# Basal ganglia volume in unmedicated patients with schizophrenia is associated with treatment response to antipsychotic medication

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## Abstract

We investigated the relationship between basal ganglia volume and treatment response to the atypical antipsychotic medication risperidone in unmedicated patients with schizophrenia. Basal ganglia volumes included the bilateral caudate, putamen, and pallidum and were measured using the Freesurfer automated segmentation pipeline in 23 subjects. Also, baseline symptom severity, duration of illness, age, gender, time off medication, and exposure to previous antipsychotic were measured. Treatment response was significantly correlated with all three regions of the bilateral basal ganglia (caudate, putamen, and pallidum), baseline symptom severity, duration of illness, and age but not gender, time off antipsychotic medication, or exposure to previous antipsychotic medication. The caudate volume was the basal ganglia region that demonstrated the strongest correlation with treatment response and was significantly negatively correlated with patient age. Caudate volume was not significantly correlated with any other measure. We demonstrated a novel finding that the caudate volume explains a significant amount of the variance in treatment response over the course of six-weeks of risperidone pharmacotherapy even when controlling for baseline symptom severity and duration of illness.

## Keywords

Schizophrenia; Treatment response; Basal ganglia; Caudate; Risperidone; Magnetic resonance imaging (MRI)

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## 1. Introduction

The schizophrenia patient population has a variable response to antipsychotic drugs (APDs). Between 20% and 30% of patients are categorized as treatment-resistant, showing little to no improvement following treatment with APDs (Conley and Buchanan, 1997). Considering that schizophrenia is a severe mental illness with a world-wide prevalence of approximately 1% (Jablensky et al., 1992), this variability in treatment response is a major problem in the field of psychiatry. Currently, it takes clinicians several weeks to decide if a treatment is ineffective and initiate an alternate treatment therapy (van den Oord et al., 2009). During these extended trial periods, patients can remain symptomatic and thus at increased risk of hospitalization (van den Oord et al., 2009). The discovery of neural biomarkers using non-invasive magnetic resonance imaging (MRI) to predict treatment response could improve both the speed and quality of treatment in psychiatric diseases such as schizophrenia. The first step in creating usable biomarkers for the clinic is to discover variables that are associated with variance in factors such as treatment response. Later these factors can be tested at the individual level in larger groups of patients using predictive techniques that employ bootstrapping techniques to yield metrics such as sensitivity and specificity. The scope of this article is not to conduct predictive modeling at the individual subject level but to further investigate if basal ganglia volume warrants such larger studies.

The goal of this study was to investigate whether the volumes of regions of the basal ganglia are associated with treatment response to an atypical APD in patients with schizophrenia. Volumes were measured from scans obtained before treatment, when patients were unmedicated, and treatment response was evaluated following 6 weeks of treatment with risperidone. Previous work has shown that the volumes of the subcortical regions included in the basal ganglia are associated with treatment response to APDs (Buchsbaum et al., 2003; Okugawa et al., 2007; Molina et al., 2010; Li et al., 2011; Molina et al., 2011). However, none of the previous articles have controlled for other factors that can also be used to explain variance in treatment response.

Treatment response to APD therapy has also been shown to be associated with baseline symptom severity (Bartkó et al., 1990; McEvoy et al., 1991; Cuesta et al., 1994; Crespo-Facorro et al., 2007), duration of psychotic illness (McEvoy et al., 1991; Keck et al., 1995), age (Keck et al., 1995), and gender (Ghafari et al., 2013; Seeman, 1997). Interestingly, lower severity of general psychopathology before exposure to medication is associated with poorer treatment response (Crespo-Facorro et al., 2007), a finding that is likely related to a floor effect. Studies have also indicated that shorter illness duration and younger age are associated with better treatment response (McEvoy et al., 1991; Keck et al., 1995). For these reasons, we investigated whether measurements of basal ganglia volume significantly improve the fit of a hierarchical multiple linear regression analysis that controls for these demographic variables.

We also took in consideration factors that could affect basal ganglia volume, such as time spent off APDs and exposure to previous APDs (Navari and Dazzan, 2009; Leung et al., 2011; Haijma et al., 2012). Since treatment with APDs can cause increases in basal ganglia volume (Navari and Dazzan, 2009; Leung et al., 2011; Haijma et al., 2012), we recorded exposure to previous APDs. We investigated patients' time off APDs as well because it has been shown that volume changes associated with APD treatment are reversible after cessation of treatment (Meshul and Casey, 1989).

To our knowledge, no previous study has investigated whether subcortical volumes of the basal ganglia, as measured with a fully automated algorithm such as Freesurfer, are associated with response to a commonly prescribed atypical APD, risperidone. The

Freesurfer technique has the advantage of reducing operator bias and also being a technique that could easily be transitioned into a clinical setting.

In this study, we investigated whether basal ganglia volume was able to significantly explain variance in treatment response after controlling for factors such as baseline symptom severity and duration of illness, and whether age, time off APDs, or exposure to previous APDs was related to basal ganglia volume or treatment response. Based on previous findings (Buchsbaum et al., 2003; Li et al., 2011), we hypothesized that (1) larger volume of basal ganglia regions (caudate, putamen, and pallidum) in unmedicated participants would be associated with greater treatment response over 6 weeks of APD treatment and (2) regions within the basal ganglia would account for a significant amount of variance in treatment response even after controlling for other non-neural variables.

## 2. Methods

### 2.1. Subjects

Thirty participants with a DSM-IV-TR defined diagnosis of schizophrenia or schizoaffective disorder, not currently taking antipsychotic medication (within 10 days), and seeking treatment at the University of Alabama at Birmingham were recruited for this study (Table 1). We *did not* ask patients to discontinue antipsychotic drugs to enroll in our study. Diagnoses were established using participants' medical records and the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). The diagnosis was made as a consensus reached by a board-certified psychiatrist and a trained Master's level program manager. The program manager also administered the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), which was used to characterize symptom severity and response to antipsychotic treatment. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, 2010) was used to characterize general cognitive function.

The exclusion criteria were other major medical conditions, substance abuse within the past 6 months, previous serious head injury, neurological disorders, loss of consciousness, and pregnancy. The University of Alabama at Birmingham Institutional Review Board approved the study, and all participants gave written informed consent. See Fig. 1 for a flowchart of the subject-exclusion process. Six subjects were excluded because they did not complete the 6-week treatment period, and one subject was excluded because the magnetic resonance imaging (MRI) data contained too much noise because of motion and could not be analyzed with the Freesurfer pipeline. This left a final group of 23 subjects with schizophrenia.

### 2.2. Treatment response

Treatment response over the course of the 6-week period was measured with the BRPS total score. The total scale, which was administered by a trained rater, comprises 20 items scored on a 1–7 Likert scale. Treatment response was defined as the absolute change in BPRS total score from baseline (off medication) to week 6 of treatment. To correct for the patients' differences in initial symptom severity, baseline BPRS total scores were entered in the first step of the hierarchical regression analysis.

### 2.3. Image analysis

Volumetric segmentation of structural MRI data was performed using the Freesurfer image analysis suite, which is documented and freely available online (version 4.5.0, http:// surfer.nmr.mgh.harvard.edu). The main Freesurfer pipeline involves removal of non-brain tissue, registration to Talairach space, segmentation of subcortical white and gray matter,

intensity normalization, identification of gray matter and white matter boundaries, topology correction, and registration to a spherical atlas.

Each of the resulting cortical maps was visually inspected to detect errors. Errors in the segmentation protocol were fixed using an automated algorithm, gcut, which adjusted the threshold boundary between brain and non-brain tissue such as dura mater and scalp. One subject who still had substantial mistakes after this step was excluded. The Freesurfer pipeline generated a total of 50 regional subcortical volumes. Only the three volumes of the basal ganglia (caudate, putamen, and pallidum) were analyzed for this study. Subcortical volumetric measures from the left and right hemisphere were averaged to reduce the number of comparisons. In total, three MRI volumes (caudate, putamen, and pallidum) from the Freesurfer output were used for further analysis. All subcortical volumes were normalized by each subject's intracranial volume (Westman et al., 2012), which is based on an affine transform in Freesurfer. This segmentation approach has been used previously for biomarker discovery (Thambisetty et al., 2010).

### 2.4. Demographic variables analyzed

To test our second hypothesis that the volume of regions within the basal ganglia would explain variance in treatment response even after controlling additional variables, we measured baseline symptom severity and illness duration. Baseline symptom severity was measured as the BPRS total score at the baseline time period while patients were unmedicated. Illness duration was obtained based on the patient's self-reported start of psychotic illness and by verifying this information against the patient's medical records. The illness duration was determined by a trained program manager and a board-certified psychiatrist. Additional variables included age, gender, time off APD, and number of different atypical or typical APDs received. The number of antipsychotics previously received was determined by reviewing the patient's medical records and by tallying up the number of medication trials (typical or atypical) the patient received since the beginning of the illness. Number of previous antipsychotic trials was used as an estimate for previous antipsychotic exposure because medical records did not allow for the calculation of chlorpromazine equivalents or a corresponding dose-years measurement (Andreasen et al., 2010). Correlations between each of these variables and both treatment response and basal ganglia volume were evaluated.

### 2.5. Statistical analysis

All data analyzed for this article were analyzed using the Statistical Package for the Social Sciences (SPSS) (version 20). All of the basal ganglia volumes and BPRS total scores were analyzed for outliers    3.3 standardized $z$-scores. The assumptions of multiple regression were tested, including normality, linearity, multicollinearity, and homoscedasticity. Pearson product-moment correlation coefficients were used to test the relationships between treatment response and basal ganglia volumes (bilateral caudate, left caudate, right caudate, bilateral putamen, and bilateral pallidum) as well as among the basal ganglia volumes. Also, correlations were used to test the relationship between treatment response and other factors (baseline symptom severity, duration of illness, caudate volume, age, gender, time off medication, and previous antipsychotic exposure) to determine which other non-volumetric factors should be controlled for in the following hierarchical multiple linear regression. Correlation analyses of the caudate volume with other factors were conducted to evaluate if any other variables measured were associated with baseline caudate volume.

The relationship between treatment response and gender was tested using an independent $t$-test. To assess laterality of the caudate, a paired sample $t$-test was used to compare the left and right caudate volumes. An independent-samples $t$-test was conducted to compare the

caudate volumes for the medication-naïve and previously medicated subjects. The basal ganglia volume that had the most significant correlation with treatment response (caudate volume) was entered into the hierarchical multiple linear regression analysis. Hierarchical multiple linear regression analyses were used to test the association between the caudate volume and treatment response while controlling for baseline symptom severity and duration of illness.

## 3. Results

### 3.1. Subject demographics

The schizophrenia group analyzed in this study consisted mainly of previously medicated subjects ($n = 15$) but also contained antipsychotic-naïve subjects ($n = 8$) (Table 1). Also, all patients recruited for this study were off medication at study entry. Our study consisted mostly of male subjects (18/23). The mean time off medication was 19.4 months. None of the subjects showed BPRS total scores that were determined to be outlier values.

### 3.2. Correlations between treatment response and basal ganglia volumes

None of the basal ganglia volumes were determined to be outliers. Analyses revealed that there were no violations of the assumptions of normality, linearity, multicollinearity or homoscedasticity. The relationship between subcortical volumes and treatment response showed significant positive correlations for all volumes (bilateral caudate nucleus: $r = 0.71$, $P < 0.005$; left caudate: $r = 0.66$, $P < 0005$; right caudate: $r = 0.75$, $P < 0.005$; putamen: $r = 0.61$, $P < 0.05$; pallidum: $r = 0.48$, $P < 0.05$). Greater volume of the bilateral caudate before the start of antipsychotic treatment was associated with greater improvements in BPRS total scores (Fig. 2).

The subcortical volumes also showed strong correlations among themselves: bilateral caudate-putamen ($r = 0.81$, $P < 0.05$), bilateral caudate-pallidum ($r = 0.81$, $P < 0.05$), left caudate-right caudate ($r = 0.96$, $P < 0.001$), and putamen-pallidum ($r = 0.86$, $P < 0.05$). To avoid collinearity, only the bilateral caudate, which had the one of the strongest correlations with treatment response, was entered into the following hierarchical multiple regression.

### 3.3. Relationship between treatment response, caudate volume, and other demographic factors

The main correlations of focus were the ones involving treatment response and other factors, which was the first row in Table 2. We found that treatment response was significantly positively correlated with baseline symptom severity and significantly negatively correlated with illness duration and age. Since illness duration and age were significantly correlated, but illness duration was more highly correlated with treatment response, we controlled for baseline symptom severity and illness duration in the hierarchical regression. Treatment response was not significantly correlated with time off APD or previous APD exposure. There was no significant difference in the treatment response scores for males ($M = 16.22$, $SD = 9.72$) and females ($M = 24.40$, $SD = 12.58$; $t (21) = -1.57$, $P = 0.30$, two-tailed). The magnitude of the differences in the means (mean difference = $-8.18$, 95% confidence interval = $-19.03$ to 2.68) was relatively large (eta squared = 0.11).

The second row in Table 2 shows factors associated with variance in caudate volumes. The caudate volume was significantly negatively correlated with duration of illness and positively with baseline symptom severity. The caudate volume did not significantly correlate with any other factors including age, time off APD, or previous APD exposure.

### 3.4. Hierarchical multiple linear regression of treatment response

In the hierarchical multiple regression analysis, baseline symptom severity and duration of illness, which were entered at step 1, explained 62.9% of the variance in treatment response. After entry of the bilateral normalized caudate volume at Step 2, the total variance explained by the model as a whole was 69.9%, $F(3, 19) = 14.68$, $P < 0.001$. The caudate volume explained an additional 7.0% of the variance in the BPRS total change scores; $R$ squared change = 0.07, $F$ change $(1, 19) = 4.39$, $P = 0.05$.

### 3.5. Comparison of caudate volumes in previously medicated vs. medication-naïve subjects

There was a trend level difference in the bilateral caudate volumes for previously medicated ($M = 0.0031$, $SD = 0.0004$) versus medication-naïve subjects ($M = 0.0034$, $SD = 0.0005$; $t$ $(21) = -1.87$, $P = 0.08$, two-tailed). The magnitude of the differences in the means (mean difference = $-0.00035$, 95% confidence interval = $-0.0007$ to $0.00004$) was fairly large (eta squared = 0.14).

## 4. Discussion

In this study, we confirmed two hypotheses as follows: (1) volumes from three regions of the basal ganglia (caudate, putamen, and pallidum) showed significant associations with treatment response to an APD, and (2) volume of the caudate significantly contributed to the variance in treatment response after controlling for baseline symptom severity and duration of illness. Neither treatment response nor caudate volumes were related to time off APD or previous exposure to APD.

Our finding that basal ganglia volumes are associated with treatment response is consistent with previous work (Buchsbaum et al., 2003; Molina et al., 2003; Okugawa et al., 2007; Molina et al., 2010) (Table 3). Three of the previous studies (Buchsbaum et al., 2003; Okugawa et al., 2007; Molina et al., 2010) that have investigated the relationship between basal ganglia volumes and treatment response have found a similar positive correlation between larger basal ganglia volumes and treatment response. However, the direction of our result was not consistent with a more recent study (Molina et al., 2011), which showed that reduced volume of the putamen was associated with greater treatment response. This study's use of a different volume-analysis technique (i.e., voxel-based morphometry (VBM) versus our use of Freesurfer) or treatment regimen (i.e., risperidone and olanzapine versus our use of risperidone only) could have contributed to the discrepancy. VBM is different from FreeSurfer in that the former classifies voxels as either gray matter, white matter, or cerebrospinal fluid, while the latter is based on surface-based representation and inter-subject registration (Winkler et al., 2010).

While many early studies showed that antipsychotic treatment is associated with volumetric increases in the caudate (Breier et al., 1992; Chakos et al., 1994; Keshavan et al., 1994; Chakos et al., 1995), more recent studies have also identified volume reductions. A study of the second generation antipsychotic (SGA) quetiapine in antipsychotic-naïve patients found volume decreases in the striatum (caudate and putamen) after 6 months of treatment (Ebdrup et al., 2011). In addition, medication-naïve patients with schizophrenia appear to have smaller caudate volumes compared with healthy controls (Ebdrup et al., 2010). A recent review of 13 longitudinal MRI studies found that volumetric changes in the basal ganglia can vary considerably depending on the drug's receptor-binding profile and the dosing regimen used (Ebdrup et al., 2013). Future work should focus on studying specific antipsychotic drugs rather than on the comparison between first and second generation APDs.

We did not find a correlation between patients' basal ganglia volumes and the number of different APDs to which patients had been exposed. This metric may not have been a sensitive enough measure of patients' cumulative exposure to APDs. A more precise metric is dose-years (Andreasen et al., 2010). In order to calculate this metric, one must calculate chlorpromazine equivalents for each medication, multiply each chlorpromazine equivalent by the dose period in years, and then add up all the resulting figures to yield a cumulative measure of dose-years exposure. Our data did not allow us to do that; we will plan to carry out this measure in future work.

To further explore the variance in basal ganglia volumes, we compared caudate volumes in previously medicated versus medication-naïve subjects, but we did not find significant differences. This finding, however, could have been the result of a lack of power. Indeed, large-scale studies trying to investigate the relationship between recent onset schizophrenia and brain structure are often conducted in medication-naïve subjects to avoid the confounding effects of previous antipsychotic exposure (Fusar-Poli et al., 2012).

The variance in basal ganglia volumes among the schizophrenia patients off-medication should be considered in light of the recent meta-analyses evaluating the effects of illness progression or medication exposure on brain volumes, including those of the basal ganglia in schizophrenia (Table 4). The studies focusing on illness progression suggest that, relative to findings in controls, caudate volumes are reduced in first episode patients with schizophrenia, while no reduction is observed in chronic patients (Ellison-Wright et al., 2008). An interpretation of this finding is that chronic patients, who have taken multiple courses of APD therapy, show increased basal ganglia volume. The meta-analyses which have focused on medication exposure indicate that striatal volumes are reduced before APD exposure and then are subsequently increased following therapy (Navari and Dazzan, 2009; Leung et al., 2011; Haijma et al., 2012). Longitudinal studies have shown that while first episode patients have decreased caudate volume, the volume may return to a normal level with antipsychotic treatment (Chua et al., 2009; Leung et al., 2011) or may even exceed that of healthy controls (Glahn et al., 2008).

The relationship between the basal ganglia volume and APD treatment response is supported by the high density of $D_2$ dopamine (DA) receptors located in this region (Chua et al., 2009). The exact mechanism behind altered basal ganglia volume seen following APD therapy is unknown, but it has been suggested that it could be due to a combination of changes in synaptic plasticity (Konradi and Heckers, 2001) and possibly neurogenesis (Kippin et al., 2005). Alternations in synaptic plasticity, such as changes in synapse morphology and synapse number, have been seen with APD administration (Benes et al., 1985; Meshul and Casey, 1989; Uranova et al., 1991; Kerns et al., 1992; See et al., 1992; Konradi and Heckers, 2001), and these micro-level changes could sum up to produce macro-level changes in regional brain volume. With regard to neurogenesis, work in the rat has shown that APDs can cause significant increases in both the total number and density of newly generated neurons and glia in the dorsal striatum (Wang et al., 2004). Wang and colleagues acknowledge that the total number of these newly generated neurons, while significant, is small and may not be related to the therapeutic effects of APD treatment. The volume changes seen in the basal ganglia following APD therapy are likely downstream effects of $D_2$ receptor blockade.

This study's finding that the caudate volume explained an additional 7% of variance in treatment response was significant, but additional work is needed to determine how this finding can be translated into clinical relevance. Future studies that investigate basal ganglia volume in larger groups of subjects (containing both medication-naïve and chronic patients) by employing individual-level predictive modeling will be necessary before measures of

caudate volume can be more definitively evaluated as a biomarker with clinical utility. Also, it is important to consider that future prediction of treatment response in schizophrenia will likely be based on multiple demographic factors and biomarkers (e.g., age, duration of illness, genetics, neuroimaging data, cerebrospinal fluid, and blood markers) and not one modality in isolation. Therefore, even though the finding in this article explained only a small amount of the variance in clinical response, it could still prove useful in future models that incorporate multiple pieces of data.

Our study was limited in that it consisted of a group of patients with schizophrenia who were heterogeneous in their medication exposure (65.2% had previously received antipsychotic medication). It is therefore unclear whether these results could be replicated in a group of medication-naïve patients.

In conclusion, we found that the volume of regions within the basal ganglia, measured when patients are unmedicated, is associated with treatment response to antipsychotic medication and that caudate volume, after controlling for baseline symptom severity and duration of illness, significantly explains a proportion of the observed variance in treatment response.

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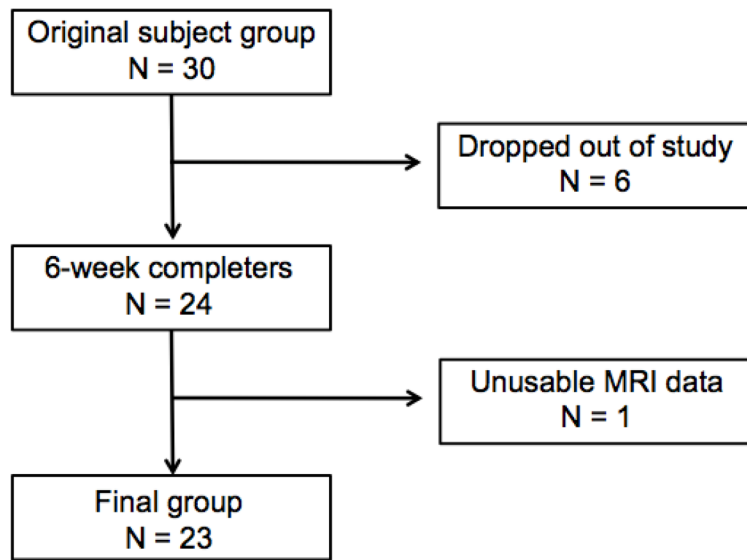
**Fig. 1.**
Flowchart showing criteria used to exclude subjects from study and reach final sample size.
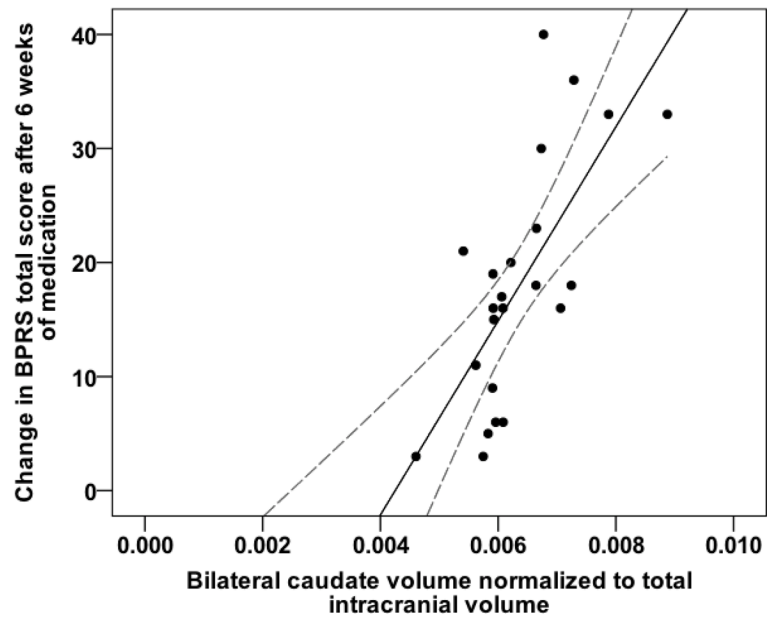
**Fig. 2.**
Scatter plot showing the positive correlation between the volume of the bilateral caudate and treatment response to antipsychotic medication. Solid line is a best-fit linear regression line and dashed lines are 95% confidence intervals around the mean.

## Table 1

Demographic and clinical data of patients with schizophrenia.

|  | Mean (SD)<br>*n* = 23 |
|---|---|
| Age (years) | 32.48 (11.24) |
| Age of onset (years) | 20.57 (5.43) |
| Gender (male/female) | 18/5 |
| Duration of illness (years) | 11.91 (9.53) |
| Parental SES[a] | 7.17 (5.32) |
| RBANS total index[b] | 67.96 (11.51) |
| BPRS[c] Total | 46.52 (11.37) |
| BPRS Positive[d] | 12.52 (4.21) |
| BPRS Negative[e] | 7.30 (2.65) |
| Antipsychotic medication naïve | 8/23 (34.8%) |
| Time since previous antipsychotic (months)[f] | 19.39 (38.62) |
| Previous atypical treatments[g, h] | 1.13 (1.39) |
| Previous typical treatments[g,i] | 0.48 (0.79) |

[a]Parental socioeconomic status ranks determined from Diagnostic Interview for Genetic Studies, DIGS (1–18 scale); higher rank (lower numerical value) corresponds to higher socioeconomic status.

[b]Repeatable Battery for the Assessment of Neuropsychological Status

[c]Brief Psychiatric Rating Scale scores recorded at the baseline

[d]Positive scale consisted of conceptual disorganization, hallucinations, unusual thought content, and suspiciousness.

[e]Negative scale consisted of emotional withdrawal, motor retardation, and blunted affect.

[f]Total amount of time since patient last took an antipsychotic medication, which was determined from the patients medical history.

[g]Total number of times that the patient was previously treated with either typical or atypical antipsychotic medication.

[h]Range of previous atypical treatments was 0 – 5 previous treatments.

[i]Range of previous typical treatments was 0 – 3 previous treatments.

**Table 2**

Pearson product-moment correlations between treatment response, caudate volume, and other factors.

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1. Treatment response[a] | -- | 0.71[*] | -0.53[*] | -0.44[*] | 0.77[*] | 0.02 | 0.11 | -0.26 | -0.15 |
| 2. Caudate volume[b] | | -- | -0.42[*] | -0.41 | 0.63[*] | 0.00 | -0.05 | -0.22 | -0.21 |
| 3. Duration of illness (years) | | | -- | 0.88[*] | -0.48[*] | 0.05 | 0.33 | 0.11 | 0.21 |
| 4. Age (years) | | | | -- | -0.43[*] | 0.03 | 0.42[*] | 0.19 | 0.31 |
| 5. Baseline symptom severity[c] | | | | | -- | -0.04 | 0.01 | -0.37 | -0.31 |
| 6. Time off medication (months)[d] | | | | | | -- | -0.13 | -0.42 | -0.30 |
| 7. Previous FGAs[e] | | | | | | | -- | 0.40 | 0.72[*] |
| 8. Previous SGAs[f] | | | | | | | | -- | 0.91[*] |
| 9. Total previous antipsychotics[g] | | | | | | | | | -- |

[a]BPRS Total score change from the baseline to week 6

[b]Bilateral caudate volume normalized to total intracranial volume

[c]BPRS Total score at the baseline before antipsychotic medication

[d]Time since patients' last antipsychotic medication treatment

[e]Number of FGAs previously received

[f]Number of SGAs previously received

[g]Number of FGAs and/or SGAs previously received

[*]$P < 0.05$

Abbreviations: FGA, first generation antipsychotics; SGA, second generation antipsychotics

**Table 3**

Summary of studies investigating relationship between the basal ganglia and treatment response to antipsychotics in schizophrenia

| Author (year)[a] | Sample size[a] | Patient medication status | Segmentation method | Finding |
|---|---|---|---|---|
| Buchsbaum et al. (2003) | 37 | NT | Manual tracing | Patients with a better outcome to medication were characterized by larger relative mean putamen volumes. Caudate size was not related to treatment outcome. |
| Molina et al. (2003) | 19 | NT | Semi-automated segmentation routine | None of the brain measures predicted response to treatment |
| Okugawa et al. (2007) | 10 | NT[b] | Semi-automated segmentation routine | Patients with schizophrenia showed significant increases in caudate volume after treatment with olanzapine that was accompanied by significant reductions in symptom severity as measured by PANSS |
| Molina et al. (2010) | 44 | NT | Voxel-based morphometry (VBM) | Patients that responded poorly to antipsychotic medication had decreased grey matter in subcortical structures such as the bilateral striatum and in the thalamus. |
| Molina et al. (2011) | 30 | 25 NT and 5 NN | VBM | Inverse association between striatal size and the degree of clinical improvement. This finding was specifically localized to the bilateral putamen. |
| Geerts et al. (2012) | NA[c] | NT | NA | A detailed computer-based mechanistic disease model of schizophrenia that included striatal circuits including medium spiny neurons as components of the cortico-striatal-thalamo-cortical loop correctly predicted the lower performance of a highly selective low-affinity $D_2$ experimental APD therapy. |

[a] Articles are listed in the references section

[b] Patients had not received medication for 1 year

[c] Study was a mathematical simulation study.

Abbreviations: APD, antipsychotic drug; $D_2$, D-2 dopamine receptor; NN, neuroleptic naïve; NT, neuroleptic treated; PANSS, Positive and Negative Syndrome Scale, symptom severity

**Table 4**

Summary of brain volume meta-analyses in schizophrenia involving progression of illness or medication exposure

| Study goal | Author (year)[a] | Sample size[b] | Patient status | Contrast | Finding |
|---|---|---|---|---|---|
| Illness progression | Woods (2005) | 982 | FES and Chronic | HC vs. SZ | WB volume reduced |
| | Steen (2006) | 1424 | FES | HC vs. FES | WB volume reduced and ventricular volume is increased |
| | Ellison-Wright (2008) | 1556 | FES and Chronic | HC vs. SZ | Bilateral reductions in caudate GM present in FES but not chronic SZ |
| | Glahn (2008) | 1195 | FES and Chronic | HC vs. SZ | Increased GM density in striatal regions |
| | Fornito (2009) | 1646 | FES and Chronic | HC vs. SZ | Reduced GM volume and concentration in frontal, temporal, thalamic and striatal regions |
| | Bora (2011) | 1999 | Chronic and FES | HC vs. SZ | Chronic illness associated with more severe GM abnormalities |
| | Chan (2011) | 466 | FES | HC vs. FES | Lower GM volume |
| | | 808 | Chronic | Chronic vs. FES | More extensive GM volume reductions than FES group |
| | Olabi (2011) | 928 | Chronic and FES | HC vs. SZ | SZ show significantly greater reductions in WB volume and WB GM volume over time |
| | De Peri (2012) | 45 studies | FES | FES vs. HC | Significant overall reduction in WB total GM |
| | Haijma (2012) | 8327 | Chronic and FES | HC vs. SZ | Larger GM reductions were associated with longer duration of illness |
| | Vita (2012) | 813 | Chronic and FES | HC vs. SZ | FES have more significant pattern of progressive loss of WB GM volume than Chronic SZ. GM volume modulated by percentage of patients taking atypical APDs |
| Medication exposure | Navari (2009) | 33 Studies | NN and NT | NT vs. HC or NN | Antipsychotics, specifically typical, cause increased volume of structures within the basal ganglia in the NT group |
| | | 8327 | Medicated | HC vs. medicated | Total brain volume of grey matter structures were significantly decreased |
| | Leung (2011) | 162 | NN-FES | HC vs. NN-FES | SZ showed GM deficits in subcortical regions including the striatum |
| | | 336 | NT-FES | NN-FES vs. NT-FES | NT SZ showed GM deficits in caudate, cingulate, and inferior TL |
| | Haijma (2013) | 771 | NN | NN vs. HC and NT | NN had more pronounced volume reductions in the caudate nucleus and thalamus than HC or NT |
| | Ebdrup (2013) | 13 studies | Medicated | Baseline vs. after medication | No studies found that specific FGAs induce basal ganglia volume increases. SGA therapy associated with volumetric increases and decreases in basal ganglia. |

Abbreviations: APD, antipsychotic; FES, first episode schizophrenia; FGA, first generation antipsychotic; GM, grey matter; HC, healthy controls; NN, neuroleptic naïve; NT, neuroleptic treated; SGA, second generation antipsychotic; STG, superior temporal gyrus; SZ, schizophrenia; TL, temporal lobe; WB, whole brain;

[a] Articles are listed in the references section

[b] Some of the articles only reported their total number of studies and not sample size.