Lack of association between dopaminergic antagonism and negative symptoms in schizophrenia: a positron emission tomography dopamine $D_{2/3}$ receptor occupancy study

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Abstract

Rationale—Several pre-clinical studies suggest that antipsychotic medications cause secondary negative symptoms. However, direct evidence for a relationship among antipsychotic medications, their direct effects on neurotransmitter systems, and negative symptoms in schizophrenia remains controversial.

Objective—The objective of this study was to examine the relationship between antipsychotic-related dopamine $D_{2/3}$ receptor occupancy and negative symptoms in patients with schizophrenia.

Methods—Forty-one clinically stable outpatients with schizophrenia participated in this prospective dose reduction positron emission tomography (PET) study. Clinical assessments and [^{11}C]-raclopride PET scans were performed before and after participants underwent gradual dose reduction of their antipsychotic medication by up to 40% from the baseline dose.

Results—No significant relationship was found between antipsychotic-related dopamine $D_{2/3}$ receptor occupancy and negative symptom severity at baseline or follow-up. Similar null findings were found for subdomains of negative symptoms (amotivation and diminished expression).

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Occupancy was significantly lower following dose reduction; however, negative symptom severity did not change significantly, though a trend toward reduction was noted. Examination of change scores between these two variables revealed no systematic relationship.

Conclusions—Our cross-sectional and longitudinal results failed to find a significant dose-dependent relationship between severity of negative symptoms and antipsychotic-related dopaminergic antagonism in schizophrenia. These findings argue against the notion that antipsychotics necessarily cause secondary negative symptoms. Our results are also in contrast with the behavioural effects of dopaminergic antagonism routinely reported in pre-clinical investigations, suggesting that the role of this variable in the context of chronic treatment and schizophrenia needs to be re-examined.

Keywords

Schizophrenia; Negative symptoms; Motivation; Apathy; Dopamine; Side effects; Extrapyramidal symptoms; Ventral striatum

Introduction

Signs and symptoms such as affective flattening and amotivation, collectively termed negative symptoms (i.e., diminutions in normal behaviour), represent prominent features of schizophrenia that characterize a sizeable number of patients (Kirkpatrick et al. 2006). While these symptoms were described in patients long before the introduction of antipsychotic medications (Bleuler 1950; Kraepelin 1919), it has also been suggested that negative symptoms are in some cases produced or worsened by antipsychotic drugs (Carpenter et al. 1988; Kelley et al. 1999; Schooler 1994). This contention is bolstered by studies showing a worsening of negative symptoms following a single dose of antipsychotic medications in healthy volunteers (Artaloytia et al. 2006; Mas et al. 2013; Saeedi et al. 2006), as well as pre-clinical investigations demonstrating reductions in motivation following administration of these drugs (Salamone and Correa 2012). However, direct evidence for a relationship between antipsychotic medications, their direct effects on neurotransmitter systems, and negative symptoms in schizophrenia remains scarce.

In contrast to the aforementioned studies, clinical studies have shown that negative symptoms generally improve or do not substantially change following treatment with antipsychotic medications (Fusar-Poli et al. 2015; Leucht et al. 2009), and withdrawal of these medications results in worsening of negative symptoms (Breier et al. 1987; Harvey et al. 1996; Miller et al. 1994; Weickert et al. 2003). Several studies have failed to demonstrate a significant association between the severity of negative symptoms and antipsychotic dosage (Fervaha et al. 2015a; Fervaha et al. 2015b; Peralta et al. 2000; Prosser et al. 1987; Tugg et al. 1997) or plasma concentrations (Levinson et al. 1995; Marder et al. 2002; Prosser et al. 1987; Tugg et al. 1997). Action at dopamine D_2 receptors (D_2R) is the central feature of all antipsychotic drugs – all having antagonistic properties at this neuroreceptor (Kapur and Mamo 2003). Studies examining the association between negative symptoms and antipsychotic $D_{2/3}R$ occupancy are limited. One previous study reported a positive relationship between antipsychotic striatal $D_{2/3}R$ occupancy and negative symptoms (de Haan et al. 2000); however, this finding was not replicated in a subsequent study (de Haan et

al. 2003). Another study also failed to observe higher antipsychotic $D_{2/3}R$ occupancy to be linked with greater negative symptom severity (Sakurai et al. 2013), though the former variable was estimated from plasma drug concentrations rather than through molecular neuroimaging techniques. Notably, all the aforementioned investigations quantified negative symptoms utilizing the negative subscale of the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) which includes items tapping into cognitive impairments (e.g., difficulty in abstract thinking). This clearly complicates the interpretation of these past findings, especially as cognition itself has been associated with the antipsychotic dosage (Knowles et al. 2010). Finally, studies to date have not explored the relationship between negative symptoms and antipsychotic occupancy in discrete subregions of the striatum including the ventral striatum, a region more closely associated with motivation than other striatal subregions (Haber and Knutson 2010). Taken together, findings to date are inconclusive regarding the idea of antipsychotic-induced negative symptoms.

In the present study we examined the relationship between antipsychotic $D_{2/3}R$ occupancy measured using carbon 11–labeled ($[^{11}C]$)–raclopride and positron emission tomography (PET) and negative symptoms in schizophrenia. We explored this relationship in a sample of clinically stable outpatients with schizophrenia undergoing a protocolized reduction of their antipsychotic dose, which allowed for the examination of cross-sectional relationships as well as longitudinal inter-relationships between $D_{2/3}R$ occupancy by antipsychotics and negative symptoms. Based on the aforementioned clinical studies, we hypothesized that we would fail to show a large and significant association between negative symptom severity and $D_{2/3}R$ occupancy by antipsychotics, i.e., higher antipsychotic-related $D_{2/3}R$ occupancy would not be positively correlated with levels of negative symptoms. Similarly, we hypothesized that there would be a lack of significant relationship between changes in occupancy and changes in negative symptom severity.

Methods and Materials

Study design and participants

This study represents an extension of a previously reported prospective dose reduction PET study in patients with schizophrenia, for which the details and main results have been published elsewhere (Graff-Guerrero et al. 2015). Briefly, we recruited patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, confirmed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al. 2002), aged 50 years or older, who were clinically stable (i.e., no inpatient hospitalization in the past 6 months) and receiving the same dose of risperidone or olanzapine monotherapy for at least 6 months. Patients receiving concomitant psychotropic medications were not excluded. Patients who met criteria for a substance use disorder within the past 6 months, had a urine drug screen positive for substances of abuse, had changed their dose of any psychotropic medication for mental health reasons within the past 6 months, or had an unstable medical condition, were excluded.

The study was approved by the institutional Research Ethics Board, authorized by Health Canada, and registered at ClinicalTrials.gov (NCT00716755). All participants had to be deemed competent to provide consent as per the MacArthur Competence Assessment Tool

for Clinical Research (Appelbaum and Grisso 2001) and provided written informed consent before the initiation of any study procedures.

Procedure

Participants were assessed with clinical scales for symptoms and adverse effects at baseline (Graff-Guerrero et al. 2015). A [^{11}C]–raclopride PET scan was performed to estimate antipsychotic $D_{2/3}R$ occupancy. Subsequently, participants underwent a gradual dose reduction of up to 40% of their baseline dose or to the lower limit of the recommended dosage range (i.e., 7.5 mg/d for olanzapine and 1.5 mg/d for risperidone) (Alexopoulos et al. 2004). The dose was reduced weekly by 2.5 mg for olanzapine and 0.5 mg for risperidone. Clinical assessments and a [^{11}C]-raclopride PET scan were performed again at least 2 weeks after the final target dose was attained to ensure steady-state antipsychotic concentration in the brain. The participants were subsequently monitored for at least 3 months with clinical assessments. Clinical deterioration was defined as an increase of at least 20% in the total Brief Psychiatric Rating Scale (BPRS)(Overall and Donald 1962) score from baseline.

On the same day of each of the 2 PET scans (baseline and post-dose reduction), participants' clinical status was evaluated using the PANSS (Kay et al. 1987), and symptom scores were based on derived factors (Wallwork et al. 2012). Medication-related side effects were evaluated using the Simpson-Angus Scale (SAS) (Simpson and Angus 1970), and the Barnes Rating Scale for Drug-Induced Akathisia (BAS) (Barnes 1989), among other scales (Graff-Guerrero et al. 2015).

Negative symptom assessment

Severity of negative symptoms were evaluated using a consensus-defined factor from the PANSS (Wallwork et al. 2012). Specifically, the following items were summed: Blunted Affect, Emotional Withdrawal, Poor Rapport, Passive/Apathetic Social Withdrawal, Lack of Spontaneity & Flow of Conversation, and Motor Retardation. This negative symptom factor score from the PANSS has been shown to be highly convergent with more detailed measurements of negative symptoms including for example, scores from the Scale for the Assessment of Negative Symptoms (van Erp et al. 2014).

Given the burgeoning evidence for a two-factor structure of negative symptoms in schizophrenia (Messinger et al. 2011), we also calculated two additional scores to evaluate amotivation and expressive deficits separately. Specifically, a social amotivation score was calculated by summing the following items from the PANSS: Emotional Withdrawal, Passive Apathetic Withdrawal, and Active Social Avoidance (Fervaha et al. 2014). This social amotivation score has been shown to have significant convergence with other measures of motivational deficits among patients with schizophrenia (Fervaha et al. 2015b; Luther et al. 2015). A diminished expression score was also calculated by summing the following items from the PANSS: Blunted Affect, Poor Rapport, Lack of Spontaneity & Flow of Conversation, and Motor Retardation (Fervaha et al. 2014). Higher scores on each of these measures reflect greater severity of negative symptom.

Image acquisition and analysis

[^{11}C]-raclopride PET scans were carried out at baseline and again at least 2 weeks after the target antipsychotic dose was reached following dose reduction. The PET scans were performed 14-16 hours after the last dose of the antipsychotic was given. Images were acquired using a high-resolution PET camera system (CPS-HRRT; Siemens Molecular Imaging, USA), which measures radioactivity in 207 brain slices with a thickness of 1.2mm each. The in-plane resolution was ~2.8mm full-width at half-maximum (FWHM). Transmission scans were acquired using a single photon point source to provide attenuation correction (^{137}Cs; $T_{1/2}$ = 30.2 yr, E = 662 KeV).

After each participant was placed on the scanning bed, a custom-fitted thermoplastic mask (True Scan Imaging) was made and then used during PET scans to decrease movement. A saline solution containing [^{11}C]-raclopride was injected as a bolus through an antecubital vein. The radiosynthesis of [^{11}C]-raclopride and the acquisition of PET images have been described in detail elsewhere (Wilson et al. 2000). The mean (SD) total mass injected, radioactivity dose, and specific activity of [^{11}C]-raclopride for the baseline and follow-up scans were 2.71 (1.96) μg and 2.95 (2.63) μg, 9.69 (0.79) mCi and 9.65 (0.72) mCi, and 1650.89 (701.51 mCi/μmol and 1549.84 (711.59) mCi/μmol, respectively, without any significant differences between the 2 PET scanning sessions (paired-samples t-test; P=0.53, P=0.65, and P=0.38, respectively). Emission data were acquired in list mode for 60 minutes, reconstructed by filtered back projection, and redefined into 28 frames (1–5 of 1-min duration, 6–25 of 2-min duration, and 26–28 of 5-min duration).

Each participant also underwent 3-dimensional, brain volume, T1-weighted magnetic resonance imaging (MRI; inversion time, 650 milliseconds; field of view, 23 cm; 256 × 256; slice thickness, 0.9 mm; flip angle, 8°), performed in a GE Discovery MR750 3.0-T scanner (General Electric Medical Systems) to permit accurate delineation of the brain regions for data analysis. The region of interest (ROI)-based analysis for [^{11}C]-raclopride has been described in detail elsewhere (Graff-Guerrero et al. 2008). Briefly, time activity curves (TACs) from ROIs were obtained from the dynamic PET images in native space with reference to each subjects co-registered MRI image. The co-registration of each subject's MRI to PET space was done using the normalized mutual information algorithm (Studholme et al. 1997) as implemented in SPM2 (SPM2, Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm). The TACs were analyzed using the Simplified Reference Tissue Method (SRTM) (Lammertsma and Hume 1996), using the cerebellum as the reference region, to derive a quantitative estimate of binding: binding potential relative to the non-displaceable compartment (BP_{ND}) as defined by the consensus nomenclature for *in vivo* imaging of reversibly binding radioligands (Innis et al. 2007). The basis function implementation of the SRTM (Gunn et al. 1997) was applied to the dynamic PET images to generate parametric voxelwise BP_{ND} maps using PMOD (v2.7, PMOD Technologies, Zurich, Switzerland). These images were spatially normalized into Montreal Neurological Institute (MNI) brain space by Nearest Neighbour Interpolation with a voxel size fixed in 2 × 2 × 2 mm^3 using SPM2. Regional BP_{ND} estimates were then derived from ROIs defined in MNI space. The ventral striatum and dorsal striatum (dorsal caudate,

hereafter caudate and dorsal putamen, hereafter putamen) were defined according with Mawlawi et al (Mawlawi et al. 2001).

Calculation of occupancy

As we were not able to obtain BP_{ND} data from our participants while they were off antipsychotics, to compute $D_{2/3}R$ occupancy we estimated participants' BP_{ND} values using data from antipsychotic-free patients with schizophrenia. Specifically, age- and sex-corrected measures of BP_{ND} were estimated for each ROI using a linear regression equation (Nakajima et al. 2015). $D_{2/3}R$ occupancy was calculated using the following formula:

$$D_{2/3}R \quad occupancy = \left(\left[BP_{ND\_ \text{Antipsychotic- free}} - BP_{ND\_ \text{Medicated}} \right] / \left[BP_{ND\_ \text{Antipsychotic- free}} \right] \right) \times 100,$$

where $BP_{ND\_Antipsychotic-free}$ is the age- and sex-corrected BP_{ND} derived from antipsychotic-free participants with schizophrenia, and $BP_{ND\_Medicated}$ is the BP_{ND} obtained from participants receiving oral risperidone or olanzapine.

Statistical analyses

Initially, a series of paired-samples t-tests were carried out to evaluate whether there were any significant changes on any of the variables of interest following dose reduction (Table 2). We then examined whether negative symptom severity in general was associated with antipsychotic-related $D_{2/3}R$ occupancy at baseline in a dose-dependent fashion using Spearman's rank correlations. We opted to employ Spearman's rank correlations rather than Pearson's product-moment correlations as the former evaluates both linear and non-linear dose-dependent relationships, whereas the latter only evaluates linear relationships. $D_{2/3}R$ occupancy was examined in 3 striatal subregions (caudate, putamen, and ventral striatum) as well as within the whole striatum. After this, we explored whether such a relationship existed for the two discrete subdomains of negative symptoms. Subsequently, and for completeness, an exploratory item-level analysis was carried out. These analyses were repeated using the follow-up values. Finally, we examined whether changes in antipsychotic-related $D_{2/3}R$ occupancy following dose reduction were related to changes in negative symptom severity using Spearman's rank correlations. For this, difference scores were calculated for both symptom and occupancy values (score at follow-up minus the score at baseline).

Notably, our study was powered to detect an association with a large effect size (i.e., 80% power to detect a correlation coefficient greater than 0.4 at a two-tailed P-value of 0.05), similar to that reported in one previous study (de Haan et al. 2000).

We also defined prominent negative symptoms as a severity score of 4 (i.e., moderate) or greater on any of the individual negative symptom items comprising the negative symptom factor from the PANSS. Whether antipsychotic-related $D_{2/3}$ receptor occupancy differed for individuals with and without prominent negative symptoms at baseline was tested using an independent-samples t-test.

Statistical significance was set at *P*<0.05 (two-tailed) and analyses were carried out using SPSS version 20 (IBM Corporation, Armonk, NY).

Results

Participant characteristics

A total of 41 participants provided both clinical and PET data at baseline, and 38 participants provided follow-up data. Baseline sociodemographic and clinical characteristics of the 41 participants are presented in Table 1. Eighteen participants (43.9%) experienced at least 1 prominent negative symptom.

Negative symptoms before and after antipsychotic dose reduction

Findings from the majority of this sample have been reported previously (Graff-Guerrero et al. 2015). The 3 individuals (7.3%) without follow-up PET data experienced clinical deterioration before reaching the target dose during the dose reduction phase of the study. For the other 38 participants with PET data at both time-points, the mean (SD) time to achieve the dose reduction was 2.2 (1.5) weeks, and the time between the 2 PET scans was 6.5 (2.3) weeks. Clinical and PET data before and after dose reduction are presented in Table 2. Participants' doses were reduced by a mean (SD) of 34.2% (4.1%). After dose reduction, both participants' antipsychotic dose and the corresponding $D_{2/3}R$ occupancy were significantly lower. Dose reduction was also associated with lower levels of antipsychotic-related motor side effects. In terms of symptom severity, negative symptoms were slightly, though not statistically significantly, lower following dose reduction; however, in an exploratory analysis using negative symptom subdomain scores, the severity of social amotivation was significantly lower following dose reduction, although the magnitude of change was modest and would not survive correction for multiple comparison testing (Table 2). Notably, though, only 5 of the 39 participants (12.8%) experienced a change in their social amotivation score over time, meaning that for the majority of participants this symptom remained stable following antipsychotic dose reduction. Other symptoms did not significantly change following dose reduction.

Negative symptoms and dopamine $D_{2/3}$ receptor occupancy

At baseline, negative symptom severity was not associated with antipsychotic-related $D_{2/3}R$ occupancy in any striatal region (Table 3; Figure 1). This finding held true for exploratory analyses with negative symptom subdomain scores and individual item scores. In fact, the magnitude for each bivariate relationship trended toward a negative association, whereby greater negative symptom severity was associated with lower occupancy. A similar pattern of results emerged at follow-up; there was no significant association between any negative symptom measure and occupancy in any striatal region (all *P*s>0.05).

For completeness, we also re-computed the above tests conducted with the full sample in the two subsamples of participants receiving either olanzapine or risperidone. The occupancy values did not differ between participants receiving olanzapine or risperidone (all *P*-values>0.05). At baseline, a similar pattern of findings emerged for each drug group as that

seen for the full sample; overall negative symptoms were not associated with antipsychotic-related $D_{2/3}R$ occupancy in any striatal region (all P-values>0.05).

Participants with prominent negative symptoms at baseline did not differ from participants without such symptoms in terms of antipsychotic-related $D_{2/3}R$ occupancy in the caudate (t=0.72, P=0.47), putamen (t=0.04, P=0.97), ventral striatum (t=0.48, P=0.63), or whole striatum (t=0.41, P=0.68; Figure 2). Consistent with the dimensional analysis above, patients with prominent negative symptoms had lower mean occupancy values for all striatal regions, with the exception of the putamen where these values differed less than 0.2%. The validity of the prominent negative symptom classification was underscored by the finding that these individuals had significantly more severe negative symptoms than individuals without prominent negative symptoms (t=8.36, P<0.001) but, importantly, did not differ in the severity of other symptom domains (all P-values>0.05; Supplemental Table 1).

In the longitudinal subsample, changes in negative symptoms were not associated with changes in antipsychotic-related $D_{2/3}R$ occupancy in the caudate (r=0.05, P=0.79), putamen (r=0.02, P=0.90), ventral striatum (r=0.15, P=0.37), or whole striatum (r=0.08, P=0.64; Figure 3). A similar pattern of null findings emerged when examining the relationship between occupancy and negative symptom subdomain scores or individual items (all P-values>0.05; Supplemental Table 2).

Discussion

The present study represents an extension of a previously reported dose reduction study (Graff-Guerrero et al. 2015), with analyses focused on negative symptom outcomes. The clinical results of the antipsychotic dose reduction echo those of our previous report in a smaller sample. Specifically, we show that antipsychotic dose can be successfully reduced in the majority of stable patients with schizophrenia who are receiving antipsychotic doses above the recommended minimum. Reduction of antipsychotic dose was associated with improvement in antipsychotic-related motor side effects in the face of stable symptoms (i.e., no substantial changes in symptoms were observed following antipsychotic dose reduction).

The present analysis was carried out to examine the relationship, or lack thereof, between negative symptoms and antipsychotic $D_{2/3}R$ occupancy. To our knowledge, the present study is the largest PET study examining the relationship between antipsychotic occupancy of striatal $D_{2/3}R$ and negative symptoms, and the first to examine the inter-relationship between these variables in the context of a longitudinal dose reduction study, which provides the unique opportunity to explore the impact of changes in dopaminergic antagonism. We failed to find a relationship linking greater occupancy with greater burden of negative symptoms. In fact, the correlation coefficients of this association were in the opposite direction - i.e., greater negative symptoms were associated with lower occupancy, though this relationship was not significant. This bolsters our confidence that the absence of an association was not simply due to a lack of power, though we were adequately powered to detect a moderate to large effect size.

We also explored whether any relationship existed for specific negative symptoms and occupancy and, again, no significant relationship emerged. These lack of associations were seen in the face of a liberal type I error acceptance rate (i.e., $\alpha < 0.05$, without correction for multiple comparison testing). All associations would, of course, be non-significant if a multiple comparison testing correction had been applied. We failed to find any dose-dependent relationship between negative symptoms and occupancy at both baseline and follow-up. Moreover, changes in antipsychotic occupancy level at striatal $D_{2/3}R$ were not related to changes in negative symptom severity. This latter finding is of particular importance as it suggests that after chronic stable treatment with antipsychotics, reduction in occupancy and, by inference, increases in dopaminergic transmission at $D_{2/3}R$ are not sufficient for improvement in negative symptoms. It should be noted that negative symptom severity did trend toward reduction following dose reduction, though the magnitude of this effect was modest. Moreover, the open-label design of the present study cannot rule out a non-specific effect of time (i.e., a placebo effect); we cannot ascribe this nominal reduction in symptom severity to the reduction of antipsychotic dose rather than the benefits of ongoing treatment for example. Therefore, in light of these considerations, this finding should be interpreted with caution.

That no association was found between dopaminergic blockade (i.e., antagonism) at the $D_{2/3}R$ and negative symptoms in general, or motivational deficits in particular, is noteworthy as it stands in contrast to predictions based on pre-clinical investigations and the hypothesized role of dopamine-dependent neural circuitry in motivated behaviour (Salamone and Correa 2012). However, our findings are not inconsistent with these findings and do not rule out dopamine as an important mediator of negative symptoms. Instead, our findings suggest that there does not exist a systematic dose-dependent relationship negative symptoms and occupancy (i.e., antagonism) of striatal $D_{2/3}R$ by antipsychotics. It is certainly possible that basal levels of striatal dopamine are implicated in negative symptom expression and there is, in fact, some evidence for this in schizophrenia (Kegeles et al. 2010). At any rate, our findings reject the notion of dose-dependent antipsychotic-induced negative symptoms. Other (non-iatrogenic) mechanisms need to be explored as causative agents in the expression of these symptoms.

Our study also raises the question of why there was no observed relationship between negative symptoms and dopaminergic blockade. We speculate that several factors might be involved (Fervaha et al. 2015b). Chief among these, we propose that differences in acute dosing paradigms used in pre-clinical and healthy volunteer studies and chronic dosing in patients with schizophrenia account for discrepancies. Some evidence supports that the effects of chronic treatment with antipsychotics are distinct from their acute effects (Amato et al. 2011; Samaha et al. 2007). Future pre-clinical studies are well positioned to resolve this question empirically, focusing on motivated behaviour and examining potential neurobiological mechanisms.

The present study examined variation in antipsychotic-related $D_{2/3}R$ occupancy of olanzapine and risperidone, two second-generation antipsychotic medications. Our study did not include an exhaustive list of other antipsychotic medications including first-generation and other second-generation drugs. While recent clinical data suggest that these two classes

of antipsychotics do not substantially differ in terms of their effect on negative symptoms (Darbà et al. 2011; Fusar-Poli et al. 2015), though see (Zhang et al. 2013), there exists evidence that these medication classes have distinct neurofunctional effects (Juckel et al. 2006; Lahti et al. 2009; Schlagenhauf et al. 2008). More specifically, there is some previous work suggesting that it is the first-generation, and not the second-generation, antipsychotics that are associated with reward system dysfunction and (secondary) negative symptoms (Juckel et al. 2006; Schlagenhauf et al. 2008). Thus, it is possible that a relationship between negative symptoms and dopaminergic blockade may be observed in a sample of patients treated with different antipsychotic medications. Data from a previous study that included patients receiving both olanzapine and haloperidol also failed to find a relationship between these two variables (de Haan et al. 2003), arguing against the idea that a relationship necessarily exists when examining patients receiving first-generation antipsychotic medications.

The present study has limitations that should be mentioned. First, it did not include very high doses of antipsychotics, but rather included doses reflective of current practice which were within the range of consensus recommendations (Gardner et al. 2010). Second, baseline medication dosing was not assigned randomly but, instead, determined based on real-world clinical decisions. Third, the present study employed a single-arm open-label study design over a few weeks. Thus the long-term effects of dose reduction or the non-specific effect of time on negative symptoms could not be assessed. However, previous research examining the clinical effects of antipsychotic dose reduction and employing a longer duration of follow-up has also failed to find significant changes in symptom severity (Harris et al. 1997). Fourth, participants included in the study were aged 50 years and above, hence the generalizability of our findings to younger patients or those with first-episode schizophrenia remains an open question. To this end, it should be underscored that our null findings are consistent with other PET studies in younger patients (de Haan et al. 2003), and that previous clinical studies have not found a significant relationship between patient age and negative symptoms (Schultz et al. 1997). Fifth, we focused on antipsychotic occupancy of stiatal $D_{2/3}R$ given their centrality to the mechanism of action of these drugs (Kapur and Mamo 2003), and did not evaluate action at other neuroreceptors (e.g., dopamine D_1, serotonin 5-HT_{2A}) or extra-stiatal regions (e.g., prefrontal cortex). Sixth, our assessment of motivational deficits was incomplete. Our measure only evaluated this domain from one perspective (i.e., social amotivation), and we did not measure motivation for non-social goals. It would be of interest to discern whether objective tasks tapping into discrete aspects of negative symptoms are related to antipsychotic occupancy.

It has long been held that antipsychotic medications can induce secondary negative symptoms (Carpenter et al. 1988; Kelley et al. 1999; Schooler 1994). However, direct evidence for this notion is limited. The present study failed to support this, and instead suggests that there is no systematic relationship between antipsychotic occupancy at striatal $D_{2/3}R$ and severity of negative symptoms in schizophrenia. The lack of association was found for both overall and specific negative symptoms, including symptoms reflective of amotivation and diminished expression. Our results therefore suggest that antipsychotic-related dopaminergic antagonism does not necessarily undermine motivation and worsen expressive negative symptoms among stable patients receiving long-term treatment with

these medications. It is possible that patients have adapted to the effects of these medications and compensate in some manner. In any case, we failed to find any robust evidence for a link between the effects of these drugs and negative symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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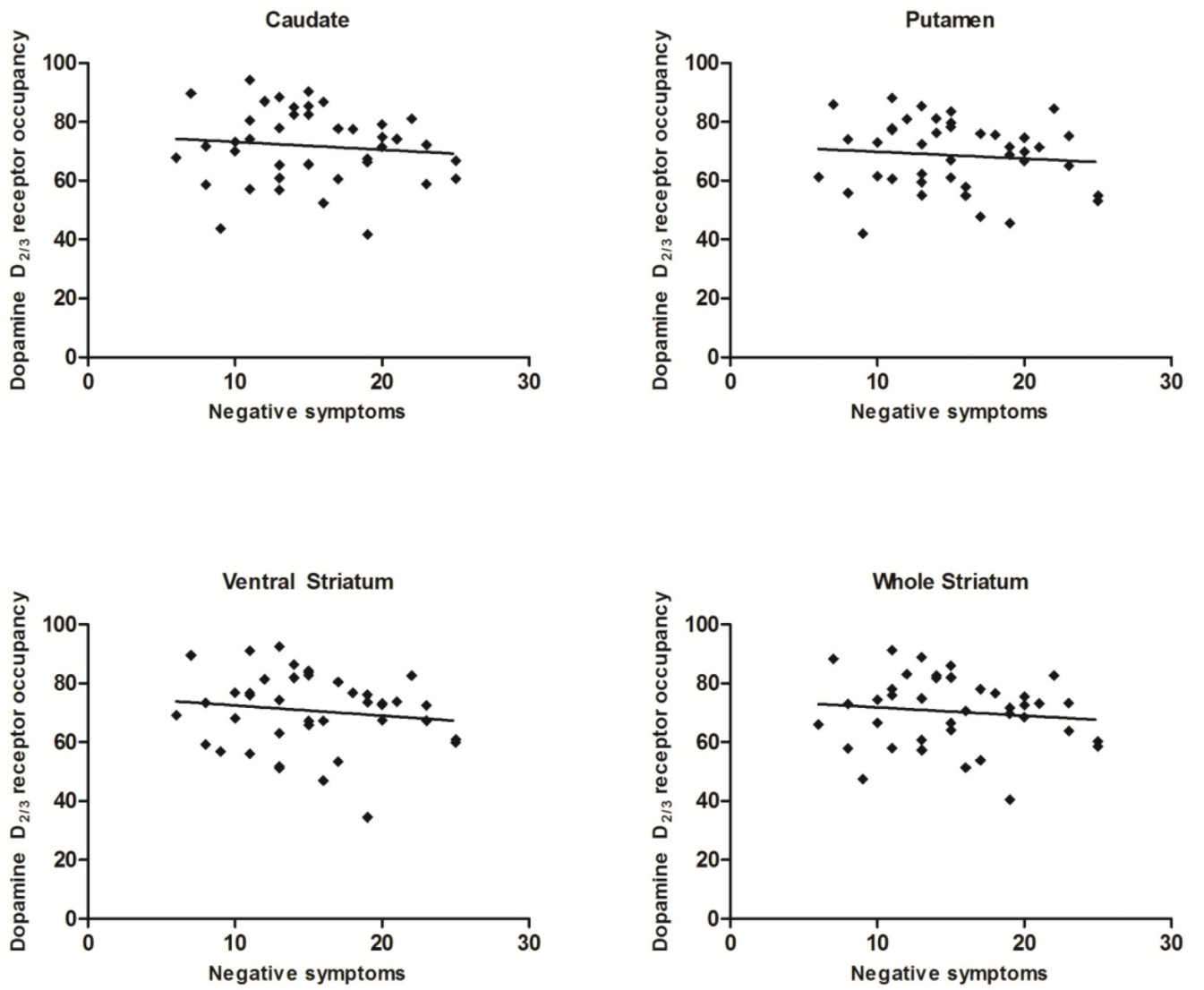
Figure 1.
Scatterplot of the relationship between negative symptom severity and antipsychotic-related dopamine $D_{2/3}$ receptor occupancy in various striatal regions.
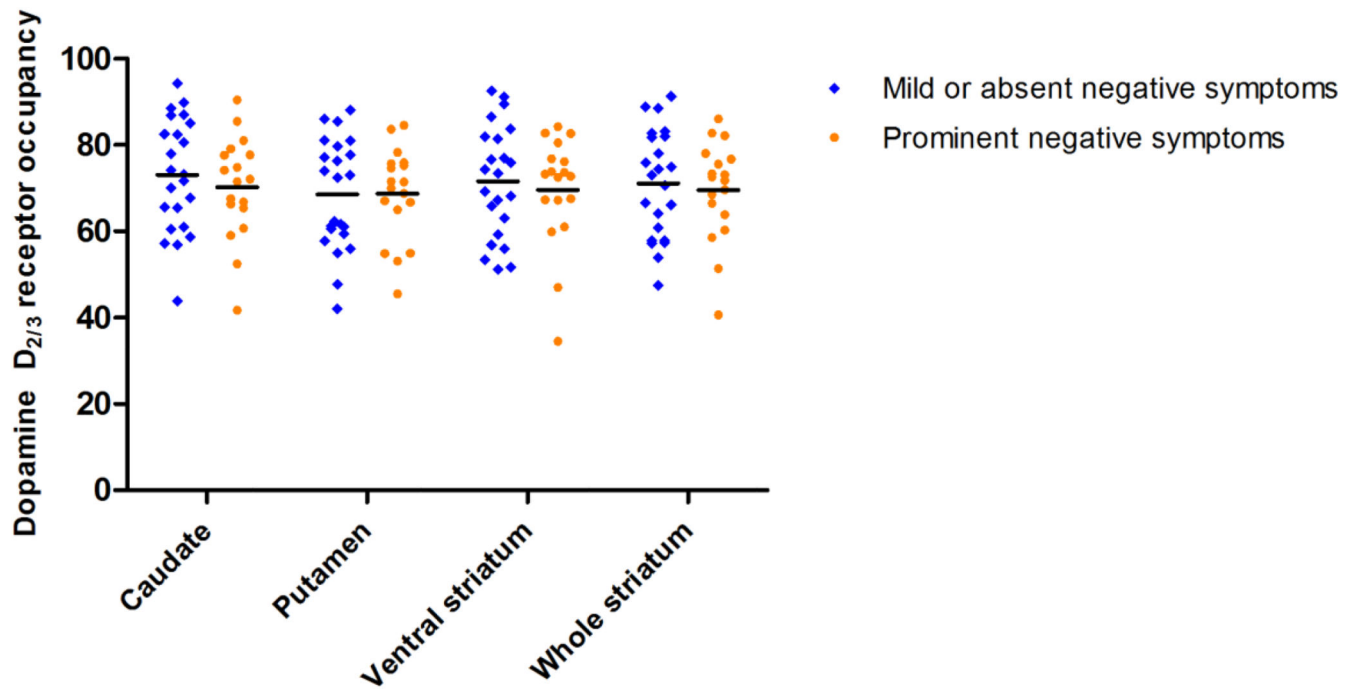
Figure 2.
Dopamine $D_{2/3}$ receptor occupancy for participants with prominent negative symptoms and those with mild or no negative symptoms. Horizontal line denotes the respective mean value.
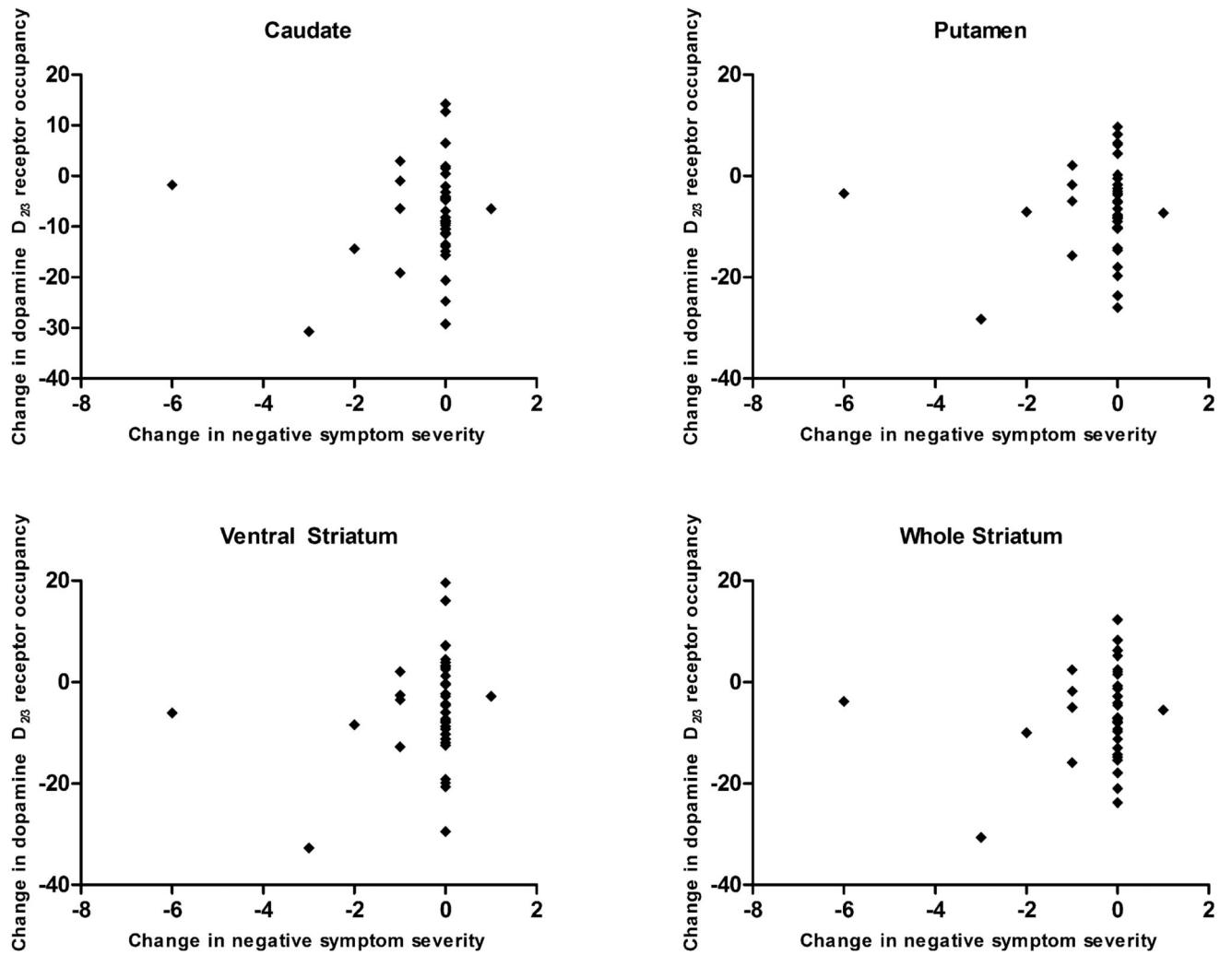
Figure 3.
Scatterplot of the relationship between changes in negative symptom severity and changes antipsychotic-related dopamine $D_{2/3}$ receptor occupancy in various striatal regions following antipsychotic dose reduction.

Table 1

Baseline demographic and clinical characteristics of 41 participants

Variable	Mean (S.D.) or %
Age (years)	60.2 (6.7)
Sex (% male)	73.2
Race (% white)	85.4
Diagnosis (%)	
Schizophrenia	80.5
Schizoaffective disorder	19.5
Illness duration (years)	34.3 (10.6)
Number of inpatient hospitalizations	5.9 (5.4)
Antipsychotic dose (mg/day)	
Olanzapine (N=24)	20.6 (6.7)
Risperidone (N=17)	4.3 (2.4)
Combined (Olanzapine equivalents[a]; N=41)	18.0 (7.9)
Participants receiving concomitant medications (N)	
Antiparkinsonian	4
Antidepressant	15
Mood stabilizer	7
Benzodiazepine	13
Any of the above	24
PANSS total score	60.2 (13.5)
BPRS total score	41.3 (8.7)

Abbreviations: BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale.

[a]Calculated using consensus-based antipsychotic dose equivalents based on Gardner et al. (20mg olanzapine = 6 mg risperidone) (Gardner et al. 2010).

Table 2

Clinical characteristics of participants before and after dose reduction of antipsychotic medication

Variable	Baseline PET Visit Mean (S.D.) or %	Follow-up PET Visit Mean (S.D.) or %	P-value[a]
Negative symptom severity			
Negative symptoms total	15.1 (5.1)	14.7 (5.1)	0.06
Social amotivation	8.0 (2.7)	7.8 (2.7)	0.03
Diminished Expression	9.4 (3.3)	9.3 (3.2)	0.17
Other symptoms			
Positive symptoms	8.1 (2.6)	8.0 (2.9)	0.42
Disorganized symptoms	7.3 (2.4)	7.2 (2.4)	0.23
Excitement symptoms	4.8 (1.3)	4.7 (1.1)	0.32
Depression symptoms	4.4 (1.7)	4.3 (1.5)	0.76
Extrapyramidal symptoms			
SAS total	3.1 (2.5)	1.8 (1.8)	<0.001
BAS global	0.7 (1.5)	0.2 (0.8)	0.005
Antipsychotic dose (mg/day)			
Olanzapine equivalents[b]	18.4 (8.0)	12.0 (5.0)	<0.001
Dopamine $D_{2/3}$ receptor occupancy (%)			
Caudate	72.9 (8.0)	65.2 (13.7)	<0.001
Putamen	69.8 (11.3)	63.1 (12.9)	<0.001
Ventral striatum	72.3 (11.3)	66.7 (13.9)	0.002
Whole striatum	71.7 (11.0)	65.0 (13.0)	<0.001

Abbreviations: BAS: Barnes Rating Scale for Drug-Induced Akathisia; PANSS: Positive and Negative Syndrome Scale; SAS: Simpson-Angus Scale.

[a] Based on paired-samples t-tests for individuals with both baseline and follow-up PET data (N=38).

[b] The dose of risperidone was converted to an olanzapine equivalent dosage, calculated using consensus-based antipsychotic dose equivalents based on Gardner et al. (20mg olanzapine = 6mg risperidone) (Gardner et al. 2010). The mean dose of olanzapine was 20.4 mg/day at baseline and 13.2 mg/day at follow-up (change: p<0.001), and the mean dose of risperidone was 4.5 mg/day at baseline and 2.9 mg/day at follow-up (change: p<0.001).

Table 3

Bivariate relationships between negative symptoms and antipsychotic-related dopamine $D_{2/3}$ receptor occupancy at baseline

	Caudate	Putamen	Ventral striatum	Whole striatum
Total score				
Negative symptoms	−0.10	−0.14	−0.13	−0.10
Subdomains				
Social amotivation	−0.10	−0.11	−0.13	−0.08
Diminished expression	−0.08	−0.12	−0.07	−0.09
Individual items				
Blunted affect	−0.03	−0.03	−0.04	−0.01
Emotional withdrawal	−0.19	−0.17	−0.16	−0.16
Poor rapport	−0.03	−0.13	−0.13	−0.09
Passive/apathetic social withdrawal	−0.10	−0.13	−0.10	−0.09
Lack of spontaneity & flow of conversation	−0.09	−0.10	−0.11	−0.07
Motor retardation	−0.01	−0.07	−0.08	−0.04

Note: All *P*-values were greater than 0.05.