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¹⁸F-Fallypride binding potential in patients with schizophrenia compared to healthy controls

Douglas S. Lehrer^{a,b,*}, Bradley T. Christian^c, Cemil Kirbas^b, Meicheng Chiang^a, Shawn Sidhu^a, Holly Short^a, Binqun Wang^b, Bingzhi Shi^b, King-Wai Chu^d, Brian Merrill^a, and Monte S. Buchsbaum^{a,b,e}

Douglas S. Lehrer: Douglas.lehrer@wright.edu; Bradley T. Christian: Bchristian@wisc.edu; Cemil Kirbas: Cemil.kirbas@khnetwork.org; Shawn Sidhu: Shawnsidhu@yahoo.com; Bingzhi Shi: Bingzhi.shi@khnetwork.org

^aWright State University Boonshoft School of Medicine, c/o Department of Psychiatry, East Medical Plaza, 1st Floor, 627 South Edwin C. Moses Blvd., Dayton, OH 45408, USA

^bBoonshoft Schizophrenia Center for Research, Innovation Center at Kettering Health Network, 3535 Southern Blvd, Kettering, OH 45429, USA

^cWaisman Laboratory for Brain Imaging, University of Wisconsin-Madison, 1500 Highland Avenue, Madison, WI, 53705, USA

^dWeill Medical College of Cornell University, Imaging Data Evaluation and Analysis Laboratory (IDEAL), 425 East 61 Street, New York, NY 10065, USA

^eDepartments of Psychiatry and Radiology, University of California, San Diego, NeuroPET Center, 11388 Sorento Valley Road, Suite #100, San Diego, CA 92121; Department of Psychiatry and Human Behavior/University of California-Irvine (emeritus); Mount Sinai School of Medicine (adjunct), New York, USA

Abstract

Background—Molecular imaging of dopaminergic parameters has contributed to the dopamine hypothesis of schizophrenia, expanding our understanding of pathophysiology, clinical phenomenology and treatment. Our aim in this study was to compare ¹⁸F-fallypride binding potential BP_{ND} in a group of patients with schizophrenia-spectrum illness vs. controls, with a particular focus on the cortex and thalamus.

Methods—We acquired ¹⁸F-fallypride positron emission tomography images on 33 patients with schizophrenia spectrum disorder (28 with schizophrenia; 5 with schizoaffective disorder) and 18 normal controls. Twenty-four patients were absolutely neuroleptic naïve and nine were previously medicated, although only four had a lifetime neuroleptic exposure of greater than two weeks. Parametric images of ¹⁸F-fallypride BP_{ND} were calculated to compare binding across subjects.

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*Corresponding author. Wright State University School of Medicine Boonshoft School of Medicine, Department of Psychiatry, East medical Plaza, 1st Floor, 627 S. Edwin C. Moses Blvd., Dayton, Ohio 45417, U.S.A. Tel.: +1 937 223 8840; fax +1 937 223 0758.

Contributors

Drs. Lehrer and Buchsbaum designed the study and wrote the protocol, performed statistical analyses, and wrote the first and revised drafts of the manuscript. Dr. Christian contributed to protocol preparation and both processed and analyzed fallypride images, providing major ligand binding kinetic expertise, and assisted in manuscript preparation and revision. Drs. Kirbas and Wang performed all image transformations and coregistrations, and Dr. Shi synthesized ¹⁸F-fallypride. Dr. Chiang and Ms. Short did MRI tracings for the Brodmann Area analyses, and Dr. Sidhu traced thalamic nuclei. Dr. Chu wrote computer programs for the above operations. Mr. Merrill materially assisted in the revision of the original manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest related to the conduct of this research or the submitted manuscript.

Results—Decreased BP_{ND} was observed in the medial dorsal nucleus of the thalamus, prefrontal cortex, lateral temporal lobe and primary auditory cortex. These findings were most marked in subjects who had never previously received medication.

Conclusions—The regions with decreased BP_{ND} tend to match brain regions previously reported to show alterations in metabolic activity and blood flow and areas associated with the symptoms of schizophrenia.

Keywords

Schizophrenia; Dopamine; Molecular imaging; Positron emission tomography; Thalamus; Cortex

1. Introduction

The dopamine hypothesis of schizophrenia has withstood many challenges over the past four decades and has emerged richly modified, anatomically refined (Garcia-Cabezas et al., 2007), elaborated and qualified. It remains intact as a central framework for hypotheses of schizophrenic pathophysiology, clinical phenomenology (Kapur, 2003) and treatment. Imaging with radiolabeled dopamine receptor ligands added a powerful tool to the study of dopamine receptors in psychotic disorders, but also highlighted the importance of each ligand's pharmacodynamic properties in defining the scope of testable hypotheses. The earliest study with radiolabeled chlorpromazine (Comar et al., 1979) showed cortical distribution abnormalities probably attributable to blood flow. Studies in the 1980's and 1990's using tracers such as ¹¹C-raclopride (Farde et al., 1990) and ¹¹C-methylspiperone (Wong et al., 1986) were by and large limited to examinations of the striatum and were inconsistent, although large studies (Tune et al., 1993) confirmed striatal abnormalities (see also reviews by Andreasen et al. (1988)).

Though these investigations produced valuable information, they contributed to a conceptual problem with a neuroanatomically constrained view of the dopamine system to the striatum and lower areas which are dense in D₂ receptors but less closely related in function to the cardinal findings in schizophrenia - auditory hallucinations (primary auditory cortex), executive function and affective modulation loss (dorsolateral prefrontal cortex), and language disturbance (left temporal lobe). Regional BP_{ND} is different across extrastriatal areas, highest in the thalamus, and then higher in temporal lobe, amygdala and hippocampus than frontal lobe. (Kegeles et al., 2008b) Percent receptor occupancy is also higher in extrastriatal regions after antipsychotic treatment (Kegeles et al., 2008a) although whether regional differences are statistically significant has not been systematically evaluated by, for example, repeated measures ANOVA comparing regions and only small samples have been studied.

The development of higher affinity ligands in the 1990's opened opportunities for in vivo measurement of D₂-type dopamine receptors in areas of the brain (especially cortico-striato-thalamic and fronto-limbic circuits) more strongly implicated in the pathophysiology of schizophrenia. Foremost among these newer compounds were the PET tracers ¹¹C-FLB457 (Olsson et al., 1999) and ¹⁸F-fallypride (Mukherjee et al., 1999) and the SPECT ligand, ¹²³I-epidepride (Kessler et al., 1992). Each has high affinity for both D₂ and D₃ (but minimally for D₄) dopamine receptors, and are commonly called D₂-type receptor ligands. Variations in cortical region D₂ binding with ¹⁸F-fallypride, for instance, can be compared within and across groups even in brain regions with relatively low D₂ density — a position supported by the finding of Mukherjee et al. (2002) of a test-retest variability of less than 10% both for striatal and temporal cortical regions. Frontal cortex was actually the most reliable area with the smallest percent error on test-retest.

Initial studies at independent labs using the newer ligands reported remarkably similar findings in separate cohorts of medication-naïve schizophrenic subjects. Groups in Sweden (Talvik et al., 2003) and Japan (Yasuno et al., 2004), performing ^{11}C -FLB457 PET, and our own group in Dayton, Ohio, using ^{18}F -fallypride PET (Buchsbaum et al., 2006), found reduced ligand binding potential (BP_{ND}) in the medial thalamus of ill subjects. While these studies each involved small samples ($n = 9, 10$, and 15 schizophrenic subjects, and $8, 19$, and 15 healthy controls, respectively) and had variations in methods and details of results, the similarity in main findings was striking. Each group also examined the relation of ligand binding to clinical symptoms, and while each reported somewhat different associations, each reported significant ligand binding-symptom correlations. Subsequent studies have extended these findings. Kessler et al. (2009) recently reported an ^{18}F -fallypride PET study in which unmedicated schizophrenic subjects ($n = 11$) had significantly higher BP_{ND} in the substantia nigra and lower BP_{ND} in the left medial thalamus than healthy controls ($n = 11$). It is also noteworthy that the thalamus has the highest D_2 binding potential of any area outside the striatum (Ito et al., 2008). Parametric analyses showed decreased BP_{ND} in the basal ganglia and increased BP_{ND} in the dorsolateral prefrontal cortex. Taken together, these findings highlighted the complex deficits across cortico-striato-thalamic circuits in people with schizophrenia.

SPECT findings have been less consistent. Tuppurainen et al. (2003) acquired ^{123}I -epidepride SPECT scans in 7 medication-naïve schizophrenic subjects and an equal number of controls, finding significantly lower BP_{ND} bilaterally in the temporal lobes of ill subjects; BP_{ND} correlated negatively with general and negative PANSS ratings. They later reported thalamic and midbrain analyses in which ill subjects had significantly lower BP_{ND} in the midbrain (roughly corresponding to the substantia nigra) but no significant group differences in the thalamus (Tuppurainen et al., 2006). Left thalamic BP_{ND} was negatively correlated with PANSS general symptoms, however. Glenthøj et al. (2006) also used ^{123}I -epidepride SPECT to scan 25 medication-naïve schizophrenic subjects and 20 controls and found no significant group differences. Ill subjects (but not controls) had significantly higher BP_{P} in the right than left thalamus, and ill male (but not female) subjects had higher frontal BP_{P} and significant positive correlation between BP_{P} and PANSS positive symptoms. The discrepancy between these SPECT studies, and the lack of statistically significant intergroup differences in the thalamus may have been due to inferior spatial resolution of SPECT as opposed to PET and the limitations that this imposed particularly on measuring discrete thalamic nuclei.

These studies have not yet exploited the potential of these high-affinity dopamine receptor ligands to systematically assess binding potential in specific cortical regions associated with both the functional anatomy and the observed imaging deficits of schizophrenia. These include the dorsolateral prefrontal cortex, left lateral temporal lobe, and primary auditory cortex as reviewed elsewhere (Andreasen et al., 1997). More recent reviews have found “clear support for hypofrontality” but suggest that “researchers should consider the entire network of regions involved in a given task when making inferences about the biological mechanisms of schizophrenia” (Glahn et al., 2005). Though striatal ^{18}F -fallypride BP_{ND} has values 8–20-fold greater than cortex (Riccardi et al., 2006), the greater volume of individual Brodmann cortical areas or groups of areas ($20\text{--}300\text{ cm}^3$) than striatal volume ($4\text{--}10\text{ cm}^3$) suggests a large and significant role of cortical D_2 binding in brain networks involved in higher cognitive function. Consideration of cortical dopaminergic function is clearly an important facet of a wider understanding of cortical activity abnormalities in schizophrenia.

Because of the earlier replication of the decreased BP_{ND} in the medial dorsal nucleus of the thalamus, a key relay center for intra-prefrontal communication-coordination and schizophrenia deficits (Alelu-Paz and Gimenez-Amaya, 2008), as well as the literature on

prefrontal FDG uptake and cerebral blood flow abnormalities, we hypothesized that prefrontal BP_{ND} would be decreased in this larger sample. Second, because of extensive reports of abnormalities of structure and function of the left temporal lobe, especially the superior temporal gyrus (Mitelman et al., 2003) and auditory cortex (Bleich-Cohen et al., 2009; van Haren et al., 2007) as well as the sensitivity of auditory hallucinations to dopamine receptor blocking drugs, we hypothesized this area would also show reduced binding potential. Additional evidence to support this hypothesis include decreases in fractional anisotropy and white matter volume in left hemisphere fasciculus underlying these areas (O'Daly et al., 2007; Seok et al., 2007), and a post-mortem examination of D₂ receptors using ¹²⁵I-epidipride that revealed dense bands of D₂ receptors with highest frequency in auditory and speech association cortices (BA 22, 39 and 42) that were disrupted in patients with schizophrenia (Goldsmith et al., 1997). Some studies have identified a primary auditory activation associated with hallucinations, most notably a large multicenter study of over 100 patients (Ford et al., 2009). Others have supported a frontal abnormality (Parellada et al., 2008), while a review examining interregional relationships has implicated primary auditory cortex connectivity with the prefrontal region (Ahveninen et al., 2006).

2. Materials and methods

2.1. Subjects

Thirty-three patients with schizophrenia spectrum disorder (25 men; 8 women; mean age, 28.8; S.D., 10.8) were recruited from the greater Dayton, Ohio, area. All participants underwent verbal and written informed consent, followed by oral administration of an informed consent "post-test" designed to cover the major aspects of the informed consent process. All participants passed this test and gave written informed consent. We clinically evaluated our earlier subject cohort (Buchsbaum et al., 2006) ($n = 15$) using the Comprehensive Assessment of Symptoms and History (CASH) and Brief Psychiatric Rating Scale (BPRS, 18-item version). We clinically assessed later subjects ($n = 18$) using the Positive and Negative Syndrome Scale (PANSS), from which BPRS scores could be estimated for the purpose of combining all subjects. A board-certified psychiatrist (author D.S.L.) diagnosed all subjects using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). We followed the very few schizophreniform subjects (i.e., duration of illness less than six months at the time of study) in order to determine whether they eventually met criteria for schizophrenia; this diagnostic conversion occurred in all such cases. We ultimately diagnosed twenty-eight subjects with schizophrenia and five with schizoaffective disorder. Twenty-four patients were absolutely neuroleptic naïve and nine were previously medicated, although only four had a lifetime neuroleptic exposure of greater than two weeks. These nine subjects received a wide variety of neuroleptics (high and low potency, first and second generation), and six of the nine had lifetime exposure to more than one drug. No subject had received neuroleptic within 30 days of study, and no subjects were concurrently treated with antidepressants, benzodiazepines, lithium salts, or anticonvulsant drugs. Subject characteristics are summarized in Table 1.

2.2. Controls

Eighteen normal control subjects (11 men; 7 women; mean age, 28.9; S.D., 9.4) were age- and sex-matched to experimental subjects. We used available funds to optimize ill subject enrollment at the expense of control sample size, hence the unequal ill vs. control numbers. Controls underwent psychiatric assessment; none had a history of psychiatric illness, substance use disorder, clinically significant head trauma, or active neurological disease.

2.3. PET scans

The subjects refrained from alcohol and caffeine 4 h before the PET scanning session. The PET scans were acquired using an ECAT EXACT HR+scanner in 3D mode (Brix et al., 1997). Subjects were placed in the scanner in the supine position, with the brain centered in the axial field of view. A 5 minute transmission scan was first acquired using a $^{68}\text{Ge}/^{68}\text{Ga}$ rod source to correct for the attenuation of photons. The head was fixed with a piece of surgical tape. Dynamic acquisition of the PET dynamic data was initiated with the 30 second bolus injection of ^{18}F -fallypride. The radiopharmaceutical was produced according to previously reported methods (Mukherjee et al., 1995) at high specific activity (>2000 Ci/mmol) with a dose of 0.7 mCi/10 kg (range of 3.7–7.4 mCi). The cohort averages for injected doses of radioactivity and fallypride mass are given in Table 1. There was no significant difference in the injected activity or the injected fallypride mass between groups.

The early subject cohort underwent 2 h of dynamic PET imaging, while the latter were scanned for 3 h from start to finish, with a 20 minute rest period mid-scan. We will discuss this further in the discussion section. The data were reconstructed using the ECAT v7.2 OSEM following the corrections applied for attenuation, normalization, and scatter. Prior to further data processing the dynamic frames were spatially aligned using the AIR 3.08 software (Woods et al., 1992) to correct for patient motion. The cerebellum was used to represent the reference region (devoid of specific ligand-receptor binding) for the data analysis. Multiple, circular regions of interest were placed over outer lobules of the cerebellum, covering two 3.5 mm thick transaxial planes to obtain cerebellar values.

Coregistration to anatomical images is by using early sum images. We register early sum ^{18}F -fallypride volumes to AC–PC aligned 3D anatomical volume with 12-parameter affine registration model using a FLIRT tool. We then applied the transformation matrix obtained previously to the distribution volume ratio (DVR) ^{18}F -fallypride volume to register the DVR volume to AC-PC aligned 3D anatomical volume using FLIRT.

2.4. MRI scans

MRI scans were acquired using a GE Signa NVi system (General Electric, Milwaukee) (TR = 24 ms, TE = 5ms, flip angle = 40° , slice thickness = 1.2 mm, pixel matrix = 256×256 , field of view = 23 cm, total slices = 128). These anatomical images were used to identify gray/white anatomical structures by individual Brodmann area.

2.5. Data analysis

2.5.1. Binding potential parametric image analysis—Parametric images of ^{18}F -fallypride BP_{ND} were generated to permit group comparison over the entire volume of the brain using the SPM software. The BP_{ND} images reported here were calculated using a multilinear variation (Ichise et al., 2002) of the Logan (Logan et al., 1996) distribution volume ratio (DVR). This model employs the use of a tissue reference region (cerebellum) to represent the kinetics of unbound radioligand in the tissue (Cunningham et al., 1991; Logan et al., 1996). More details of these methods can be found in our previous report (Buchsbaum et al., 2006).

2.5.2. Brodmann's area measurements and tissue type quantification—Perry et al. (unpublished) (Perry et al., 1996) provided a coronal atlas, composed of 33 axial maps of Brodmann's areas (BA), based on microscopic examination of entire hemisphere of a post-mortem brain (see Fig. 1). Our earlier use of the Perry atlas (Hazlett et al., 1998; Mitelman et al., 2005b; Simeon et al., 2000; Stein et al., 1998) describes the method in greater detail. Coronal slices perpendicular to the anterior commissure–posterior commissure (AC–PC) line were reconstructed in a 256×256 pixel matrix. First we determined the front (first slice

containing the cortical ribbon) and back of the brain (last slice containing the cortical ribbon) and identified 33 evenly spaced slices such that the first slice began 1/34th of the distance from front to back. For each temporal lobe, we identified the temporal pole and the most posterior extent of the Sylvian fissure and divided the space into 13 equally spaced slices. The brain edge was obtained on the approximately circular 33 non-temporal slices and 26 (13 in each hemisphere) temporal slices by depositing points visually on the tips of the gyri and then fitting a spline curve to the points. Each slice was then divided into 20 radial sectors on each hemisphere surface and 10 midline sectors (Hazlett et al., 1998). BA's were then assessed for the gray, white and CSF pixels within each sector (see segmentation method below); means are weighted according to the number of sectors in each region of interest and proportionately combined to obtain a single measure. Some of the smallest BA's are combined (e.g. 3-1-2-5) for conservative simplicity. Data from 39 BA's areas identified by Perry (1-2-3-5, 4, 6, 8, 9, 10, 11, 12, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 7a and 7b) were obtained.

BP_{ND} was defined as an average value for the region-of-interest outline. Reliability of the tracing method and consistency across two scans for gray matter volumes and FDG obtained 8 weeks apart is described elsewhere (Mitelman et al., 2005a).

We used repeated measures MANOVA to test our major hypotheses of abnormalities in temporal and frontal lobes, as well as the thalamus. We used diagnosis (normal, patient) as an independent group dimension and hemisphere (right, left) and region (Brodmann area) as repeated measures. This approach mitigates against Type I error associated with multiple *t*-testing of each area since one single *F* confirms a regional difference between groups while it combines areas and may also minimize Type II error by averaging across regions and hemispheres. Note that uninterpretable main effects (e.g., hemisphere) are not reported.

3. Results

3.1. Lateral Temporal Lobe (Fig. 2)

Ill subjects (medication-naïve and previously treated) displayed lower BP_{ND} in the superior temporal gyrus (BA 22) compared with healthy controls (MANOVA design of Diagnosis × BA, $F = 3.91$, $df = 4,96$, $p = 0.0055$; Wilks, $F = 3.74$, $df = 4,94$, $p = 0.0071$; Fig. 2).

3.2. Auditory cortex (Fig. 3)

Similarly, normals had greater BP_{ND} than previously-medicated patients who, in turn, had greater BP_{ND} in the auditory cortex than drug-naïve patients. This was confirmed in an analysis of Medication History × Hemisphere × BA ($F = 3.52$, $df = 2,48$, $p = .037$. This effect was more prominent on the left than on the right (diagnostic group by hemisphere, $F = 3.67$, $df = 2,48$, $p = 0.032$; Fig. 3).

3.3. Prefrontal cortex (Fig. 4)

BP_{ND} in the prefrontal cortex was lower in ill subjects than normal volunteers in anterior and dorsolateral prefrontal cortex and this was most marked in drug naïve patients (diagnostic group by prefrontal area by BA by hemisphere, group by prefrontal area by BA area interaction, $F = 2.35$, $df = 12, 282$, $p = 0.0068$, Wilks multivariate $F = 1.94$, $df = 12,84$, $p = 0.040$). This was confirmed in post-hoc testing for the anterior prefrontal cortex, BA 8, 9, and 10 ($F = 3.74$, $df = 4,96$, $p = 0.0071$, Huynh-Feldt $df = 2.76$, 66.23 , $p = 0.018$) but not dorsolateral ($F = 1.68$, $df = 2,96$, $p = 0.16$). We examined the normality of distribution for the binding potential and the Kolmogorov–Smirnov tests did not reveal significant departure from normal across the entire group (Fig. 4).

3.4. Thalamus

The medial dorsal nucleus of the thalamus showed lower BP_{ND} in medication naïve and previously medicated patients (1.83, S.D. = .36) than in normal controls (2.09, S.D. = .20) and this also was confirmed in the three-group ANOVA ($F = 5.61$, $df = 2, 49$, $p = 0.0064$).

3.5. Correlations with demographic and clinical variables in patients

The patients had a restricted age range and there were no significant correlations between BP_{ND} and age. Symptom severity as assessed by total BPRS was significantly associated with motor and sensory areas (left BA 1, 4, 7 and right BA 1, 4, and 7, all $r > 0.35$, $df = 1, 32$, $p < 0.05$). Because left primary auditory areas were found to have low BP_{ND} and because of their potential involvement in auditory hallucinations, we examined the left auditory area correlation but it did not reach significance (-0.25 , lower BP_{ND} correlated with higher BPRS positive scores, $p = 0.3$).

Because the finding of reduced BP_{ND} in the medial dorsal nucleus of the thalamus has been previously reported, we examined the correlation between BP_{ND} in the medial dorsal nucleus (right+left) and symptom severity as assessed by total BPRS score and found low BP_{ND} associated with total BPRS ($r = -0.37$, $df = 31$, $p = 0.044$) when age and sex were partialled out (age was significantly correlated with total BPRS). A trend towards significance was found between the BPRS positive symptom subtotal and BP_{ND} in the right MDN ($r = -0.31$, $df = 31$, $p = 0.087$).

We evaluated whether the cortical BP_{ND} were differentially affected in normal volunteers and patients by combining the two and three hour uptake periods. No group by uptake period interaction was significant for any of the ANOVA designs reported, including frontal, thalamic, lateral temporal, or auditory cortex.

Five patients were identified as schizoaffective. We conducted analyses omitting these patients and found the effect sizes essentially unchanged. Despite reduced sample size, results were very similar. The differential reduction in superior temporal gyrus (without division into previously medicated and never medicated) was strongly confirmed $F = 5.58$, $df = 2, 88$, $p = 0.00521$; MANOVA Wilks 0.77, $F = 6.52$, $p = 0.0033$) as was differential reduction in auditory cortex $t = 2.08$, $df = 44$, $p = 0.043$). Prefrontal Brodmann regions 8, 9, and 10 yielded a similar effect (group by region interaction, $F = 7.65$, $df = 2, 88$, $p = 0.00086$, MANOVA Wilks .82, $F = 4.57$, $df = 2, 43$). Thus removal of the patients diagnosed as schizoaffective had little effect on the significance levels of our findings.

4. Discussion

This report describes, to our knowledge, the largest cohort of unmedicated and neuroleptic-naïve schizophrenic subjects ever imaged using a high-affinity D₂/D₃ dopamine receptor PET ligand. We were able to gain a large sample size of ill subjects by augmenting our previously-published group of treatment-naïve subjects with additional never-medicated patients, in addition to a number of previously-treated subjects and additional controls. Our larger sample permitted examination of (1) cortical gray matter in individual BA's implicated in both neuropsychological and functional imaging studies as salient to the symptoms of schizophrenia, and (2) the effect of prior treatment on ligand binding. To our knowledge, this represents the first report of cortical in vivo human D₂/D₃ receptor ligand binding by individual Brodmann area, thus establishing a means for further refining the dopamine hypothesis of schizophrenia. This technique (or similar ones) can also be applied to studies of the functional anatomy of dopaminergic pathways in humans, complimenting post-mortem work published by Garcia-Cabezas et al. (2007). Finally, the larger sample

extended our previous demonstration of reduced ^{18}F -fallypride BP_{ND} in the medial thalamus of unmedicated patients with schizophrenia-spectrum illness.

4.1. Lateral temporal cortex

BA 41 and 42, the anterior and posterior transverse temporal areas, respectively, collectively constitute the primary auditory cortex. This area is clearly a candidate for the origin of hallucinations, a key symptom in schizophrenia and the schizophrenia spectrum (Oertel et al., 2009). Our finding of reduced BP_{ND} in ill subjects reinforces the application of dopaminergic hypotheses to the auditory cortex, and by implication, to the phenomenon of schizophrenic symptoms. Our failure to demonstrate a significant correlation between BP_{ND} and BPRS positive symptom ratings may have resulted from the myriad symptoms (hallucinations, delusions, conceptual disorganization, etc) that compose that particular subscale. A more detailed and specific clinical rating tool (e.g., the Auditory Hallucinations Rating Scale) may have yielded different results, and could be considered in future studies pertaining to this cortical region.

Ill subjects had decreased BP_{ND} in the superior temporal gyrus (STG, BA 22), an area characterized by gray matter volume reductions across the schizophrenia spectrum. A recent report (Venkatasubramanian, 2010) found a significant negative correlation between PANSS Positive Syndrome scores and STG gray matter volume. Though we did not find a significant correlation between BA 22 BP_{ND} and BPRS ratings, the sample size and heterogeneity and our use of the BPRS (vs. another tool) may well have limited our ability to probe this relationship. Nonetheless, this remains an area of interest with respect to psychopathology and perhaps antipsychotic drug response.

4.2. Frontal cortex

Decreased BP_{ND} was found in prefrontal cortex and confirmed in post-hoc testing for BA 8, 9, and 10 but was of smaller magnitude for dorsolateral areas 44, 45 and 46. Most studies reviewed did not specifically compare the frontal cortex between normal volunteers and patients, perhaps partly because dopaminergic transmission in prefrontal cortex is considered to be related to D_1 dysfunction (Howes and Kapur, 2009).

4.3. Thalamus

Five earlier PET studies with high-affinity D_2/D_3 receptor ligands have shown reduced BP_{ND} (Buchsbaum et al., 2006; Kessler et al., 2009; Talvik et al., 2006, 2003; Yasuno et al., 2004). In one negative study with six patients, a medium effect size was found (0.51) which was not significant with that sample (Tuppurainen et al., 2006). Our earlier study overlaps with 30 subjects (15 case, 15 control) with the current data analysis and the current sample has an effect size of 0.89. It has been suggested that because there is an association between increased dopaminergic activity in the thalamus and decreased sensory gating (Young et al., 1995) that the decreased BP_{ND} in the thalamus may be an important contributor to defects in sensory gating observed in patients with schizophrenia (Takahashi et al., 2006). Path coefficient analysis of D_2 receptor binding revealed differential connectivity of the thalamus in patients with schizophrenia, consistent with disturbed prefrontal cortex-thalamus dopamine signaling (Yasuno et al., 2005). SPECT imaging of ^{123}I -epidepride binding did not reveal low values in either cortex or thalamus in patients with schizophrenia (Glenthøj et al., 2006), but low resolution may have diminished the possibility of finding medial dorsal decreases. The data analysis combined relatively large areas of the frontal and temporal region and it is possible that smaller regions of interest would have revealed a more complex pattern of differences. MRI spectroscopy has also recently implicated thalamic dysfunction. In a longitudinal study, glycerophosphoethanolamine was lower in the left thalamus at 30

months compared with patients at baseline and volunteers at 30 months, consistent with a neurodegenerative process in certain cases of schizophrenia (Miller et al., 2009).

4.4. Previous neuroleptic exposure

Patients who had previous medication exposure tended to show BP_{ND} values midway between normal volunteers and entirely medication naïve subjects. This is a very low sample size of previously medicated patients, especially those with substantial medication history. Moreover, the ill sample includes subjects early in a first episode of psychosis with short durations of untreated psychosis (DUP), while others had chronic untreated illness with long DUP. Because DUP was not known for a substantial number of subjects, we were unfortunately unable to incorporate DUP into our analyses. However we note several speculative possibilities that could explain our observations. First, patients who were never medicated (especially over prolonged periods of active psychosis) may represent a subtype of schizophrenia associated with fewer disruptive behavioral symptoms of the sort that typically trigger referral for clinical evaluation and treatment. Second, patients who receive very brief treatment and then choose to stop taking the drugs, may have a pathophysiologic variant that makes them more prone to drug-induced hypodopaminergia, and thus suffer intolerable dysphoria. This might even represent a non- D_2 receptor (or other variant) form of psychosis. Finally, antipsychotic treatment may result in changes in dopamine receptor density or affinity. Further expanded sample studies will be necessary to address this question.

4.5. Binding potential, receptor occupancy and symptom severity

The finding of a correlation between BP_{ND} and symptom severity would support the relationship between regional dopaminergic function as assessed by high affinity D_2 ligands and the clinical expression of schizophrenia. Significant correlations between total BPRS and medial thalamus BP_{ND} were -0.64 in an ^{11}C -FLB457 study (Yasuno et al., 2004) and -0.37 in our own study, replicating the earlier report. These findings further suggest that extrastriatal receptors may be at least partly responsible for clinical improvement. Interestingly, Agid et al. (2007) found a correlation of -0.36 between receptor drug occupancy in the thalamus and change in PANSS ratings, consistent with the concept that medial dorsal receptor blockade was related to symptom improvement. While this correlation missed statistical significance in their smaller sample, their study was powered to detect striatal occupancy vs. symptom improvement correlations based on their earlier ^{11}C -raclopride studies. Detailed study of individual symptoms and specific cortical and subcortical extrastriatal areas in a larger sample may reveal not only important relationships between D_2 abnormalities and schizophrenic pathophysiology, but relationships with the pharmacology of individual differences in treatment response as well.

4.6. Additional limitations

Some limitations of the use of the cerebellum as a reference are suggested by the significant findings in some frontal areas of mean values under 1.0. These may relate to different proportions of gray white and CSF in the cerebellum reference area and imperfections in the kinetic model. A comparison examination of test-retest values for ^{11}C -FLB457 (Vilkman et al., 2000) using several different models produced thalamic values similar to ours and frontal values somewhat lower but still with significant interclass correlation coefficients for different models, suggesting that frontal cortex findings are relatively reliable and can be interpreted even if the values are under 1.0. In an interesting editorial, Eckelman et al. (2009) comment on our fallypride quantification method and note that while BP_{ND} measures “do not always match in vitro values but can maintain rank order and in some cases show sufficient dynamic range to be useful measures of changes in evaluating pharmacology or disease”. Small levels of significant cerebellar D_2/D_3 receptor binding have been reported in

literature (Delforge et al., 1999; Mukherjee et al., 2002; Olsson et al., 2004; Olsson et al., 1999; Pinborg et al., 2007) and can introduce a bias in the estimation of BP_{ND} and distribution volume ratio (DVR) (Asselin et al., 2007). The effects of specific binding in the reference region are of greatest concern in drug occupancy studies, where competing drugs will alter binding in both the target and reference regions. In this work, we report only baseline measurements of ^{18}F -fallypride BP_{ND} and can estimate that the variation due to specific binding in the reference region will be less than 5% (Christian et al., 2009).

Missing clinical information prevents us from considering some very important variables in our analyses. For instance, we lack a full data set concerning the substance use histories for all ill and control subjects, and are unable to assess the effects of recent or past recreational drug use/abuse on dopamine receptors. Finally, the heterogeneity of our sample with respect to length of illness, duration of untreated psychosis, medication history, etc, represents a limitation. Future studies with more homogeneous (or larger) samples will be able to address the effect of these variables on D_2/D_3 ligand binding.

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Fig. 1.

Brodmann area method. Left upper row: Original drawing by Perry. Middle upper row: Application of sectors to Perry drawing with sector tips originating at computer-located hemispheric centroid and sector borderlines drawn to traced edge. Right upper row: MRI with sector lines applied in same way and sectors numbered. Left bottom row: Perry atlas in 3D position Right: Perry atlas with Brodmann areas identified as colored spokes; area 10 in cerise, area 46 in yellow, area 9 in blue.

Fig. 2.
Binding potential in lateral temporal lobe. Superior temporal gyrus shows marked decrease in binding potential in medication-naïve patients.

Fig. 3.
Primary auditory cortex.

Fig. 4.
 ^{18}F -Fallypride binding potential in prefrontal regions.

Table 1

Subject characteristics.

	Patients (<i>n</i> = 33)	Controls (<i>n</i> = 18)
Sex, No. M/F	25/8	11/7
Race, No. White/African American/Biracial	26/7/0	15/2/1
Age, y (S.D.)	28.8 (10.8)	28.9 (9.4)
¹⁸ F-fallypride injected dose, mCi (S.D.)	5.4 (1.2)	5.5 (1.1)
Fallypride mass, µg/kg (S.D.)	0.011 (0.0006)	0.011 (0.0014)
Social Class ^a , Mean (S.D.)	39.2 (17.1)	35.7 (8.5)
Handedness, No. Right/Left-handed	31/2	15/3
Duration of illness, median/mean (S.D.), wk	78/204 (241)	
Less than one year	14	
One to five years	9	
Five to ten years	6	
Greater than ten years	4	
BPRS Total Score (S.D.)	51.8 (12.3)	
Lifetime neuroleptic exposure		
Never previously medicated	24	
Less than one week of lifetime doses	3	
1–2 weeks of lifetime doses	2	
12 weeks of lifetime doses	1	
~3 years of lifetime doses	1	
At least 4 years of lifetime doses	2	

^a Hollingshead Two Factor Index of Social Position for family of origin.