth, six patients were on long-acting injectable antipsychotics, which control for adherence but have different pharmacokinetic properties relative to oral antipsychotics (Nayak *et al.*, 1987). Future studies may benefit from plasma levels to better understand the effect of dose on neural activation in the context of adherence and pharmacokinetic variables. Finally, treatment-resistance and severity of illness (sicker patients requiring higher antipsychotic dosages) may have affected these results. In other words, we were unable to disentangle the higher dose of antipsychotic from the reason for the higher dose of antipsychotic (illness severity, treatment-resistance). We did not find a relationship between symptom severity and the selected components, but the cross-sectional nature of this study precludes firm conclusions on antipsychotic dose and illness severity.

5. Conclusion

Our findings suggest that antipsychotics alter specific neural networks. The dose and type of antipsychotic appear to be mediating factors that explain this relationship. Antipsychotics are a potential confound limiting interpretation of fMRI studies on the disease process of schizophrenia. FMRI investigations of first-degree relatives, unmedicated prodromal, or antipsychotic naïve patients are immune to this potential confound. Several working memory studies have compared activation patterns with medicated, unmedicated patients and first-degree relatives and found similar activation patterns (Callicott *et al.*, 1998;

Callicott *et al.*, 2003; Meda *et al.*, 2008). The effect of antipsychotics may therefore be task-dependent. The motor tasks in this block-design paradigm may be especially susceptible and sensitive to the effect of antipsychotics in the patient group due to the recruitment of networks strongly modulated by dopamine.

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Figure 1.

The axial slices ($z = +30, +10, -10$ mm from anterior commissure/posterior commissure plane) of the components of interest: a) unimotor/bitemporal, b) posterior default mode network, c) inferior frontal, d) motor/posterior cingulate, e) anterior default mode/medial frontal f) motor/caudate, g) anterior default mode/caudate, h) right fronto-parietal, i) bimotor, j) left fronto-parietal, and k) occipital. The spatial maps represent regions of the brain related to the ICA time course from a one- sample t -test.

Figure 2.

A two-sample t-test revealed significant differences between the patients with schizophrenia (SP) and the healthy comparison subjects (HC) in the betas of eight of the eleven selected components. The positively modulated components are in green/dark and the negatively modulated components are in gray/light. The lines represent standard error.

Figure 3.

This figure is the scatter plot and linear fit for the chlorpromazine equivalents and the following components: A) unimotor/bitemporal network ($\rho = -0.32$, $P = 0.0039$), B) motor/caudate ($\rho = -0.22$, $P = 0.046$), C) posterior default mode network ($\rho = 0.26$, $P = 0.020$), and D) anterior default mode network ($\rho = 0.24$, $P = 0.030$).

Figure 4.

Patients on typical antipsychotics had significantly less positive modulation in the motor/caudate network relative to the patients on atypicals ($t_{77} = 2.01$, $P = 0.048$). Patients on typical antipsychotics had trend a trend towards less negative modulation in the anterior default mode network/caudate network relative to patients on atypical antipsychotics ($t_{77} = -1.92$, $P = 0.058$).

Table 1

This table displays demographic information for patients with schizophrenia and healthy comparison subjects. The Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) Global Rating ranged from 1 (absent) to 5 (severe). WRAT-3 = Wide Range Achievement Test, Third addition; SES = socioeconomic status. SES ranges from 1 (higher executives, major professionals) to 7 (unskilled employees).

Demographics	Schizophrenia Mean (SD)	Comparison Group Mean (SD)	Statistics (t or χ^2), P
Sex (M/F)	60/19	72/42	$\chi^2 = 3.53$, P = 0.06
Age (years)	32.77 (11.00)	32.08 (11.64)	$t_{191} = 0.41$, P = 0.68
Education	13.19 (2.52)	15.14 (2.07)	$t_{188} = -5.77$, P < 0.01
Maternal Education	13.25 (3.41)	13.96 (2.70)	$t_{185} = -1.37$, P = 0.17
Paternal Education	14.32 (3.39)	14.82 (3.22)	$t_{178} = -0.99$, P = 0.32
WRAT 3RT	47.55 (5.68)	50.63 (4.41)	$t_{188} = -4.19$, P < 0.01
SES	3.43 (0.98)	2.58 (0.62)	$t_{189} = 7.33$, P < 0.01
Parent SES	2.78 (1.00)	2.63 (0.77)	$t_{191} = 1.20$, P = 0.23
Handedness (Left/Mixed)	7/1	4/5	$\chi^2 = 4.48$, P = 0.11
Duration of Illness	10.91 (9.76)		
SAPS (Global Rating)			
Delusions	2.59 (1.40)		
Hallucinations	2.40 (1.76)		
Bizarre Behavior	0.97 (1.14)		
Thought Disorder	1.00 (1.24)		
SANS (Global Rating)			
Affect	1.53 (1.28)		
Alogia	0.96 (1.15)		
Avolition	2.53 (1.30)		
Anhedonia	2.57 (1.36)		
Attention	1.58 (1.31)		

Table 2

The patient medication information is displayed by type of antipsychotic, number of patients and chlorpromazine equivalents. The chlorpromazine equivalents had trend level significance between typical and atypical groups ($p = 0.07$).

Typicals	Patients (n)	Chlorpromazine Equivalents (mg) mean (SD)
Haloperidol	3	433.33 (57.74)
Haloperidol decanoate	1	1175
Fluphenazine	1	500
Fluphenazine decanoate	1	1350
Thiothixene	1	667
<i>Totals</i>	7	713 (389.02)
Atypicals		
Clozapine	10	880 (404.97)
Aripiprazole	12	283.33 (180.07)
Olanzapine	7	675 (232.29)
Quetiapine	11	486.36 (317.88)
Risperidone	18	169.44 (96.85)
Risperidone consta	4	225 (104.08)
Ziprasidone	5	157.5 (100.62)
Combination atypical *	5	930 (516.72)
<i>Totals</i>	72	439.76 (516.72)

* The combination atypical antipsychotics included the following five combinations: aripiprazole and quetiapine, aripiprazole and risperidone consta, aripiprazole and olanzapine, clozapine and quetiapine, clozapine and olanzapine. Patients were excluded from the analysis if they were on combination typical and atypical antipsychotics.

Table 3

The top five brain regions within each component that show the highest significance from a one-sample t test ($P < 1.0 \times 10^{-10}$, false discovery rate).

Area	R/L random effects: Max Value (x, y, z)
Unimotor/bitemporal	
Superior Temporal Gyrus	58.9 (-53, -14, 3)/61.6 (48, -20, 7)
Transverse Temporal Gyrus	50.9 (-45, -26, 10)/60.3 (45, -26, 10)
Insula	54.5 (-45, -17, 4)/54.8 (45, -17, 6)
Postcentral Gyrus	37.0 (-50, -25, 15)/49.0 (50, -15, 48)
Precentral Gyrus	36.0 (-50, -8, 6)/46.1 (48, -12, 48)
Posterior DMN	
Precuneus	64.0 (-3, -59, 42)/62.5 (3, -59, 42)
Cingulate Gyrus	63.5 (-3, -42, 35)/58.8 (3, -57, 28)
Cuneus	62.0 (-3, -65, 31)/61.1 (3, -65, 31)
Posterior Cingulate	57.9 (-6, -57, 25)/54.8 (6, -57, 22)
Paracentral Lobule	48.1 (0, -41, 49)/44.0 (3, -38, 49)
Inferior Frontal	
Insula	57.2 (-42, 11, -3)/56.5 (42, 9, -3)
Inferior Frontal Gyrus	55.9 (-45, 14, -6)/52.3 (39, 17, -6)
Superior Temporal Gyrus	50.9 (-48, 11, -3)/50.2 (45, 11, -3)
Anterior Cingulate	44.2 (-3, 30, 23)/41.5 (3, 30, 23)
Clastrum	34.9 (-33, 9, 2)/43.2 (33, 12, 2)
Motor/Posterior Cingulate	
Posterior Cingulate	40.3 (-6, -43, 8)/36.2 (3, -46, 13)
Parahippocampal Gyrus	35.6 (-9, -43, 5)/26.1 (9, -43, 5)
Culmen	30.0 (-6, -44, 2)/26.1 (6, -44, 2)
Cerebellar Tonsil	26.7 (-21, -40, -41)/27.1 (18, -40, -41)
Lentiform Nucleus	21.8 (-18, -3, -5)/22.3 (15, -3, -5)
Anterior DMN/Medial Frontal	
Medial Frontal Gyrus	71.7 (-3, 47, 14)/73.1 (3, 56, 17)
Anterior Cingulate	67.4 (-3, 47, 9)/68.9 (3, 47, 9)
Superior Frontal Gyrus	65.3 (-3, 56, 22)/68.1 (3, 56, 22)
Cingulate Gyrus	39.7 (-3, 36, 26)/45.8 (3, 36, 26)
Precuneus	38.1 (0, -54, 33)/39.0 (3, -54, 30)
Motor/Caudate	
Caudate	61.3 (-12, -2, 14)/60.9 (12, -2, 14)
Thalamus	56.1 (-6, -2, 8)/56.6 (12, -5, 11)
Lentiform Nucleus	55.7 (-15, 0, 8)/46.8 (15, 6, 5)
Anterior Cingulate	34.3 (-3, 9, -3)/33.0 (3, 9, -3)
Subcallosal Gyrus	15.2 (-21, 11, -11)/16.7 (18, 8, -11)
Anterior DMN/Caudate	
Caudate	44.6 (-6, 15, 2)/44.2 (6, 15, 2)

Area	R/L random effects: Max Value (x, y, z)
Anterior Cingulate	44.5 (-3, 11, -3)/43.2 (3, 11, -3)
Medial Frontal Gyrus	29.1 (-3, 43, -10)/28.9 (3, 43, -10)
Subcallosal Gyrus	23.9 (-15, 14, -11)/28.3 (12, 20, -11)
Lentiform Nucleus	21.6 (-15, 14, -6)/17.3 (21, 17, -6)
Right Fronto-Parietal	
Medial Frontal Gyrus	50.0 (-3, 34, 37)/38.7 (3, 31, 40)
Superior Frontal Gyrus	49.1 (-6, 31, 43)/35.5 (3, 34, 43)
Inferior Parietal Lobule	44.4 (-50, -41, 46)/29.1 (42, -53, 50)
Middle Frontal Gyrus	43.2 (-45, 22, 38)/20.9 (39, 22, 38)
Cingulate Gyrus	42.4 (-3, 36, 29)/32.8 (3, 36, 29)
Bimotor	
Cingulate Gyrus	65.4 (-3, -3, 47)/56.6 (3, -3, 47)
Medial Frontal Gyrus	63.1 (-3, 0, 50)/54.5 (3, 0, 50)
Paracentral Lobule	56.5 (-3, -9, 47)/52.0 (3, -9, 47)
Inferior Parietal Lobule	50.6 (-33, -38, 57)/55.2 (33, -38, 57)
Postcentral Gyrus	53.9 (-36, -35, 57)/54.4 (30, -38, 60)
Left Fronto-Parietal	
Superior Parietal Lobule	16.3 (-33, -62, 50)/41.7 (39, -56, 53)
Inferior Parietal Lobule	17.1 (-36, -59, 47)/41.2 (48, -47, 49)
Middle Frontal Gyrus	16.7 (-50, 19, 27)/40.4 (50, 19, 27)
Inferior Frontal Gyrus	16.2 (-50, 16, 24)/38.9 (53, 19, 24)
Supramarginal Gyrus	11.2 (-48, -57, 30)/36.7 (53, -57, 33)
Occipital	
Lingual Gyrus	36.9 (-12, -88, -13)/38.9 (12, -88, -13)
Inferior Occipital Gyrus	37.6 (-33, -91, -6)/37.5 (33, -91, -6)
Fusiform Gyrus	37.4 (-21, -88, -13)/37.2 (27, -85, -13)
Cuneus	35.9 (-6, -96, 2)/32.5 (24, -99, 0)
Middle Occipital Gyrus	35.2 (-33, -93, 0)/34.6 (39, -82, -9)

Table 4

Component statistics included regression from the temporal sort, group differences from a two-sample *t*-test, and Spearman correlations between component beta weights and chlorpromazine equivalents.

	Temporal Sort Linear Regression	Two-sample <i>t</i> -test	Component Beta and CPZ Equivalents
Component	r^2	t_{191}, P	Spearman's rho, P
Unimotor/bitemporal	0.47	(-) 2.07, 0.040	(-) 0.32, 0.0039
Posterior DMN	0.14	2.89, < 0.01	0.26, 0.020
Inferior Frontal	0.11	(-) 0.83, 0.41	(-) 0.11, 0.32
Motor/Posterior Cingulate	0.097	(-) 2.41, 0.017	(-) 0.12, 0.27
Anterior DMN/Medial Frontal	0.081	2.39, 0.018	0.16, 0.16
Motor/Caudate	0.08	(-) 2.65, < 0.01	(-) 0.22, 0.046
Anterior DMN/Caudate	0.079	2.06, 0.04	0.24, 0.03
Right Fronto-Parietal	0.073	(-) 4.05, < 0.01	(-) 0.14, 0.22
Bimotor	0.067	5.06, < 0.01	(-) 0.033, 0.77
Left Fronto-Parietal	0.054	1.10, 0.27	(-) 0.19, 0.091
Occipital	0.063	1.37, 0.17	0.068, 0.55

¹ The Spearman rank correlations within the patient group had 79 observations.