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Heli Tuppurainen

Extrastriatal Dopamine D2/3 Receptors in Schizophrenia

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UNIVERSITY OF EASTERN FINLAND

HELI TUPPURAINEN

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ABSTRACT:
Several lines of studies on schizophrenia have suggested abnormalities in dopaminergic neurotransmission and dopamine receptor densities. The aim of this study was to evaluate putative alterations of the dopamine D2/3 receptor density in extrastriatal brain regions among drug-naïve schizophrenic patients compared to healthy subjects, to compare drug-induced extrastriatal dopamine D2/3 receptor binding between different antipsychotic agents, as well as to investigate the relationship between extrapyramidal side-effects and dopamine D2/3 binding.

The densities of D2/3 receptors were studied in seven antipsychotic-naïve patients with schizophrenia and seven healthy controls using single-photon emission computed tomography (SPECT) ligand [123I]epidepride. The results indicated significantly reduced dopamine D2/3 receptor density in the temporal cortex and substantia nigra among patients compared with healthy subjects. Dopamine D2/3 receptor density correlated inversely with general psychopathological schizophrenic symptoms in the temporal cortex and thalamus.

To determine dopamine D2/3 apparent binding potential and occupancy, [123I]epidepride SPECT imaging was performed on 13 schizophrenia patients treated with medication (seven with clozapine, four with olanzapine and two with haloperidol), six drug-naïve patients and seven healthy controls. The results suggested divergent dopamine D2/3 apparent binding potential and occupancy by different antipsychotics in substantia nigra, showing the lowest D2/3 binding indices for clozapine, followed by olanzapine, when compared to haloperidol. Extrapyramidal symptoms were also found to correlate negatively with antipsychotic-induced D2/3 binding in substantia nigra among medicated patients. In the temporal cortex, D2/3 binding did not differ significantly between typical and second-generation antipsychotics.

These imaging findings in extrastriatal D2/3 receptor density support the hypothesis on the dysfunction of mesocortical dopamine transmission underlying cognitive symptoms in schizophrenia, as well as emphasizing the role of thalamo-cortical dopaminergic function in the pathophysiology. The observed decrease of D2 autoreceptors in the substantia nigra contributes to the dysregulation of dopamine neurotransmission in the striatum of schizophrenic patients. Furthermore, results from studies with medicated patients provide clues concerning the differences in clinical profile and therapeutic efficacy, as well as the side-effects between different antipsychotic drugs.

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TIIVISTELMÄ

Lukuisat tutkimustulokset ovat viitanneet poikkeavuuksiin dopaminergisessä hermovälityksessä ja dopamiinireseptoritiheydessä skitsofreniassa. Tämän tutkimuksen tavoitteena oli arvioida mahdollisia dopamiini D2/3 reseptoripaikkojen muutoksia ekstrastriataalisilla aivoalueilla lääkkeettömillä skitsofreniapotilailla verrattuna terveisiin ja verrata lääkityksen aiheuttamaa ekstrastriataalista dopamiini D2/3 reseptoreiden salpausta eri antipsykoottien välillä, sekä tutkia ekstrapyramidaalisten haittaoireiden ja dopamiini D2/3 sitoutumisen yhteyttä.

D2/3 reseptoritiheyttä tutkittiin seitsemällä, aiemmin lääkitsemättömällä skitsofreniapotilaalla, sekä seitsemällä terveellä verrokilla käyttäen yksifotoniemissiotietokonetomografia (SPECT) tutkimuksessa [123I]epidepridi merkkiaineetta. Tulokset osoittivat D2/3 reseptorien määrän olevan merkitsevästi alentunut ohimolohkojen kuorikerroksella ja substantia nigrassa lääkitsemättömillä skitsofreniapotilailla terveisiin verrattuna. Dopamiini D2/3 reseptoritiheys korreloi käänteisesti psykopatologisiin skitsofreniaoireisiin ohimolohkojen kuorikerroksella ja thalamuksessa.

Dopamiini D2/3 sitoutumispotentiaalin ja lääkityksen aikaansaaman reseptorimiehityksen määrittämiseksi suoritettiin [123I]epidepridi SPECT tutkimus 13 lääkitylle skitsofreniapotilaalle (seitsemän sai klotsapiinia, neljä olantsapiinia ja kaksi haloperidolia), kuudelle lääkitsemättömälle potilaalle ja seitsemälle terveelle verrokille. Tulokset viittasivat eroihin dopamiini D2/3 sitoutumispotentiaalissa ja reseptorimiehityksessä eri antipsykoottien välillä substantia nigrassa. Matalimmat D2/3 sitoutumisindeksit olivat klotsapiinilla, mitä seurasi olantsapiini ja korkeimmat olivat haloperidolilla. Ekstrapyramidaalioireiden havaittiin myös korreloivan negatiivisesti antipsykoottien aiheuttamaan D2/3 reseptorisalpaukseen substantia nigrassa. Ohimolohkojen kuorikerroksella D2/3 sitoutuminen ei eronnut merkitsevästi perinteisen ja toisen polven antipsykoottien välillä.

Nämä ekstrastriataalista D2/3 reseptoritiheyttä koskevat kuvantamislöydökset tukevat hypoteesia, jonka mukaan skitsofrenian kognitiivisten oireiden taustalla on mesokortikaalisen dopamiinihermovälityksen toimintahäiriö. Tulokset myös painottavat thalamo-kortikaalisen dopaminergisen toiminnan merkitystä skitsofrenian patofysiologiassa. Havaittu D2 autoreseptorien alenema substantia nigrassa myötävaikuttaa striatumin dopamiinihermovälityksen säätelyhäiriöön skitsofreniapotilailla. Lisäksi tutkimustulokset antavat viitteitä eri antipsykoottien eroista kliinisen profiilin ja lääkehoidon tehon, sekä haittaoireiden välillä.

Luokitus: QV 77, WL 102.8, WM 203
Yleinen suomalainen asiasanasto (YSA): dopamiini – reseptorit; kuvantaminen – lääketiede; skitsofrenia – lääkehoito

To my family with love

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Heli Tuppurainen

List of original publications

This dissertation is based on the following original publications referred to in the text by their Roman numerals I-IV.

I. Tuppurainen H, Kuikka J, Viinamäki H, Husso-Saastamoinen M, Bergström K, Tiihonen J. Extrastriatal dopamine D2/3 receptor density and distribution in drug-naïve schizophrenic patients. Mol Psychiatry 8:453-455, 2003.

II. Tuppurainen H, Kuikka JT, Laakso MP, Viinamäki H, Husso M, Tiihonen J. Midbrain dopamine D2/3 receptor binding in schizophrenia. Eur Arch Psychiatry Clin Neurosci 256:382-387, 2006.

III. Tuppurainen H, Kuikka JT, Viinamäki H, Husso M, Tiihonen J. Dopamine D2/3 receptor binding potential and occupancy in midbrain and temporal cortex by haloperidol, olanzapine and clozapine. Psychiatry Clin Neurosci 63:529-537, 2009.

IV. Tuppurainen H, Kuikka JT, Viinamäki H, Husso M, Tiihonen J. Extrapyramidal side-effects and dopamine D2/3 receptor binding potential in substantia nigra. Nord J Psychiatry 64:233-238, 2010.

The publishers of the original publications have kindly granted permission to reprint the articles to this dissertation.

Contents

ABBREVIATIONS

AC	Adenyl cyclace
AMPA	α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid
α-MPT	α -methyl-para-tyrosine
ANCOVA	Analysis of variance
BMI	Body mass index
BPapp	Apparent binding potential
BPRS	Brief psychiatric rating scale
C	Radioactivity
CA	Catecholamine
cAMP	Cyclic adenosine monophosphate
CT	Computed tomography
DA	Dopamine
DAT	Dopamine transporter
DSM-III-R	Diagnostic and statistical manual of mental disorders, version number III-R
DTI	Diffusion tensor imaging
EEG	Electroencephalogram
ES	Effect size
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GLU	Glutamate
5-HT	5-hydroxytryptamine
ICD-10	International statistical classification of diseases and related health problems 10th revision version
L-DOPA	L-dihydroxyphenylalanine
MB	Midbrain
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRS	Magnetic resonance spectroscopy
NA	Noradrenalin
NMDA	N-methyl-D-aspartate
O	Occupancy
PANSS	Positive and negative syndrome scale for schizophrenia

PCP	Phencyclidine
PET	Positron emission tomography
PFC	Prefrontal cortex
ROI	Region of interest
SANS	Scale for the Assessment of Negative Symtoms
SAPS	Scale for the Assessment of Positive Symtoms
SAS	Simpson and Angus Scale
SB	Specific binding
SCID	Structured clinical interview for DSM-III-R
SD	Standard deviation
SN	Substantia nigra
SPECT	Single-photon emission computed tomography
TAC	Time activity curve
TP	Temporal pole
VTA	Ventral tegmental area

1 INTRODUCTION

Schizophrenia is considered to be one of the most important diseases in psychiatry. Although it is less common than some other disorders, the social influence of schizophrenia is emphasized by early age of onset, the usually chronic course of the illness and the long-term requirement for medical care. Despite intensive research striving to understand the cause of schizophrenia, the aetiology has largely remained unknown.

The invention of neuroleptic drugs in 1952 provided a novel strategy for seeking the biological basis of schizophrenia. Since then, any model of schizophrenia is confronted by the fact that dopamine D2 receptor blockade is an essential feature in effective treatment, at least for positive symptoms, thus suggesting that dopaminergic transmission could form a prominent component of schizophrenia (Seeman, 1987).

During the last twenty years, new methodologies have been introduced into neuropsychiatric research, contributing significant new information concerning the aetiology and pathophysiology of schizophrenia. Advancements in brain imaging techniques have enabled functional imaging of neuroreceptors with either positron emission tomography (PET) or single photon emission computed tomography (SPECT), thus

offering direct examination of the in vivo neurochemistry and neuropharmacology. With the introduction of high-affinity radioligands, it has also become possible to quantify receptor populations - even in low density brain regions - suggested to be affected in schizophrenia. Knowledge of how different disease processes and medications influence the nervous system will aid in the development of better treatments and allow a better prognosis for affected patients.

2 REVIEW OF THE LITERATURE

2.1 SCHIZOPHRENIA

2.1.1 Epidemiological and aetiological aspects

Schizophrenia is the most serious and deteriorating mental illness affecting about 1% of the population worldwide (Sartorius et al., 1986; Schultz and Andreasen, 1999; Perälä et al., 2007). The onset of symptoms of schizophrenia occurs in early adulthood, and the duration is generally lifelong (Mueser and McGurk, 2004). Men have been demonstrated to have a higher incidence and prevalence for schizophrenia than women (Aleman et al., 2003). The characterization of this complex syndrome has its origins in the observations of Kraepelin and Bleuler from the late 19th century. Kraepelin presented the term "dementia praecox" to cover the symptoms of catatonia, hebephrenia and dementia paranoides, as well as emphasizing the early onset and debilitating course of the illness (Kraepelin, 1971). The concept of schizophrenia was augmented by Bleuler, who described the primary, core schizophrenic symptoms of altered associations, altered affect, ambivalence and autism (Bleuler, 1950).

The aetiology of schizophrenia encompasses multiple environmental and genetic factors (Mäki et al., 2005). Based to adoption and twin studies, the risk for schizophrenia increases as high as 10-fold with the occurrence of one affected first-degree family member, almost 50-fold when both parents are affected and 60–84-fold when a twin-sibling is affected by the disease (Cardno et al., 1999; Tienari et al., 2000). Although the genetic aetiology of schizophrenia remains unclear, several genes have been demonstrated to associate with schizophrenia (Harrison and Owen, 2003). Biological and psychosocial environmental risk factors have been shown to bring neurodevelopmentally vulnerable individuals towards the onset of schizophrenia (Howes et al., 2004).

2.1.2 Symptoms and diagnosis

Schizophrenic symptoms can be divided into three different dimensions: positive symptoms, negative symptoms and cognitive dysfunction (Liddle, 1987). Positive, i.e. psychotic, symptoms include delusions, hallucinations, disorganized speech or thought and bizarre behavior (Mueser and McGurk, 2004). Hallucinations are commonly auditory, but can also be visual, olfactory, gustatory or tactile. The most characteristic delusions in schizophrenia are persecutory, grandiose or somatic, and often include delusions of control. In most cases,

positive symptoms are present episodically. Negative symptoms reflect basic emotional and behavioral deficit syndromes, including diminished affect, lack of pleasure, apathy, and reduced content or amount of speech. Negative symptoms tend to be more persistent than other features of the illness. In schizophrenia, cognitive symptoms comprise difficulties in attention, memory, learning and psychomotor speed, in addition to abstract thinking and problem solving. The depression/anxiety component of the general psychopathological symptoms poses most of the subjective distress, and more so than positive or negative symptoms (Tomida et al., 2010).

In European countries, the diagnostic criteria for schizophrenia are based on the International Classification of Diseases, tenth edition (ICD-10) (World Health Organization, 1992). The American Psychiatric Association started development work to improve the reliability of psychiatric diagnostics in the 1970s, resulting in the revision of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) in 1987 (American Psychiatric Association, 1987). The diagnostic criteria between these two systems differed to some extent, which led to the development of DSM-IV in 1994 (Flaum and Andreasen, 1991).

The ICD-10 diagnosis for schizophrenia has been demonstrated to hold high descriptive and clinical validity

(Peralta and Cuesta, 2003; Jäger et al., 2003). In the evaluation of diagnostic instruments, clinical ICD diagnoses of schizophrenic psychoses has been shown to correlate with DSM-III-R diagnoses obtained with structured interviews in over 90% of the cases (Vares et al., 2006). Structured and semistructured diagnostic interviews were designed to increase the reliability of clinical diagnoses. The Structured Clinical Interview (SCID) is a semistructured interview protocol for generating major axis I DSM diagnosis (Spizer et al., 1992). The SCID has been found to produce solid diagnoses for most axis I disorders (Segal et al., 1994).

The Positive and Negative Syndrome Scale (PANSS) is the most commonly used rating scale for estimating symptom severity in schizophrenia (Kay et al., 1987; Van den Oord et al., 2006). The PANSS is a 30-item clinician-rated scale that traditionally has been divided into three subscales: Positive, Negative and General Psychopathology. During or shortly after the interview, the rater assesses patients' symptom severity level by scoring each item on a scale from 1 to 7. The PANSS has shown high internal reliability in addition to criterion-related, constructive validity for measuring the severity of illness (Kay et al., 1988; Peralta and Cuesta, 1994; Santor et al., 2007).

2.1.3 Dopamine hypothesis

Over the last five decades, the dopamine hypothesis of schizophrenia has remained one of the major pathopsysiological models of schizophrenia (Seeman, 1987). The origin of this hypothesis is based on pharmacological evidence that relates antipsychotic drug-effect to dopamine receptor blockade (Van Rossum, 1967; Creese et al., 1976; Farde et al., 1988). The dopamine hypothesis was further supported by observations in studies with psychoactive drugs (Conell, 1958; Randrup and Munkvad, 1967; Jacobs and Trulson, 1979; Lieberman et al., 1987). For example, the psychotomimetic effect of amphetamine imitated symptoms of schizophrenia, especially hallucinations and paranoid thinking, mainly by releasing dopamine. Thus, it was suggested that there exists a hyperdopaminergic state at least in some brain regions.

It was also observed that chlorpromazine and haloperidol, the main antipsychotic agents used at that time, increased central catecholamine (i.e., dopamine and noradrenalin) metabolites in rodent brain (Carlsson and Lindqvist, 1963). The observation of elevated dopamine metabolism was confirmed with postmortem human studies (Bird et al., 1977; Toru et al., 1982). In addition, increased dopamine D2 receptor density was found in the striatum and nucleus accumbens of deceased schizophrenic patients (Lee and Seeman, 1980).

Subsequently, the dopamine hypothesis has passed through several reformulations due to incongruent findings in neurochemical, postmortem and pharmacological studies (Carlsson, 1988; Davis et al., 1991). Some transmitter-specific imaging and experimental animal studies reported that dopamine D2 receptor elevation in the striatum is associated with preceding neuroleptic treatment (Burt et al., 1977; Clow et al., 1980; Mackay et al., 1980), and some postmortem studies did not support an increase in central dopamine turnover among schizophrenics (Crow et al., 1979).

Findings in subsequent studies suggested a decrease in tonic or baseline dopamine release among patients with schizophrenia (Grace, 1991; Moore et al., 1999). Dopamine cell tonic activity was shown to consist of regular spike firing of ~1–6 Hz without prominent stimuli, strictly regulated by frontal and temporal cortical projections (Grace and Bunney, 1984a). Tonic dopaminergic firing preserves the basal extracellular dopamine level in afferent regions, and can be moderately affected by visceral stimuli (Grace, 1991). In contrast, transient and phasic dopamine release occurs via dopamine neuron firing as a stimulus-evoked response and is rapidly terminated especially by synaptic uptake. Phasic activation of dopamine neurons increases the firing rate to ~20 Hz, resulting in a large and protracted increase in extracellular dopamine concentration (Grace and Bunney, 1984b). The volume of the phasic dopamine

response is at least partially controlled by the effects of tonic dopamine tone on extracellular dopamine levels. Eventually, this was proposed as the cause of an abnormally high phasic release of dopamine in the striatum of schizophrenic patients (Moore et al., 1999).

It has been suggested that schizophrenia is characterized by abnormally low mesocortical dopamine activity, leading to cognitive deficits and negative symptoms, as well as by elevated dopamine transmission in subcortical regions, which has been associated with positive symptoms (Moore et al., 1999; Finlay, 2001). Dysregulation of dopamine neurotransmission has been observed in patients with schizophrenia at the onset of illness and during acute episodes without previous antipsychotic-drug treatment (Laruelle et al., 1999).

2.1.4 Glutamate hypothesis

Recently, the glutamate hypothesis has captured much attention in the neuropathology of schizophrenia (Goff and Coyle, 2001). Ionotropic glutamate receptors (N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid [AMPA], and kainate) supply the main excitatory neurotransmission in the human brain (Dingledine et al., 1999). The glutamate model of schizophrenia is based on the discovery that phencyclidine (PCP) and ketamine, the non-competitive

antagonists of the glutamate NMDA receptor, induce a schizophrenia resembling syndrome among healthy persons (Cohen et al., 1962; Javitt and Zukin, 1991). In addition to psychotic symptoms (paranoia, hallucinations), subanesthetic doses of PCP and ketamine can provoke negative and cognitive symptoms of schizophrenia, such as impaired psychomotor performance, reduced motor activity and blunted affect. Schizophrenic patients treated with traditional antipsychotics have been demonstrated to suffer from a worsening of acute psychotic symptoms after ketamine intake (Lahti et al., 1995).

In postmortem studies, alterations in glutamate receptor expression have been found in brain regions implicated with the illness among schizophrenics compared to healthy controls (Meador-Woodruff and Healy, 2000). A decrease in glutamate AMPA and kainate receptor density have been consistently observed, while the abnormal subunit structure of NMDA receptors has been reported in some cortical regions among patients with schizophrenia. Modulation of the NMDA receptor with full or partial agonist of glysine site has been manifested by improvements in negative symptoms and cognitive deficit (Watson et al., 1990; Tsai et al., 1998).

2.1.5 Other pathophyciological theories

It has been proposed that the efficacy of atypical antipsychotics may depend on their effects on serotonin (5-HT) receptors coupled with weak D2 antagonism (Meltzer et al., 2003). Blockade of the 5-HT2 receptor type and agonism of 5-HT1 receptors have been suggested to mediate the atypical antipsychotic profile. The majority of excitatory 5-HT2 receptors are located in cortical pyramidal glutamatergic and GABAergic interneurons (Jakab and Goldman-Rakic, 1998; Abi-Saab et al., 1999). Serotonin can thereby increase extracellular glutamate and GABA levels in the cortex. Expression of 5-HT2 receptors in dopaminergic midbrain neurons may also have relevance to atypical drug-efficacy (Nocjar et al., 2002). The function of the 5-HT1 receptor has been considered to be opposite to 5-HT2 receptors, as stimulation of 5-HT1 receptors inhibits cortical glutamatergic pyramidal cell firing (Meltzer et al., 2003).

One of the potent candidate genes for schizophrenia is dysbindin (Straub et al., 2002). Decreased density of dysbindin messenger ribonucleic acid (mRNA) has been found in substantia nigra among patients with schizophrenia (Weickert et al., 2004). According to a recent rodent study, reduced dysbindin expression has been shown to correlate with an increase in dopamine release in the substantia nigra (Kumamoto et al., 2006). In studies with cortical primary cell cultures (consisting mainly of glutamatergic neurons), diminished

endogenous dysbindin produced a decrease in cortical glutamate release (Numakawa et al., 2004). It has been suggested that reduced expression of dysbindin in the cortex and midbrain may contribute to both the hyperdopaminergic and hypoglutamatergic state observed in schizophrenia.

2.1.6 Neuropathological findings in schizophrenia

As early as 1897, Alzheimer reported neuropathological abnormalities in the cerebral cortex of schizophrenic, or rather "dementia praecox", patients. The following postmortem studies over several decades failed to determine concordant neuropathological features of the illness mainly due to the rough methodology. Since the 1970s, with advanced methods, postmortem studies have revealed numerous structural changes in the schizophrenic brain, especially in limbic regions and the temporal lobe (Bogerts, 1993). Most studies reported structural anomalies in the amygdala-hippocampal complex and parahippocampal gyrus, and enlarged lateral ventricles. Several studies also demonstrated minor anomalies in some subregions of the basal ganglia, thalamus and cortex (Bogerts, 1993). Disturbed cytoarchitecture and an absence of gliosis in limbic brain areas, in addition to a lack of normal cerebral asymmetry were also observed.

The first computerized tomography (CT) study with schizophrenic patients confirmed previous postmortem findings of increased size in lateral ventricles (Johnstone et al., 1976). Magnetic resonance imaging (MRI) studies have provided strong evidence for dilatation of lateral and third ventricles (reviewed thoroughly by Shenton et al., 2001). The majority of MRI studies have also demonstrated abnormalities in medial temporal lobe regions, including the amygdala, hippocampus and parahippocampal gyrus, neocortical temporal lobe structures and cavum septi pellucidi. Moderate proof of frontal and parietal lobe abnormalities, as well as structural anomalies in the basal ganglia, corpus callosum and thalamus, have been observed.

According to a recent large meta-analysis of MRI studies with first episode schizophrenia, the strongest volumetric changes were observed in the hippocampus (approximately 8% volume loss) and in ventricles (an average of a 30% increase in volume), and a reduction (less than 3%) in whole brain volume has also been demonstrated (Steen et al., 2006). Using automated, voxel-based morphometry to evaluate changes in brain volume or density, the majority of studies have reported volumetric decreases in left temporal superior gyrus and left medial temporal lobe (Honea et al., 2005). The structural brain changes in schizophrenia are not generally related to gender, though

enlargement of the ventricles is nonsignifically greater in studies with male patients (Wright et al., 2000).

A novel magnetic resonance technique, diffusion tensor imaging (DTI), has been introduced for the evaluation of brain white matter anomalies. The findings in schizophrenia have not been entirely concordant, but the most significant findings have been observed in the frontal and temporal white matter (Kyriakopoulos et al., 2008).

The most consistently described brain structural changes have been found to associate with neurocognitive function in schizophrenia. Larger whole brain and cerebellar volumes have been shown to correlate with general intelligence in healthy controls and female patients. Enlarged lateral and third ventricles have predicted deficiency in attention, and executive and premorbid cognitive function in patients. Prefrontal neurostructural changes are linked to regulation of control in schizophrenia. In addition, temporal lobe alterations have been demonstrated to associate with a deficit on cognitive performance, and thalamic malformation with executive problems in patients with schizophrenia (Antonova et al., 2004; Crespo-Facorro et al., 2007).

2.1.7 Medication and neurological side-effects

Antipsychotic medication constitutes the basis for disease management in schizophrenia (Emsley and Oosthuizen, 2004). Since the discovery of the first antipsychotic compound chlorpromazine in 1952, the ability to block postsynaptic dopamine D2 receptors has remained the most essential feature for antipsychotic drug action (Strange, 2001; Kapur and Mamo, 2003). Conventional or typical antipsychotics have shown a dose-related subcortical dopamine D2 receptor affinity that correlates with clinical efficacy on positive schizophrenic symptoms (Seeman et al., 1976). However, some imaging studies have demonstrated high striatal drug occupancy levels in patients with a minor clinical response (Wolkin et al., 1989; Pilowsky et al., 1993).

With the invention of the first atypical antipsychotic drug, clozapine in 1958, it became clear that mechanisms other than mere D2 antagonism are involved in or contribute to the antipsychotic drug-action (Hippius, 1999). Clozapine has shown weak D2 antagonism but has effects on other receptor types, such as dopamine D1 and D4, histamine H1, serotonin 5-HT2 and muscarine M1 (Schotte et al., 1996). Newer atypical or second generation antipsychotics share many of the clozapines properties, especially lower D2 receptor affinity when compared with typical antipsychotics. Atypical antipsychotics have illustrated benefits in the treatment of negative symptoms and

cognitive deficits, in addition to fewer relapses and rehospitalizations (Conley and Kelly, 2002). However, there has been increasing concern over potentially serious metabolic adverse effects, such as weight gain, hyperlipidemia and glucose intolerance, related to atypical antipsychotics especially (Haddad and Sharma, 2007). The mechanisms underlying the superiority of clozapine in clinical efficacy over traditional and other second-generation antipsychotics still remain unresolved (Kane et al., 2001; Davis et al., 2003).

More recently, neuroimaging and pharmacological evidence has supported the view that limbic cortical dopamine D2 receptors may be the main target of antipsychotic drug treatment (Takahashi et al., 2006). Other promising objects for antipsychotic drug action that have recently emerged include dopamine D1, serotonin 5-HT2 and 5-HT1, and glutamatergic receptors (Stone and Pilowsky, 2007).

Occasionally, clinical and research usage of antipsychotics necessitates the quantification of dose equivalence between different compounds. The equivalence ratios are calculated in correspondence to the dosage of chlorpromazine. Chlorpromazine-equivalent doses for a few commonly used antipsychotics are shown in Table 1 (Kane, 1996; Woods, 2003).

Table 1: Chlorpromazine-equivalent (CPZ-eq) doses for some typical and atypical antipsychotics (Kane, 1996; Woods, 2003).

Antipsychotic	CPZ-eq (mg)
Chlorpromazine	100
Levomepromazine	100
Perphenazine	10
Haloperidol	2
Risperidone	2
Olanzapine	5
Aripiprazole	7.5
Clozapine	50

Typical antipsychotic medication is frequently associated with a wide range of adverse events that have a disabling influence on the patient's quality of life and general health (Arana, 2000). The most essential difference between typical and second-generation antipsychotic drugs is that the classical antipsychotics (with high-affinity for D2 receptors) pose a higher risk of extrapyramidal side-effects than second-generation antipsychotics (Miller et al., 1998; Wirshing, 2001). The exact mechanisms causing drug-induced movement disorders (i.e., extrapyramidal symptoms and tardive dyskinesia) have remained unresolved. Several hypotheses have been presented to explicate the pathophysiology of motor side-effects relating to subcortical dopaminergic activity (Casey, 2004). It has been suggested that lower affinity of the second-generation antipsychotics for dopamine D2 receptors is associated with a

rapid release from the receptor site preventing motor side-effects (Kapur and Seeman, 2001). Striatal dopamine D2 receptor blockade by both conventional and second-generation antipsychotics has been shown to correlate with extrapyramidal symptoms according to in vivo neuroimaging studies (Farde et al., 1992; Kapur et al., 2000a; Agid et al., 2007).

2.2 BRAIN DOPAMINE NEURON SYSTEM

2.2.1 Dopaminergic pathways

Dietary amino acid tyrosine is transported into neurons by amino acid transporter systems, and first converted to L-dihyroxyphenylalanine (L-DOPA) and later to dopamine by cytosolic enzymes. In dopaminergic neurons, concentrated dopamine is stored in vesicles for subsequent release into the synaptic cleft and extracellular zone after an action potential evoked calcium ion influx into cytosole, and fusion of vesicles and cellular membrane (Elsworth and Roth, 1997).

The mesencephalic DA neurons localized in the ventral midbrain are essential for the control of various cognitive and motor behaviors. According to original histofluorescence mapping, these cell groups are named as A8, A9 and A10 (Dahlström and Fuxe, 1964). Anatomically midbrain DA neuron groups matches with the DA cells of the substantia nigra (SN, A9), the ventral tegmental area (VTA, A10), and the retrorubral

area (A8) (Williams and Goldman-Rakic, 1998). Over 70% of the 400 000–600 000 DA cells in human midbrain are located in the SN (Björklund and Dunnett, 2007).

The major ascending dopaminergic nerve bundles from midbrain region were classically divided into three completely discrete systems: the mesocortical, mesolimbic and nigrostriatal (or precisely, mesostriatal) pathways, which innervate widely forebrain structures (Björklund and Dunnett, 2007). Based on morphological findings and axonal connectivity, DA neurons in the mesencephalon can be separated into a dorsal and a ventral tier. The dorsal tier consists of DA cells localized in dorsal parts of the SN and VTA, and the retrorubral area (A8) projecting to the ventral striatal, limbic and cortical regions, as well as the matrix of the dorsal striatum. The ventral tier includes cells located in ventral parts of the VTA and SN, which innervates the striatum, as well as the SN pars reticulata (Gerfen et al., 1987; Lynd-Balta and Haber, 1994).

Despite intermixing of the cells of origin, all three dopaminergic pathways have been considered to be functionally and anatomically separate. The mesolimbic and mesocortical DA pathways are derived from cells located in the dorsal tier, dispersed among cells projecting to the striatum (Williams and Goldman-Rakic, 1998). The cells of origin of nigrostriatal pathway are found in the ventral and dorsal tiers of SN pars compacta, comprising the main DA innervations of the

sensorimotor striatum. Since the anteromedial and ventral parts of the striatum (limbic striatum) receives DA projections from the lateral part of the VTA and A8 cell group, the definition "mesostriatal DA pathway" would contain all elements that innervate the striatum. The DA cells of ventral tier of the SN pars compacta also sends projections to a large part of the SN pars reticulata, enabling the regulation of DA transmission in striatum at the nigral level (Björklund and Dunnett, 2007).

In spite of the distinct function and anatomy, interaction of the DA pathways in ventral midbrain is compatible integrated. In a recent [11C]raclopride PET study significant differences were found in amphetamine-induced dopamine release between different functional subdivisions of the striatum, which was suggested to be due to the asymmetrical regulative feedback connections resulting in dopaminergic information to proceed from the limbic to the cognitive, and finally, to the sensorimotor striatum (Martinez et al., 2003).

2.2.2 Dopamine receptors

The released dopamine binds to pre- and postsynaptic receptors, eliciting modulatory effects on the target neurons (Elsworth and Roth, 1997). The five different subtypes of dopamine receptors are further divided into two subfamilies, dopamine D1-like and D2-like receptors, based on their pharmacological and

physiological properties, in addition to the regional distribution summarized in the following two paragraphs.

2.2.2.1 Dopamine D1-like receptors

The D1-family consists of D1 and D5 receptors, which generally couple to the Gs-family of the G-proteins, thus stimulating adenyl cyclace (AC) activity and formulation of cyclic adenosine monophosphate (cAMP) (Sokoloff and Schwartz, 1995; Missale et al., 1998). Although it has not been possible to pharmacologically distinguish D1 and D5 receptors, some differences in profiles exist (Bourne, 2001). The majority of the antagonists display a slightly higher affinity for D1 than D5 receptors, though agonists show an equal affinity (Missale et al., 1998). The most significant disparity is that endogenous dopamine exhibits ~10 times higher affinity for D5 than for D1 receptors. In dopaminergic cell cultures that express D5 receptors, higher AC activity has been observed compared to D1 receptors containing cell groups (Sunahara et al., 1991).

The D1 receptor is the most widely distributed and highly expressed DA receptor in the human brain. Using an in situ hybridization technique, D1 mRNAs are detected in DA-rich regions, i.e., striatum, substantia nigra, nucleus accumbens and olfactory tubercle, as well as in the limbic system, hypothalamus, thalamus (Missale et al., 1998). The D1 receptors are also located

in the prefrontal, temporal and occipital cortices, where D1 mRNA expression is the more abundant than that of other DA receptors (Meador-Woodruff et al., 1996). The presence of the D5 receptor is scarce and regionally restricted to the hippocampus, thalamic and hypothalamic nuclei, and temporal cortex (Sokoloff and Schwartz, 1995; Meador-Woodruff et al., 1996).

The D1 receptors have been shown to participate in the regulation of motor functions via ventral striatal receptor activation, and cognitive functions via cortical receptor stimulation (Sawaguchi and Goldman-Rakic, 1991; Jackson and Westlind-Danielsson, 1994). A significant role for D1 receptors in the prefrontal cortex and nucleus accumbens in modulation of reward and reinforcement mechanisms has also illustrated (Missale et al., 1998). Although the function of the D5 receptor has remained obscure, the regional distribution refers to cognitive functions (Missale et al., 1998).

2.2.2.2 Dopamine D2-like receptors

D2, D3 and D4 receptors are members of the D2-family, which preferentially couples to the Gi/o-family of the G-proteins, activation of which results in the inhibition of AC activity (Sokoloff and Schwartz, 1995; Missale et al., 1998). However, D3

and D4 receptors inhibit formation of cAMP only in a few cell lines and the level of inhibition is lower. D2-like receptors stimulate Na+-dependent extracellular acidification equally, but regulatory mechanisms between receptor subtypes differ. Cellular responses have also been demonstrated for arachidonate release by D2 and D4 receptors, in addition to the mitogenic properties of D2 and D3 receptors, as illustrated in a Chinese hamster ovary (CHO) cell line (Sokoloff and Schwartz, 1995).

Within the D2-like receptor subfamily, two different isoforms of D2 receptors (D2L and D2S) are recognized, but clear pharmacological differentiation of these two variants has not been possible (Missale et al., 1998). Few dopamine antagonists, including sulpride, raclopride and haloperidol, have displayed a marginal difference in affinities for these splice variants (Missale et al., 1998; Usiello et al., 2000). In a recent in vivo rodent study, D2L-mediated postsynaptic effects and D2S served as a presynaptic autoreceptor (Usiello et al., 2000). In the human brain, presynaptic D2 autoreceptors have been localized in dopaminergic projections arising mainly from substantia nigra, while mesolimbic and mesocortical DA neurons lack this receptor type. Generally, all dopamine autoreceptors are solely considered to be D2-like receptors (Meador-Woodruff et al., 1994; Elsworth and Roth, 1997).

Most antagonists have higher affinity for the D2 receptor than for the D3 and D4 receptors. Pharmacologically, D3 receptors can be distinguished from D2 by some agonistic and antagonistic agents. Dopamine shows a 20-fold higher affinity for D3 than D2 receptors, and preferential affinity is also observed with some other agonists, including TL-99, pergolide, quinpirole and 7-hydroxy-dipropylaminotetralin (7-OH-DPAT). The majority of antipsychotics (e.g., sulpride, clozapine and raclopride) express equal affinity for both receptor types, while haloperidol and spiperone display up to a 20-fold higher affinity at the D2 than they do at the D3 receptor. Various D3 selective antagonists with ~10–30 times difference have been developed, such as nafadotride, S-14297 and U-99194A (Missale et al., 1998).

The pharmacological profile of the D4 receptors is rather similar to those of the D2 and D3 receptors with some exceptions. Clozapine shows preferential affinity at the D4 receptor compared to the D2 and D3 receptors, while raclopride, remoxipride and chlorpromazine show a 10–20-fold lower affinity for D4 receptor compared to other D2-like receptors (Missale et al., 1998).

Among the dopamine D2-like receptors, D2-subtype is the most commonly expressed in the human brain and found mostly in DA-rich areas, with the highest density being observed in the striatum, followed by the nucleus accumbens and substantia nigra. Moderate levels of D2 receptors are

present in the hypothalamus and amygdala, in addition to the thalamus, which shows heterogeneous expression between different subregions. Low levels of D2 receptors are found in the prefrontal, cingulate, temporal and enthorinal cortices (Hall et al., 1996; Missale et al., 1998; Hurd et al., 2001). In contrast to D1 and D2 receptors, D3 and D4 receptors are weakly expressed in the striatum, and predominantly (but at relatively lower levels) distributed to the limbic regions. D3 receptors are most notably detected in the nucleus accumbens, olfactory tubercle, with lower levels being found in the substantia nigra and ventral tegmental area. The lowest density of D3 receptors is found in the hippocampus and various cortical areas. Despite the low overall level of D4 receptor expression in the brain, receptor D4 mRNA is particularly enriched in the frontal cortex, amygdala, hippocampus and hypothalamus (Sokoloff and Schwartz, 1995; Missale et al., 1998).

The most important dopamine receptor for control of movements is the D2-subtype. Within the nigrostriatal DA pathway, stimulation of postsynaptic D2 receptor increases locomotion, whereas activation of presynaptic D2 receptor reduces motor function (Jackson and Westlind-Danielsson, 1994). Reward-seeking behavior has been linked mainly to D2 receptor-mediated DA release in mesolimbic structures. Moreover, activation of cortical D2 receptors is suggested as contributing to learning and memory (Missale et al., 1998). The

opposite role of the D3 receptor relative to that of the D2 receptor has been detected in several DA-dependent behavioral functions. Stimulation of the D3 receptor has been shown to inhibit reward-seeking behavior and locomotion, as well as striatal DA transmission. The function of the D3 receptor as an autoreceptor has also been suggested. Although the function of the D4 receptor is equivocal, expression in the corticolimbic areas refers to modulation of emotions and cognition (Sokoloff and Schwartz, 1995; Missale et al., 1998).

2.2.3 Factors affecting dopamine D2/3 receptor density

2.2.3.1 Age

In the human brain, dopamine activity has been shown to be one of the most affected neurotransmitter systems during normal aging (Trollor and Valenzuela, 2001). An age-related decrease of dopamine function in humans was first observed in the basal ganglia with post-mortem and later with in vivo imaging studies (Carlsson and Winblad, 1976; Garnett et al., 1983). The age-dependent decrease has been illustrated in dopamine D1 receptor density and dopamine transporters (Suhara et al., 1991; Volkow et al., 1996a). Results on dopamine metabolism have been inconsistent showing either no age-effect or a moderate age-dependent decline (Eidelberg et al., 1993;

Cordes et al., 1994). A recent post-mortem study on human striatum suggested that the decrease in DA-related markers during aging is caused by diminished DA release in adulthood/senescence (Haycock et al., 2003).

In post-mortem human studies, the results on striatal dopamine D2 receptor density has been discordant demonstrating either no significant age-effect (Seeman et al., 1984), or only minor age-dependent losses of less than 3% per decade (Seeman et al., 1987). Nevertheless, findings in imaging studies have consistently indicated a decrease (7–13% per decade) in striatal D2 receptors with aging. It has been suggested that this age-related decline may occur before 40 years of age, and that the shape of the slope is non-linear (Volkow et al., 1996b; Ichise et al., 1998). Although an age-induced decrease in striatal dopamine D2 receptor density has been shown to associate with reduced motor and cognitive performance in healthy elderly subjects, the correlation between D2 receptor availability and motor and cognitive performance may be independent of age (Volkow et al., 1998).

The age-related reduction of D2 receptors in extrastriatal regions have been shown to be comparable with that of the striatum. In a recent positron emission tomography (PET) study with [11C]raclopride, the decline in dopamine D2 receptor density was 6.6% per decade in the caudate, 8.2% in the putamen, 7.6% in the thalamus and 13% in the temporal cortex

(Wang et al., 1996). An age-dependent decrease in D2 receptors has been demonstrated for several extrastriatal brain areas using high affinity radiotracer [11C]FLB 457 with PET: 13% per decade in the anterior cingulate cortex, 11–14% in the frontal cortex, 10–12% in the hippocampus, 9–12% in the temporal cortex, 13% the parietal cortex, 12% in the occipital cortex, 7% in the amygdala and 5–6 % in the thalamus (Kaasinen et al., 2000; Inoue et al., 2001). No general gender difference in the rate of age-induced decline has been measured (Kaasinen et al., 2001). Age-related D2/3 receptor loss in the striatum and in some extrastriatal regions (frontal and temporal cortices) has also been observed among patients with schizophrenia (Wong et al., 1997; Talvik et al., 2003).

2.2.3.2 Gender

Several gender-associated functional and morphological differences have been delineated in normal human brain (de Courten-Myers, 1999). Sex steroid hormones have been suggested to affect dopamine-mediated control of movements and behavior among healthy humans. In particular, estrogens have been implicated in basal ganglia-mediated behavior (Di Paolo, 1994). In human striatum, some PET studies have found lower dopamine D2 receptor density among women than in men (Pohjalainen et al., 1998), while others have failed to detect

any gender difference in D2 receptor affinity (Farde et al., 1995). Earlier PET studies suggest variation of striatal D2 receptor density caused by menstrual cycle (Wong et al., 1988), though this is not supported by the findings of a more recent imaging study (Nordström et al., 1998a). In addition, one PET study has found significantly higher dopamine D2 receptor levels in the frontal cortex of middle-aged women than those of coeval men (Kaasinen et al., 2001).

A left-sided striatal D2 receptor binding asymmetry has been observed among drug-naïve male schizophrenic patients (but not among female) in few imaging studies (Pilowsky et al., 1994; Schröder et al., 1997), though this asymmetry was reduced after antipsychotic treatment (Schröder et al., 1997). In a recent SPECT study, no gender-related differences in D2 binding values or laterality were detected in drug-naïve patients with schizophrenia (Parellada et al., 2004).

2.2.3.3 Personality

Human hereditable personality traits can be divided into four dimensions: novelty seeking, harm avoidance, reward dependence and persistence. These traits form a person's basic behavioral pattern and the basis for responses to emotional stimuli (Cloninger et al., 1993). Several lines of evidence have linked dopaminergic neurotransmission with the initiation of

behavior, motivational and reward processes (Schultz, 1998). Dopamine D2 receptor affinity, as well as dopamine transporter (DAT) density in the putamen (a subregion of the striatum), have been reported to correlate negatively with detached personality trait in healthy subjects using PET and Karolinska scales of personality (Farde et al., 1997a; Laakso et al., 2000a). Nevertheless, using a different personality measurement scale, NEO Personality Inventory-Revised, no statistical correlation was detected between striatal D2 density and detachment-like feature in healthy participants (Kestler et al., 2000). However, polymorphism in the dopamine D2 receptor gene (–141Cins/del) that correlates with dopamine D2 density has been observed to associate with detached personality features, thus supporting the involvement of dopamine in certain personality traits (Jönsson et al., 2003). Participation of dopamine in socially rewarding behavior has been further supported by a recent PET study with [11C]raclopride that found strong negative correlation between socially desirable responding and D2 receptor binding in the right putamen of healthy elderly women (Reeves et al., 2007).

The novelty-seeking personality trait has been observed to be common among substance abusers, a finding most likely related to dopamine D2 receptor availability (Compton et al., 1996). One PET study with [11C]FLB 457 (high affinity D2 receptor ligand) revealed a significant negative correlation between D2 receptor

binding values in the right insular cortex of healthy young men and the novelty-seeking behaviour (Suhara et al., 2001). A more recent [18F]fallypride PET study found that novelty-seeking personality traits associated inversely with D2–like (auto)receptor density in the midbrain of healthy adults (Zald et al., 2008). The authors speculated that the decreased midbrain (substantia nigra/VTA) autoreceptor binding observed among high novelty seekers may necessitate pronounced stimulus-evoked dopamine release. Using the same imaging method, this result was further confirmed by the finding of negative correlation between trait impulsivity and D2/3 autoreceptor availability in the substantia nigra/ventral tegmental area, as well as positive correlation between impulsivity and the extent of amphetamine-induced dopamine release in striatum mediated through reduced midbrain autoreceptor control (Buckholtz et al., 2010).

2.2.3.4 Reinforcing behavior and substance use

Dopaminergic neurotransmission has been demonstrated to play a major role in brain reward mechanisms: deficits in dopamine function induce pathological drug and alcohol seeking behavior (Nakajima, 1989). Particularly, dopamine D2 receptors have been frequently implicated in the etiology of impulsive-addictive-compulsive behavior, also termed “reward

deficiency syndrome". Defects in dopamine D2 receptor gene variants have been shown to relate with obesity, smoking, alcoholism and drug dependency, in addition to other compulsive behaviors (Blum et al., 1995).

The reinforcing properties of food have been discovered to associate with the activation of the mesolimbic dopamine pathway (Martel and Fantino, 1996; Carr, 2007). In a PET study of healthy humans with normal weight, feeding raised dopamine levels in the dorsal striatum, correlating significantly with self-ratings in experienced pleasure (Small et al., 2003). In a PET study with [11C]raclopride, obese subjects displayed decreased striatal D2 receptor binding sites compared to controls, and showed an inverse association between body mass index (BMI) and D2 receptor density (Wang et al., 2001). In another PET study with [11C]FLB 457, the dopamine D2 receptor binding potential in the amygdala correlated positively with BMI, and negatively with the personality trait of harm avoidance (Yasuno et al., 2001a).

According to neuroanatomical, neurophysiological and neuro-pharmacological studies, psychoactive substances of abuse provide their reinforcing properties in the dopaminergic reward system of the mesocorticolimbic tracks, although opioid and GABA systems are also involved (Koob, 1992). Results from animal models of alcoholism indicated the involvement of D2 receptors in ethanol self-administration. Reduced D2 receptor

availability has been observed in the striatum and VTA, as well as in the nucleus accumbens among ethanol-preferring rats compared to non-preferring rats (Stefanini et al., 1992; McBride et al., 1993). By contrast, one rodent study found no alterations in dopamine D2 receptor densities within the mesolimbic system, but detected a 35% higher D2 receptor levels in the SN pars compacta of high alcohol-drinking rats than in low alcohol-drinking animals (McBride et al., 1997).

Human in vivo PET studies have reported reduced striatal D2 receptor availability among non-selected group of alcoholics compared to controls (Hietala et al., 1994; Volkow et al., 1996c). In addition, lower D2 receptor density has been detected in the temporal lobe of late onset alcoholics than in controls using SPECT with [123I]epidepride (Kuikka et al., 2000). Nevertheless, findings from imaging studies on striatal dopamine transporters (DAT) have been inconsistent. Some studies found reduced DAT availability in striatum among alcoholics (Tiihonen et al., 1995; Laine et al., 1999; Repo et al., 1999), while one PET study observed no differences in DAT density between alcoholics and controls (Volkow et al., 1996c). However, no in vivo data exists concerning dopamine D1 and D3 receptors of alcoholics.

Post-mortem human studies have revealed a substantial decrease both in DAT and in dopamine D2/3 receptor sites in the nucleus accumbens, as well as a decrease in D2/3 receptor density in the amygdala of late onset alcoholics (Tupala et al.,

2001). In addition, reduced dorsal striatal D2/3 receptor density has been found among alcoholics compared with controls (Tupala et al., 2003).

In experimental animal studies, the reinforcing effects of nicotine, a central component of cigarette smoke, has been shown to occur within the mesolimbic dopamine system (Corrigall et al., 1992). Nicotine administration has been detected to increase extracellular DA levels and DA metabolism dose-dependently in the nucleus accumbens of male Sprague Dawley rats (Benwell and Balfour, 1992). Elevated striatal dopamine activity has also been demonstrated among smokers compared to controls using [18F]DOPA PET (Salokangas et al., 2000). However, chronic nicotine treatment has not been observed to affect DA receptors or DAT in the striatum according to animal and post-mortem human studies (Kirch et al., 1992; Court et al., 1998). Results from most recent in vivo imaging studies have been contradictory. No changes were detected in striatal dopamine D2/3 receptor levels of male smokers compared to matched controls in a [123I]IBZM SPECT study (Yang et al., 2006), while a recent [18F]fallypride PET study indicated significantly reduced D2/3 receptor density in the dorsal striatum of heavy-smoking nicotine-dependent individuals compared to controls (Fehr et al., 2008).

2.3 BRAIN IMAGING

Brain imaging techniques enable examination of physical brain structure as well as the electrical and functional brain activity of the living human brain. Electroencephalography (EEG) was introduced in the early 1920s. Applications of this basic methodology include evoked potentials (visual, auditory, somatosensory and cognitive) and quantitative, computerized assessments of topographic EEG signals. Standard X-ray-based methods, including computed tomography (CT), depict anatomical structure of the brain. The nuclear magnetic resonance technique is used in magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS). These methods use exogenously created changes in the magnetic field of nuclei to image brain anatomy (MRI) and function (fMRI and MRS). (Seibyl et al., 2004; Grebb, 2005)

Two major emission tomography techniques are positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Both typically use usually intravenously injected radioactive pharmaceuticals (i.e., radiotracers or radioligands) to assess cerebral blood flow, metabolism or receptor and transporter density, as well as study their possible interconnections to emotional, cognitive and behavioral activity. These functional imaging techniques depict multiple cross-sectional slices of a target region, in which the

distributed radiotracer can be detected. For PET imaging, the commonly used radionuclides 15O, 13N, 11C and 18F display a rather short half-life, while typical SPECT isotopes (e.g., 99mTc, 133Xe and 123I) have a relatively longer half-life, thus facilitating the clinical use of SPECT. (Wernick and Aarsvold, 2004; Fujita et al., 2005)

Requirements for suitable radioligands include the stability of labeling, affinity and selectivity for the specific receptor combined with low non-specific binding, and rapid permeation through the blood-brain barrier in addition to exiguous amount of metabolites (Heiss and Herholz, 2006). Examples of PET and SPECT radiotracers for use in human studies are presented in Table 2.

Table 2. Examples of PET and SPECT tracers for brain receptor characterization in human studies.

Receptor system	SPECT	PET
Dopamine		
D1	123I-SCH 23982	11C-SCH 23390
	(Beer et al. 1993)	(Farde et al. 1992)
D2	123I-IBZM	11C-raclopride
	(Seibyl et al. 1992)	(Farde et al. 1986)
	123I-IBF	11C-FLB-457
	(Laruelle et al. 1994)	(Halldin et al. 1995)
	123I-epidepride	18F-fallypride
	(Kornhuber et al. 1995)	(Mukherjee et al. 1995)
DAT	123I-β-CIT	11C-WIN 35428
	(Innis et al. 1993)	(Wong et al. 1993)
		11C-β-CIT
		(Farde et al. 1994)
Serotonin		
5-HT2	123I-5-I-R91150	11C-N-methylspiperone
	(Busatto et al. 1997)	(Wong et al. 1984)
5-HTT	123I-β-CIT	11C-McN5652
	(Innis et al. 1993)	(Szabo et al. 1995)
Acetylcholine muscarinic		
M1, M2, M3	4-123I-IQNB	11C-tropanyl benzilate
	(Weinberger et al. 1991)	(Koeppe et al. 1994)
Opioid		
mu, kappa, delta	123I-TPCNE	11C-diprenorphine
	(Stone et al. 2006)	(Jones et al. 1994)
GABA-A		
Benzodiazepine	123I-iomazenil	11C-flumazenil
	(Beer et al. 1990)	(Pappata et al. 1988)

2.3.1 [123I]Epidepride SPECT studies

(S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodo-2,3-dimethoxybenzamide, epidepride was independently synthesized and characterized in 1987–1988 by three different laboratories using various methods (de Paulis, 2003). Epidepride, as well as corresponding PET tracers (S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-bromo-2,3- dimethoxybenzamide (FLB-457) and (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[18F]fluoropropyl)-2,3-dimethoxybenzamide (fallypride), belong to a new class of ultra high-affinity dopamine antagonist radioligands that were initially developed from the structures of (S)-sulpride and remoxipride. In the assessment of several [125I]iodine substituted analogs of raclopride, epidepride was found to have very high affinity for dopamine D2 receptors and relatively low lipophilicity that resulted in unusually high in vivo contrast of [125I] epidepride between dopamine-rich and dopamine-poor regions in rat brain (Kessler et al., 1991). In post-mortem human studies [125I]epidepride was shown to be suitable for labeling dopamine D2 receptors in the striatum as well as low-density extrastriatal areas (Joyce et al., 1991; Kessler et al., 1993a; Hall et al., 1996).

Subsequently, dopamine D2 receptor sites were quantified in vivo using SPECT and [123I]epidepride in healthy humans (Kessler et al., 1992; Kornhuber et al., 1995; Kuikka et al., 1997), and in patients with neurological disease (Pirker et al., 1997;

Naumann et al., 1998). Due to the high specific binding of [123I]epidepride to D2 receptors, the displacement from receptor sites by endogenous dopamine after amphetamine challenge was not found when examined in primates or humans (Kessler et al., 1993b; Tibbo et al., 1997). However, [123I]epidepride binding in high-density regions (i.e. striatum) has been reported to be sensitive to endogenous dopamine levels in the short term (Gatley et al., 2000). Evidence also exists for the competitive effects of endogenous dopamine on epidepride binding in the temporal cortex (but not in the thalamus) after dopamine depletion (Fujita et al., 2000).

Kinetic studies have demonstrated a peak level of radioactivity in the striatum 2.5–4 hours after tracer bolus injection and after 45–60 minutes in extrastriatal regions, respectively (Kessler et al., 1992; Kornhuber et al., 1995; Kuikka et al., 1997). Radiotracer uptake in the cerebellum (defining free and non-specific binding) peaked at 28.5 minutes, decreasing thereafter relatively fast (Kessler et al., 1992). The washout period (biological half-time) for [123I]epidepride has been observed to be 29 $\pm$ 8 hours in the striatum, while washout of tracer in the temporal cortex required only 2.8 $\pm$ 0.5 hours (Kuikka et al., 1997). Subsequent studies with constant infusion, or bolus injection combined with continuous infusion of [123I]epidepride have required longer scanning time (24 hours

and 10 hours) to attain equilibrium steady-state conditions in order to quantify binding parameters (Fujita et al., 1999).

Labeled lipophilic metabolites of [123I]epidepride have been detected, which might pass the blood-brain barrier affecting specific binding by non-specific binding in different brain regions or affinity to the binding site of [123I]epidepride (Bergström et al., 1997; Kuikka et al., 1997). The maximum volume of the lipophilic labeled metabolite has been found to be approximately 10–15%, which has decreased 30–60 minutes after the tracer injection. Thus, the lipophilic labeled metabolite may not interfere severely in the quantification of dopamine D2 receptor sites at later imaging time points. In high-density D2 receptor regions, the amount of lipophilic labeled metabolite has shown a negative correlation with specific [123I]epidepride binding (Bergström et al., 2000).

Bloodless analyses do not permit correction for the influence of the lipophilic metabolites of [123I]epidepride. Both the bolus-injection paradigm (three-compartment kinetic analysis) and the constant-infusion paradigm (equilibrium analysis) have been used to assess the effect of the metabolite in quantifying [123I]epidepride D2 binding, though these have confronted some problems in technical or patient facilities (Fujita et al., 1999). Graphical analysis of reversible [123I]epidepride D2 receptor binding (demonstrated to be extended to account for metabolites), in addition to a simplified analysis for measuring

the specific volume of distribution with one blood sample, are considered valid methods for generating reliable binding parameters both in striatal and extrastriatal regions (Ichise et al., 1999).

2.4 SPECT AND PET IMAGING FINDINGS IN SCHIZOPHRENIA

2.4.1 Presynaptic dopamine metabolism

Presynaptic dopaminergic function has been studied using radiolabeled analogues of DOPA (the precursor of dopamine), i.e. 6-[18F]-fluoro-L-DOPA ([18F]-DOPA) and L-[11C]-DOPA ([11C]-DOPA) with PET. Reith et al. (1994) reported increased [18F]-DOPA uptake in the striatum of five chronically ill schizophrenic patients (one with medication), indicating elevated DOPA decarboxylase activity. The majority of the subsequent studies with [18F]-DOPA, as well as one [11C]-DOPA study, have replicated the result of elevated striatal DOPA metabolism in schizophrenia studied in drug-naïve, drug-free or medicated patients (Hietala et al., 1995; Hietala et al., 1999; Lindström et al., 1999; Meyer-Lindenberg et al., 2002; McGowan et al., 2004; Kumakura et al., 2007). One research group has also detected a lack of asymmetry (observed in healthy persons) in the caudate [18F]-DOPA uptake of patients with schizophrenia (Hietala et al., 1995; Hietala et al., 1999). Increased dopamine metabolism in extrastriatal areas was

observed in one study reporting an elevated [11C]-DOPA influx rate in the medial prefrontal cortex among 12 drug-free (10 drug-naïve) psychotic patients with schizophrenia (Lindström et al., 1999).

A previous [18F]-DOPA PET study found no difference in striatal dopaminergic turnover between study groups, though the variation in [18F]-DOPA uptake values was higher in untreated schizophrenic patients than in healthy controls (Dao-Castellana et al., 1997). Exaggerated striatal dopaminergic function in schizophrenia has been challenged by one study that observed a decrease in [18F]-DOPA uptake in the ventral striatum of medication-free patients (Elkashef et al., 2000).

Direct in vivo proof of altered striatal dopamine release in schizophrenia has been obtained using [123I]3-iodo-6-methoxybenzamide ([123I]IBZM) and SPECT or [11C]raclopride and PET for measuring amphetamine (a potent releaser of endogenous dopamine) challenged decrease in tracer binding potential, showing greater amphetamine-related reductions in D2 receptor availability among patients with schizophrenia than in control subjects (Laruelle et al., 1996; Breier et al., 1997; Abi-Dargham et al., 1998). These findings have suggested an excessive concentration of psychostimulant-provoked synaptic dopamine in schizophrenia, which has also been associated with acute worsening of psychotic symptoms.

Pharmacologically induced acute DA depletion achieved by α-methyl-para-tyrosine (α-MPT) has been shown to correlate with elevated striatal D2 receptor availability among schizophrenic patients studied with [123I]IBZM and [11C]raclopride referring to an increased dopamine function in striatum (Abi-Dargham et al., 2000; Kegeles et al., 2010). In a recent [123I]IBZM SPECT study, an amphetamine-induced reduction in D2 binding potential correlated positively with increased D2 binding values after DA depletion (caused by α-MPT) in the striatum of drug-naïve schizophrenic patients, suggesting increased activity of midbrain DA cells in schizophrenia (Abi-Dargham et al., 2009).

2.4.2 Dopamine transporters

The presynaptic dopamine transporter (DAT) is a membrane-bound protein located on DA nerve terminal and has a key role in regulating the DA concentration in the synaptic cleft by transporting it into neurons (Jaber et al., 1997). The findings from neuroimaging studies on DAT availability in schizophrenia have varied primarily depending on prior antipsychotic medication. A summary of the neuroimaging studies of dopamine transporters are presented in Table 3.

The majority of the studies have reported no changes in striatal DAT density among drug-naïve or drug-free

schizophrenic patients (Laakso et al., 2000b; Laruelle et al., 2000; Yang et al., 2004; Schmitt et al., 2006). Decreased striatal DAT density on the right and an increase in DAT availability on the left striatum (resulting in a lack of right-left asymmetry) was observed in one technetium-99m labeled tropane ([99mTc]TRODAT-1) SPECT study (Hsiao et al., 2003). Similarly, despite unaltered average striatal DAT binding, the absence of hemispheric asymmetry in caudate DAT density has been detected in untreated schizophrenic patients compared with control subjects (Laakso et al., 2000b). A recent SPECT study with [123I]N-ω-fluoropropyl-2β-carbomethoxy-3β-tropane ([123I]FP-CIT) illustrated reduced striatal DAT binding sites in never-medicated schizophrenic patients (Mateos et al., 2007).

Some research groups have also found correlations between striatal DAT density and schizophrenic symptoms. Laruelle et al. (2000) reported a trend-level association between low DAT binding and the severity of negative symptoms while failing to detect alterations in striatal DAT density in schizophrenia. In addition, striatal DAT availability has been observed to correlate inversely with the extent of hallucinations among 18 patients with first exacerbation of schizophrenia (Schmitt et al., 2006).

Utilizing high-affinity DAT ligand [18F]2β-carbomethoxy-3β-(4-fluorophenyl)tropane ([18F]CFT), decreased striatal DAT density has been detected in chronic schizophrenic patients with medication compared to matched control subjects (Laakso et al.,

2001). The same result was found among first-episode patients after 4 weeks of risperidone-treatment with [123I]FP-CIT PET, though the authors observed no antipsychotic effect on DAT availability when compared to baseline DAT density (Mateos et al., 2007). By contrast, an increase was found in striatal DAT binding sites of 6 chronic schizophrenic patients treated with traditional antipsychotics using iodine-123 labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane ([123I]β-CIT) and SPECT, suggesting an increased amount of presynaptic dopaminergic nerve terminals (Sjøholm et al., 2004).

Table 3. Summary of imaging studies on dopamine transporters.

Method	Patients (*n*)	Findings	Ref.
[18F]CFT PET	Drug-naïve (9)	No change in average DAT density; lack of right-left asymmetry in caudate DAT	Laakso et al. 2000b
[123I]β-CIT SPECT	Drug-free (24)	No change in striatal DAT density; slight association between low DAT binding and severity of negative symptoms	Laruelle et al. 2000
[18F]CFT PET	Medicated (8)	↓ striatal DAT density	Laakso et al. 2001
[99mTc]TRODAT-1 SPECT	Drug-naïve (12)	↓ DAT density in right striatum and ↑ DAT density in left striatum; lack of right-left striatal DAT asymmetry	Hsiao et al. 2003
[123I]β-CIT SPECT	Medicated (6)	↑ striatal DAT density	Sjøholm et al. 2004
[99mTc]TRODAT-1 SPECT	Drug-naïve (11)	No change in striatal DAT density; positive correlation between striatal DAT and D2/3 receptor densities	Yang et al. 2004
[123I]FP-CIT SPECT	Medicated (10)	↓ striatal DAT binding	Mateos et al. 2005
[99mTc]TRODAT-1 SPECT	Drug-naïve (28)	No change in striatal DAT density; extent of hallucinations correlated inversely with DAT availability	Schmitt et al. 2006
[123I]FP-CIT SPECT	Drug-naïve /medicated (20)	↓ striatal DAT binding at baseline and after treatment	Mateos et al. 2007

2.4.3 Striatal dopamine D2 receptors among drug-naïve and drug-free patients

The neurotransmitter system most widely examined with PET and SPECT is a dopamine system, mainly due to the availability of suitable radiotracers and suggested relevance of dopamine in the pathophysiology of schizophrenia. Striatal D2 receptors

have been studied using PET/SPECT with various radiotracers, including butyrophenones ([11C]N-methylspiperone, i.e., [11C]NMSP, and [76Br]bromospiperone), benzamides ([11C]raclopride, [123I]IBZM, and [18F]fallypride), and an ergot derivative ([76Br]lisuride). The study subjects have consisted of both drug-naïve and drug-free patients in the greater part of the studies, while only a minority has examined drug-naïve patients alone. A summary of the studies on striatal D2 receptors is presented in Table 4.

Four out of the 20 studies summarized here have revealed a significantly increased D2 receptor availability in the striatum among drug-naïve and/or antipsychotic-free schizophrenic patients (Crawley et al., 1986; Wong et al., 1986; Tune et al., 1993; Corripio et al., 2006). Crawley et al. (1986) conducted a [77Br]bromospiperone SPECT study on 4 drug-naïve and 8 drug-free (minimum washout period of 6 months) schizophrenic patients with ages ranging 28 to 80 years. Despite the statistically significant difference in D2 binding between patients and controls, the authors could not confirm the result due to a large variation in specific activation and technical difficulties related to radionuclide imaging, as well as a noted source of error in head fixation among the patient group. Almost simultaneously, Wong et al. (1986) reported two- to threefold elevations in striatal D2 receptors in 10 drug-naïve chronic schizophrenic patients compared to controls using

[11C]NMSP, a tracer with a high affinity for both dopamine D2 and serotonine 5-HT2 receptors. The same study group scanned 13 additional chronic patients with schizophrenia, of whom 7 were medication-free for at least 4 months (Tune et al., 1993). The results showed an increased D2 receptor density among untreated schizophrenic patients compared with healthy subjects. The authors suspected that the observed D2 receptor alterations may reflect a late stage of schizophrenia. In a recent [123I]IBZM study, significantly elevated dopamine D2 receptor binding in striatum was found among 18 patients with untreated first-episode psychosis (Corripio et al., 2006). The results also implicated that the high D2 density at the outset predict an increased risk for schizophrenia outcome after 2-year follow-up.

Farde et al. (1990) utilized the selective D2 receptor ligand [11C]raclopride for studying 18 young, newly-admitted antipsychotic-naïve patients. The findings showed no general schizophrenia-related changes in striatal D2 binding, though left-sided asymmetry of D2 density in the putamen was observed among patients. Other studies confirmed the results of unaltered striatal D2 density using different radioligands, such as [76Br]bromospiperone (Martinot et al., 1990), [76Br]lisuride (Martinot et al., 1991; Martinot et al., 1994), [123I]IBZM (Pilowsky et al., 1994; Laruelle et al., 1996; Knable et al., 1997a; Abi-Dargham et al., 1998; Abi-Dargham et al., 2000), [11C]NMSP

(Okubo et al., 1997) and [11C]raclopride (Breier et al., 1997) on a group of drug-naïve and drug-free or simply drug-free patients (medication-free period varying from 2 weeks to 5 years) , and [11C]NMSP (Nordström et al., 1995a), [123I]IBZM (Yang et al., 2004) and [11C]raclopride (Talvik et al., 2006) among drug-naïve patients. A left lateralized asymmetry in the striatal D2 receptor density of male patients was observed in one study (Pilowsky et al., 1994).

Another [11C]raclopride PET study found no general changes in striatal D2 density or affinity of 13 young antipsychotic-naïve patients, but did discover a subgroup of 4 patients with comparatively high D2 binding in the striatum (Hietala et al., 1994). A more recent study utilizing the same radiotracer with high resolution 3-dimensional (3D) PET examined 18 drug-naïve patients with schizophrenia compared to 17 controls suggesting no differences between the groups for D2 binding in striatal subregions, or hemispheric imbalance in any brain areas (Talvik et al., 2006).

Martinot et al. (1994) reported a negative correlation between striatal D2 density and negative symptoms of schizophrenia (flattened affect and alogia) among a patient group consistingof 8 antipsychotic-naïve and 2 drug-free subjects. This finding was confirmed by a [123I]IBZM SPECT study that detected a correlation between a change in negative symptoms and a change in ligand uptake among a subgroup of 13 medication-

free patients of 21 scanned subjects (Knable et al., 1997a). Recently, Kessler et al. (2009) reported a significant positive correlation between hallucinations and D2 receptor levels in left ventral striatum among 4 drug-naïve and 7 drug-free schizophrenic patients with [18F]fallypride and PET.

Table 4. Summary of imaging studies on striatal D2 receptors.

Method	Patients (*n*)	Findings	Ref.
[77Br]bromospiperone SPECT	Drug-naïve (4) + drug-free (8)	↑ D2 density	Crawley et al. 1986
[11C]NMSP PET	Drug-naïve (10)	↑ D2 density	Wong et al. 1986
[76Br]bromospiperone PET	Drug-naïve (9) + drug-free (3)	No change in D2 density	Martinot et al. 1990
[11C]raclopride PET	Drug-naïve (18)	No change in D2 density; left-sided striatal D2 asymmetry	Farde et al. 1990
[76Br]lisuride PET	Drug-naïve (10) + drug-free (9)	No change in D2 density	Martinot et al. 1991
[11C]NMSP PET	Drug-naïve (18) + drug-free (7)	↑ D2 density	Tune et al. 1993
[123I]IBZM SPECT	Drug-naïve (17) + drug-free (3)	No change in D2 density; left-sided striatal D2 asymmetry in males	Pilowsky et al. 1994
[11C]raclopride PET	Drug-naïve (12) + drug-free (1)	No general change in D2 density, subgroup of 4 patients with high D2 density	Hietala et al. 1994
[76Br]lisuride PET	Drug-naïve (8) + drug-free (2)	No change in D2 density; negative symptoms (flattened affect and alogia) correlated negatively with D2 binding	Martinot et al. 1994
[11C]NMSP PET	Drug-naïve (7)	No change in D2 density	Nordström et al. 1995a
[123I]IBZM SPECT	Drug-free (15)	No change in D2 density	Laruelle et al. 1996
[11C]NMSP PET	Drug-naïve (10) + drug-free (7)	No change in D2 density	Okubo et al. 1997
[11C]raclopride PET	Drug-naïve (6) + drug-free (5)	No change in D2 density	Breier et al. 1997
[123I]IBZM SPECT	Drug-free (21)	No change in D2 density; negative symptoms correlated negatively with D2 binding	Knable et al. 1997a
[123I]IBZM SPECT	Drug-free (21)	No change in D2 density	Abi-Dargham et al. 1998
[123I]IBZM SPECT	Drug-naïve (8) + drug-free (10)	No change in D2 density	Abi-Dargham et al. 2000
[123I]IBZM SPECT	Drug-naïve (11)	No change in D2 density	Yang et al. 2004
[11C]raclopride PET	Drug-naïve (18)	No change in D2 density	Talvik et al. 2006
[123I]IBZM SPECT	Drug-naïve (18)	↑ D2 density	Corripio et al. 2006
[18F]fallypride PET	Drug-naïve (4) + drug-free (7)	No change in D2 density; hallucinations correlated positively with D2 binding in left ventral striatum	Kessler et al. 2009

2.4.4 Extrastriatal dopamine D2/3 receptors among drug-naïve patients

Newly invented ultra high-affinity dopamine D2/3 radiotracers have enabled the visualization of dopamine D2/3 receptor sites even in the very low-density extrastriatal brain regions involved in schizophrenia. Suhara et al. (2002) were the first to reveal abnormalities in the availability of extrastriatal D2/3 in schizophrenia, reporting a reduced D2/3 density in the anterior cingulate cortex among 11 drug-naïve male patients studied with [11C]FLB 457 PET. A negative correlation was observed between D2/3 binding in the anterior cingulate cortex and positive symptoms assessed using the Brief Psychiatric Rating Scale (BPRS). The authors suggested that altered regulation of dopamine transmission in the anterior cingulate cortex may contribute to the conceptual disorganization and hallucinations commonly found in schizophrenia.

2.4.5 Striatal D2 receptor occupancy by antipsychotics

During the past two decades, PET and SPECT have been widely used to characterize the association between doses of antipsychotic drugs and their D2 receptor occupancy. Clinically effective doses of typical antipsychotics have been demonstrated to occupy from 65% to 90% of D2 receptors in the striatum of medicated schizophrenia patients determined with

[11C]raclopride (Farde et al., 1988; Farde et al., 1992). Striatal D2 occupancy has been shown to predict an antipsychotic response, since for clinical efficacy, striatal drug-occupancy level has been suggested to range between 60% and 80% induced by classical drugs (Nordström et al., 1993; Kapur et al., 2000a). In addition, the findings illustrated that the risk of extrapyramidal side effects increases as central D2 occupancy approaches 80%.

Several PET and SPECT studies using various radiotracers have demonstrated that clozapine, the prototype atypical antipsychotic drug, has lower D2 occupancy than typical antipsychotics. Utilizing [123I]IBZM SPECT, Tauscher et al. (1999) reported mean striatal D2 receptor occupancy of 33% for 6 clozapine-treated patients at doses ranging from 300 to 600 mg/day, compared to 84% for 10 patients medicated with haloperidol doses of 5–20 mg/day. Using the same method, a large individual variation has been reported in the D2 occupancy (18–80%) of clozapine-treated patients with a favorable clinical response to clozapine (mean dose of 510 mg/day) (Pickar et al., 1996). One [11C]raclopride PET study has determined striatal D2 receptor occupancy for clozapine (doses of 125–600 mg/day) of between 20–67%, which was also lower than that for to typical compounds (Nordström et al., 1995b).

Clozapine-induced striatal D2 occupancy has also been shown to differ from that evoked by other atypical drugs. Kapur et al. (1999) examined a total of 44 schizophrenic patients, of

which 17 were treated with olanzapine 5–60 mg/day, 16 with risperidone 2–12 mg/day, and 11 with clozapine 75–900 mg/day, respectively. Clozapine produced a clearly lower D2 occupancy (16–86%) than olanzapine (43–89%) and risperidone (63–89%). The authors commented that olanzapine and risperidone at their common clinical dose induce D2 occupancy levels equal to typical antipsychotic drugs. In a SPECT study with [123I]IBZM, olanzapine showed a significantly lower mean striatal D2 occupancy (49%) than haloperidol (64%) during a fixed dose of 10 mg/day maintenance therapy in 13 haloperidol-treated and 14 olanzapine-treated patients (Bernardo et al., 2001). Using the same method, the result was replicated in low-dose treatment with olanzapine (7.5 mg/day) and haloperidol (2.5 mg/day), resulting in a lower mean dopamine D2 occupancy for olanzapine (51%) than haloperidol (65.5%) (de Haan et al., 2003). Striatal D2 occupancy for olanzapine was 43–80% for patients taking olanzapine 5–20 mg/day and 83–88% for patients taking 30–40 mg/day assessed with [11C]raclopride and PET (Kapur et al., 1998). Another [11C]raclopride PET study reported occupancy values ranging from 68% to 84% in 3 patients treated with olanzapine at doses of 10–20 mg/day (Nordström et al., 1998b). Utilizing [123I]IBZM with SPECT yielded a mean dopamine D2 receptor occupancy for olanzapine of 75% at a mean dose of 18 mg/day (Tauscher et al., 1999). According to some imaging studies, striatal D2 occupancy has been found to

be dose-related for olanzapine (Kapur et al., 1998; Raedler et al., 1999; Dresel et al., 1999).

A mean striatal occupancy of 59% was detected using [123I]IBZM and SPECT in patients treated with risperidone at clinically recommended doses of 2–8 mg/day, showing no differences with respect to striatal occupancy induced by olanzapine (Schmitt et al., 2002). Later, using the same method, significantly higher striatal occupancy levels were found in patients treated with risperidone 6 mg/day (69 $\pm$ 8%) compared to olanzapine 10 mg/day (55 $\pm$ 11%) (Frankle et al., 2004). Similar to olanzapine, D2 occupancy levels for risperidone appears to be dose-dependent as follows: 66% at 2 mg/day, 73% at 4 mg/day, and 79% at 6 mg/day, as measured with [11C]raclopride PET (Remington et al., 1998). Corresponding risperidone-induced D2 occupancy levels have also been observed with the same method, showing 72% mean striatal D2 occupancy for 3 mg/day, and 82% for 6 mg/day, respectively (Nyberg et al., 1999). In a [123I]IBZM SPECT study, Knable et al. (1997b) have demonstrated comparable striatal D2 occupancy levels of 60–90% for risperidone and haloperidol at typical clinical doses, when antipsychotic-induced extrapyramidal side effects were detected at occupancy levels above 60%.

It has been suggested that quetiapine resembles clozapine in producing low striatal D2 occupancy even at high doses. A mean occupancy of 20% for quetiapine at doses 300–700 mg/day,

and 32% for clozapine at doses 300–600 mg/day were obtained with [123I]IBZM, revealing lower occupancy levels in comparison to haloperidol at 10–20 mg/day, which induced a very high mean occupancy of 87% (Küfferle et al., 1997). Using [11C]raclopride PET, mean D2 receptor occupancies of 41% and 30% were demonstrated at quetiapine doses of 750 and 450 mg/day, while D2 occupancies could not be quantified at lower doses (Gefvert et al., 2001). Although quetiapine doses of 150–600 mg/day induced extremely low D2 occupancy levels (0–27%) scanned with [11C]raclopride PET 12 hours after the last dose, an additional investigation showed transiently high striatal occupancies (58–64%) 2–3 hours after the last drug administration in patients receiving a single 400- or 450-mg dose of quetiapine (Kapur et al., 2000b). Utilizing the same imaging method for defining mean striatal D2 occupancies of different atypical antipsychotics, the following rank order was observed: 81% for risperidone at doses 3–6 mg/day, 79% for olanzapine at 15–22.5 mg/day, 61% for clozapine at 400–600 mg/day, and 30% for quetiapine at 300–700 mg/day (Tauscher et al., 2004).

A recent PET study with high affinity tracer [18F]desmethoxyfallypride found D2 occupancy levels of 43–85% in putamen and 67–90% in caudate among 9 patients receiving atypical antipsychotic amisulpride at clinical doses (Vernaleken et al., 2004). This result was supported by a study using [123I]epidepride SPECT that reported a 37% mean D2

occupancy in the putamen and 51% in the caudate of amisulpride-treated (mean dose of 406 mg/day) patients, and in patients treated with risperidone (mean dose of 3 mg/day), yielding a mean occupancy of 31% in the putamen and 42% in the caudate (Stone et al., 2005). The authors concluded that the atypical antipsychotics amisulpride and risperidone demonstrate selective occupancy for D2/3 receptors in limbic and associative regions of the striatum (defined as the caudate) compared to sensorimotor striatal regions (the putamen). Patients treated with recommended doses of ziprasidone (range of 40–160 mg/day), a novel antipsychotic compound, have shown moderately high striatal D2 occupancy levels of 10–73% (mean 55%), as measured with [11C]raclopride PET suggesting that ziprasidone is identical to risperidone and olanzapine in D2 occupancy profile (Mamo et al., 2004).

Aripiprazole has a mechanism of action that differs from all other antipsychotics because it functions as a partial agonist to dopamine D2 receptors. A very high striatal D2 occupancy was observed in 12 schizophrenic patients receiving clinical doses of aripiprazole (range 10–30 mg/day) showing a mean occupancy of 87% in the putamen, 93% in the caudate, and 91% in the ventral striatum (Mamo et al., 2007). These findings indicated that D2 occupancy in the putamen was significantly lower than in the caudate or ventral striatum. Unlike typical antipsychotics,

the extrapyramidal side-effects induced by aripiprazole were seen only with D2 occupancies exceeding 90%.

2.4.6 Extrastriatal D2/3 receptor occupancy by antipsychotics

Recently, neuroimaging and pharmacological evidence has supported the view that limbic cortical dopamine D2/3 receptors may be the main target of antipsychotic medication (Lidow et al., 1998; Takahashi et al., 2006; Stone et al., 2009). During the last decade, a substantial number of studies have been published on drug occupancies in extrastriatal regions. A summary of these studies is presented in Table 5.

The vast majority of these studies have reported both striatal and extrastriatal D2/3 occupancies utilizing the same ralioligand. Imaging extrastriatal regions with [11C]FLB 457, and concomitantly striatal regions with [11C]raclopride have been performed in few cases (Farde et al., 1997b; Talvik et al., 2001; Agid et al., 2007). Some of the studies have not reported or measured striatal occupancies, as in high-density receptor regions (e.g., striatum) where the binding of high-affinity radioligands does not reach equilibrium (Yasuno et al., 2001b; Takano et al., 2006; Arakawa et al., 2009).

Studies on extrastriatal drug occupancy have generally provided conflicting results. A proportion of these studies have reported equally high extrastriatal D2 occupancy levels for both

atypical and traditional antipsychotics, demonstrating occupancy levels varying between 68–92% for atypical compounds and 71–96% for typical antipsychotics in limbic cortical regions using various methods such as [76Br]FLB 457 and [18F]fallypride with PET, and [123I]epidepride with SPECT (Pilowsky et al., 1997; Xiberas et al., 2001a; Kessler et al., 2005). Two PET studies have found a lower extrastriatal occupancy of 24–41% with clozapine compared to 63–68% with haloperidol visualized with [11C]FLB 457 (Farde et al., 1997b; Talvik et al., 2001). Similarly high D2/3 mean occupancy levels were detected in the striatum (73%) and in the temporal cortex (82%) of typical antipsychotic-treated patients with schizophrenia, as determined with [123I]epidepride SPECT (Bigliani et al., 1999). Aripiprazole-induced high D2/3 occupancy levels were found using [18F]fallypride PET both in the extrastriatal (range 83–85%) and striatal (range 83–84%) regions (Gründer et al., 2008).

Some research groups using [123I]epidepride SPECT have discovered regional or limbic selectivity by atypical antipsychotics, where significantly higher D2/3 occupancy levels were found in extrastriatal areas than in the striatum. Pilowsky et al. (1997) initially reported significantly lower striatal mean occupancy of 58% compared to that of 90% in the temporal cortex of clozapine-treated patients. Moreover, for olanzapine and sertindole, regional mean occupancy levels have been observed to differ between the temporal cortex (83% and 83%)

and the striatum (41% and 62%) (Bigliani et al., 2000). A similar pattern of limbic cortical selectivity over the striatum was detected for amisulpride, showing a higher D2/3 occupancy in the thalamus (78%) and temporal cortex (82%) than in the striatum (56%) (Bressan et al., 2003b). When studied in quetiapine-treated patients, a regional difference was also observed between occupancy levels, resulting in 32% for the striatum and 60% for the temporal cortex (Stephenson et al., 2000). Low-dose treatment with risperidone (a mean dose of 2.6. mg/day) has been demonstrated to achieve equal selectivity of limbic D2/3 receptors than other atypicals showing occupancy levels of 71% in the thalamus, 75% in the temporal cortex and 50% in the striatum (Bressan et al., 2003a).

Utilizing [18F]fallypride PET Gründer et al. (2006) observed a significantly higher mean D2/3 receptor occupancy in the inferior temporal cortex (55%) than in the putamen (36%) or the caudate (43%) of clozapine-treated patients. The findings suggested preferential occupancy in cortical dopamine D2/3 receptors over a large range of plasma concentrations, though the selectivity was found to be lost at very high plasma levels. A dose-dependent differential binding profile for amisulpride was found in a [76Br]FLB 457 PET study that demonstrated a moderate extrastriatal D2/3 occupancy of 41% in the thalamus and 56% in the temporal cortex, and a low D2/3 occupancy of 13% in the striatum at low plasma concentrations, whereas

substantial occupancies were seen both in the striatum (41%) and in the extrastriatal regions (73–78%) included by higher plasma levels (Xiberas et al., 2001b). As for clozapine, a recent experimental PET study measuring the time course of extrastriatal D2/3 occupancy with an [11C]FLB 457 occupancy of one patient with a high plasma drug level produced a 75% occupancy at its peak and 60% 26 hours after taking the last drug dose, and for patients with a moderate plasma concentration occupancy of 43% being observed at its peak and 17% after 25 hours (Takano et al., 2006). Patients receiving a high or low dose of risperidone (1 mg vs. 4 mg) or olanzapine (2.5 mg vs. 15 mg) revealed D2/3 occupancies ranging from 50% to 92% in the striatum and 4% to 95% in extrastriatal regions (the frontal and temporal cortex, and the thalamus) obtained with [11C]FLB 457 PET (Agid et al., 2007). These findings demonstrate that striatal and extrastriatal occupancies showed correlation with drug dose and striatal D2/3 occupancy with a response in positive symptoms. A similar dose relationship for limbic cortical D2/3 occupancy with risperidone was also illustrated in another [11C]FLB 457 PET study, revealing mean occupancies ranging from 38% to 80% in extrastriatal regions (the temporal cortex, thalamus, anterior cingulate cortex and amygdala) of patients treated with at risperidone 1–6 mg/day (Yasuno et al., 2001b).

Preferential D2/3 occupancy of the temporal cortical vs. striatal was found for clozapine and quetiapine using [18F]fallypride PET (Kessler et al., 2006). The results showed mean occupancies of 60% in the temporal cortex and 48% in the putamen for clozapine, and 47% in the temporal cortex and 34% in the putamen for quetiapine; however, in the substantia nigra, occupancy of 18% was discerned for clozapine and 34% for quetiapine, thus differentiating these two atypical antipsychotics. Utilizing the same tracer, no regional selectivity for D2/3 occupancy was observed in the putamen, ventral striatum, thalamus, amygdala or temporal cortex for olanzapine, and mean occupancy levels for olanzapine (range 68–72%) did not differ from haloperidol (range 71–78%) (Kessler et al., 2005). However, a significantly lower occupancy of the substantia nigra D2/3 receptors was found in olanzapine-treated patients (40%) than that in haloperidol-treated patients (59%). In a recent [11C]FLB 457 PET study, D2/3 receptor occupancy ranged from 61% to 86% in the temporal cortex of patients taking olanzapine at 5–20 mg/day, suggesting the limbic occupancy of olanzapine to be similar to that in the striatum (Arakawa et al., 2009). Ziprasidone induced approximately 10% higher D2 occupancy levels in extrastriatal areas (59–66%) than in striatal regions (57–59%), as assessed in two parallel studies using [18F]fallypride and [11C]raclopride with PET (Vernaleken et al., 2008).

Table 5. Summary of studies on extrastriatal D2/3 occupancy by antipsychotics.

Method	Medication (*n*)	Mean O % in extrastriatal region	Mean O % in striatum	Ref.
[123I]epidepride SPECT	Clozapine (7)	90 (tc)	58	Pilowsky et al. 1997
	Typicals (5)	96 (tc)	90	
[11C]FLB 457+ [11C]raclopride PET	Clozapine (1)	24 (tc)/34 (th)	32	Farde et al. 1997b
	Typicals (3)	67 (tc)/68 (th)	79	
[123I]epidepride SPECT	Typicals (12)	82 (tc)	73	Bigliani et al. 1999
[123I]epidepride SPECT	Olanzapine (5)	83 (tc)	41	Bigliani et al. 2000
	Sertindole (4)	83 (tc)	62	
[123I]epidepride SPECT	Quetiapine (6)	60 (tc)	32	Stephenson et al. 2000
[76Br]FLB 457 PET	Haloperidol (4)	92 (tc)/94 (th)	82	Xiberas et al. 2001a
	Risperidone (3)	92 (tc)/90 (th)	63	
	Clozapine (3)	78 (tc)/63 (th)	33	
	Amisulpride (5)	81 (tc)/73 (th)	42	
	Olanzapine (4)	84 (tc)/64 (th)	45	
[11C]FLB 457+ [11C]raclopride PET	Clozapine (4)	41 (tc)/30 (th)	37–43	Talvik et al. 2001
	Haloperidol (3)	63 (tc)/68 (th)	78–81	
[76Br]FLB 457 PET	Amisulpride (6) (50–300 mg)	56 (tc)/41 (th)	13	Xiberas et al. 2001b
	Amisulpride (4) (400–1200 mg)	78 (tc)/73 (th)	41	
[11C]FLB 457 PET	Risperidone (7)	67 (tc)/61 (ac)/ 66 (hip)/63 (am)	-	Yasuno et al. 2001b
[123I]epidepride SPECT	Risperidone (6)	75 (tc)/71 (th)	50	Bressan et al. 2003a
[123I]epidepride SPECT	Amisulpride (8)	82 (tc)/78 (th)	56	Bressan et al. 2003b
[18F]fallypride PET	Olanzapine (6)	68 (tc)/71 (th)/ 72 (am)/40 (sn)	69 (pu)/ 71 (vs)	Kessler et al. 2005
	Haloperidol (6)	71 (tc)/78 (th)/ 76 (am)/59 (sn)	77 (pu)/ 76 (vs)	
[18F]fallypride PET	Clozapine (15)	56 (tc)/44 (th)/ 44 (am)/43 (sn)	36 (pu)/ 44 (cn)	Gründer et al. 2006
[11C]FLB 457 PET	Clozapine (1) (600 mg)	76 (peak)/ 60 (26 h)	-	Takano et al. 2006
	Clozapine (1) (200 mg)	43 (peak)/ 17 (25 h)		
[18F]fallypride PET	Clozapine (6)	60 (tc)/55 (th)/ 52 (am)/18 (sn)	48 (pu)/ 46 (vs)	Kessler et al. 2006
	Quetiapine (7)	47 (tc)/40 (th)/ 43 (am)/34 (sn)	34 (pu)/ 34 (vs)	
[11C]FLB 457+ [11C]raclopride PET	Olanzapine (9) + Risperidone (5)	4–95 (range)	50–92 (range)	Agid et al. 2007
[18F]fallypride PET	Aripiprazole (16)	83 (tc)/85 (th)/ 85 (am)	83 (pu)/ 84 (cn)	Gründer et al. 2008
[18F]fallypride PET	Ziprasidone (15)	66 (tc)/64 (th)/ 59 (am)	57 (pu)/ 59 (cn)	Vernaleken et al. 2008
[11C]FLB 457 PET	Olanzapine (10)	72 (tc)	-	Arakawa et al. 2009

O = occupancy, tc = temporal cortex, th = thalamus, ac = anterior cingulate cortex, hip = hippocampus, am = amygdala, sn = substantia nigra, pu = putamen, vs = ventral striatum, cn = caudate nucleus

2.5 SUMMARY BASED ON THE LITERATURE

These findings from neuroreceptor-specific imaging studies consolidate the position of the dopamine hypothesis in schizophrenia, regardless of any particular inconsistency between the results of individual studies. In addition to dopamine, at least such brain transmitters as glutamate and serotonin, and several potent candidate genes (e.g., dysbindin) have considerable influence on the pathophysiology of schizophrenia. The evidence from different theoretical models can be considered largely contributory and interconnected with each other.

Several studies on presynaptic dopamine function have shown an elevated striatal dopaminergic turnover in schizophrenia, which was associated with an acute deterioration in psychotic symptoms. However, findings from imaging studies on striatal presynaptic dopamine transporter (DAT) density have been inconsistent, though the majority of the studies with drug-naïve or drug-free patients have found no changes when compared to healthy persons. Few studies have reported elevated D2 receptor density in the striatum of patients with schizophrenia, while most of these works found no general schizophrenia-related changes. Only a minority of the studies concerning striatal D2 binding has examined drug-naïve patients alone.

Typical antipsychotics have been found at their clinically effective doses to occupy between 65% and 90% of the striatal D2 receptors. Several neuroimaging studies have demonstrated that clozapine has lower striatal D2 occupancy with greater individual variation compared to typical antipsychotics. Clozapine-induced striatal D2 occupancy has repeatedly been seen to differ from that produced by other atypical antipsychotics, except for quetiapine. However, few studies have shown a transiently high striatal D2 occupancy in patients treated with quetiapine or clozapine shortly after the last drug dose. Many studies have reported lower central D2 occupancy levels for the atypical antipsychotics olanzapine and risperidone, as well as for amisulpride and ziprasidone, at their common clinical doses compared to typical compounds.

With the invention of ultra high-affinity dopamine D2/3 radiotracers, it became possible to visualize dopamine D2/3 receptors even in very low receptor density regions, i.e., extrastriatal brain areas, involved in schizophrenia. Previously, one PET study has reported decreased D2/3 density in the anterior cingulate cortex among drug-naïve patients compared to healthy controls. In addition, dopamine D2/3 binding in the anterior cingulate cortex was shown to associate with positive symptoms of schizophrenia.

As the neuroimaging and pharmacological evidence has supported the view that clinical efficacy of antipsychotic

medication may be mediated by blocking limbic cortical dopamine D2/3 receptors, a substantial number of imaging studies have been published on drug occupancies in extrastriatal areas. The findings of these studies on extrastriatal drug occupancy have been contradictory on the whole. A proportion of the studies have reported equally high extrastriatal D2/3 occupancy for both atypical and typical antipsychotics. In contrast, two PET studies have found lower extrastriatal occupancy of clozapine compared to haloperidol. Limbic cortical selectivity over the striatum was detected for atypical antipsychotics in some imaging studies. In many studies using various imaging methods, similarly high D2/3 occupancy levels have been observed in the striatum and limbic cortical regions for typical antipsychotics. Dopamine D2/3 occupancy in the substantia nigra has been determined in two PET studies, which found lower occupancy levels in clozapine-treated patients than in quetiapine-treated patients, and lower levels in patients medicated with olanzapine than in those with haloperidol, respectively.

The majority of the extrastriatal occupancy studies have used the baseline values of normal controls in calculating D2/3 occupancies. Few of these studies have calculated drug occupancies using regional D2/3 binding values obtained either from an off-medication period of study subjects or from a control group of drug-free schizophrenic patients. Of these

studies, only two have defined the occupancy values on the basis of a drug-naïve patient group.

Because of these apparent limitations and methodological disparities, as well as discrepancies between their results, further research is warranted. Suspected alterations have not been identified in the dopamine D2/3 receptors from extrastriatal brain regions other than those in the anterior cingulate cortex. Moreover, it is not known whether extrastriatal D2/3 binding associates with the symptomatology of schizophrenia in these regions. Furthermore, regional differences in the apparent binding potential or drug occupancy between typical and atypical antipsychotics in extrastriatal areas have not been completely clarified, especially when a significant divergence exists in the baseline D2/3 density values used in the calculation of occupancies. It also remains unclear whether extrapyramidal side-effects may be associated with D2/3 blockade in any of the extrastriatal brain regions.

3 AIMS OF THE STUDY

I. To test the hypothesis that extrastriatal D2/3 density in temporal and anterior cingulate cortex is lower among drug naive schizophrenic patients than among healthy controls.

II. To explore dopamine D2/3 densities in the thalamus and midbrain in drug-naïve schizophrenic patients compared to healthy controls, and to evaluate the possibility of an association between D2/3 binding and both the nature and severity of associated specific symptoms.

III. To compare dopamine D2/3 apparent binding potential and drug occupancy in extrastriatal regions between clozapine-, olanzapine- and haloperidol-treated patients with schizophrenia.

IV. To examine relationships between dopamine D2/3 receptor binding in substantia nigra or temporal cortex and extrapyramidal symptoms among antipsychotic-treated patients with schizophrenia.

4 SUBJECTS AND METHODS

4.1 STUDY PROTOCOL AND SUBJECTS

The study protocol was approved by the Kuopio University Hospital and University of Kuopio Ethics committee. Written, informed consent was obtained from each patient and control volunteer after a full explanation of the study. Patients were recruited from psychiatric hospitals (Julkula Hospital, Kuopio University Hospital, and Niuvanniemi Hospital) and outpatient units (Psychiatric Outpatient Clinic, Kuopio University Hospital) in Kuopio, Finland.

The diagnoses were verified with the Structured Clinical Interview for the DSM III-R (SCID) (Spitzer et al., 1992) by a trained psychiatrist. Co-existing substance abuse and any organic brain disorder were criteria for exclusion. Psychopathological symptoms of the patients were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

4.1.1 Extrastriatal dopamine D2/3 receptor density and distribution in drug-naïve schizophrenic patients (I)

The study subjects comprised seven right-handed drug-naive patients (3 males and 4 females) fulfilling ICD-10 criteria for schizophrenia or schizophreniform disorder aged 19–51 years, mean 31.9 (SD = 13.9). The duration of illness ranged from 1 month to 3 years (mean 1.2 years). The controls consisted of seven right-handed healthy volunteers (4 males and 3 females) aged between 20–42 years, mean 31.4 (SD = 8.7). The mean PANSS scores among patients were 88.71 (SD = 18.03) for total, 23.43 (SD = 6.08) for positive, 21.86 (SD = 6.82) for negative, and 43.43 (SD = 8.68) for general psychopathological score.

4.1.2 Midbrain dopamine D2/3 receptor binding in schizophrenia (II)

This study was a reanalysis with new ROIs of the cohort of schizophrenic patients reported in Study I. One of the previously reported patients was excluded from this reanalysis because of a loss of data caused by damage to the DAT archiving tape. The sample consisted of six drug-naïve patients (4 females, 2 males) aged 19–50 years (mean $\pm$ SD; 33 $\pm$ 14). The duration of illness ranged from 1 month to 3 years (mean 11 months). All patients were right-handed. The antipsychotic-naïve state was confirmed by clinical records and interviews

with both patients and proxy informants. Although none of the patients had ever used antipsychotic medications, two patients received small doses of benzodiazepines (diazepam 5 mg or oxazepam 15 mg) occasionally a few days before the scan. (The results of these patients did not differ from those of the other patients.) None of the patients received other medications (e.g., antidepressants, beta blockers or antiepileptic drugs) that might confound D2/3 receptor binding measurements. Seven healthy, right-handed volunteers (4 males and 3 females) of 19–42 years (mean ± SD; 31 ± 9) were used as controls in this study. The controls had no history of neuropsychiatric disorder or alcohol/drug abuse. The mean PANSS scores of the patients were 84.7 (SD = 15.9) for total symptoms, 21.3 (SD = 2.7) for positive symptoms, 20.7 (SD = 6.6) for negative symptoms, and 42.7 (SD = 9.2) for the general psychopathological score.

4.1.3 Dopamine D2/3 receptor binding potential and occupancy in midbrain and temporal cortex by haloperidol, olanzapine and clozapine (III)

The study subjects consisted of 13 right-handed patients who met the ICD-10 criteria for either schizophrenia or a schizophreniform disorder. Two of the patients were treated with haloperidol (age 51 ± 8 years, F/M 1/1), four with olanzapine (age 35 ± 7 years, F/M 1/3) and seven with clozapine

(age 35 ± 13 years, F/M 0/7), respectively. The mean PANSS scores of haloperidol-treated patients were 102 (SD = 2) for total, 25 (SD = 6) for positive, 25 (SD = 4) for negative, and 52 (SD = 4) for general psychopathological score, olanzapine-treated patients 73 (SD = 10) for total, 17 (SD = 5) for positive, 19 (SD = 2) for negative, and 36 (SD = 6) for general psychopathological score, and clozapine-treated patients 81 (SD = 16) for total, 20 (SD = 4) for positive, 22 (SD = 4) for negative, and 39 (SD = 10) for general psychopathological score. The comparison groups consisted of six drug-naïve patients (age 33 ± 14 years, F/M 4/2) and seven healthy subjects (age 31 ± 9 years, F/M 3/4).

The antipsychotic-treated patients had been on the same, single medication after being drug-naïve, or drug-free for at least one month, in which case the required washout period for previous medication was three months for oral and six months for depot antipsychotics prior to the study. At the time of entry into the study the patients were treated within ordinary settings when drug dosages were clinically optimized and freely titrated for control of symptoms by the patients' own doctors. The mean daily drug dose was 6 mg (range 2.4–10 mg) for haloperidol, 19 mg (range 15–20 mg) for olanzapine and 593 mg (range 400–800 mg) for clozapine, respectively. The mean dosages of each drug were within the recommended dose range (for haloperidol 5–20 mg/day, olanzapine 10–30 mg/day and clozapine 150–600 mg), though one haloperidol-treated patient received a lower daily

dose (haloperidol depot injection 50 mg every 3 weeks) and the drug dose of three clozapine-treated patients was over 600 mg/day (American Psychiatric Association, 2004). The chlorpromazine-equivalent mean dose for haloperidol was 300 mg/day, for olanzapine 400 mg/day and for clozapine 1200 mg/day (Kane, 1996; Woods, 2003). One haloperidol patient and all clozapine-treated patients received their last drug-dose 2–3 hours, and olanzapine-treated 14–15 hours before the first SPECT scan, while the subject receiving depot haloperidol was scanned 2 weeks following his last injection. Patients received no other medications that might interfere with D2/3 receptor binding during this study (e.g., antidepressants, beta blockers or antiepileptic drugs).

4.1.4 Extrapyramidal side-effects and dopamine D2/3 receptor binding in substantia nigra (IV)

This study provided a supplementary analysis of the cohort of schizophrenic patients reported in Study III. The study subjects comprised 13 antipsychotic-medicated (two with haloperidol, four with olanzapine and seven with clozapine; two female) patients mean aged 37.5 (SD = 11.4) years who met the ICD-10 criteria for schizophrenia (paranoid, hebephrenic or undifferentiated subtype). The patients' extrapyramidal side-effects were evaluated along with clinical examination by a

trained psychiatrist on preceding day prior to the SPECT scan using the Simpson and Angus Scale (SAS) for extrapyramidal side effects (Simpson and Angus, 1970). None of the patients received anticholinergic medication. The controls consisted of six drug-naïve patients (four female) with schizophrenia mean aged 33.2 (SD = 14.1) years who had been scanned earlier.

4.2 SPECT PROCEDURE AND IMAGE ANALYSIS

After a bolus injection of [123I]epidepride (185 MBq; supplied by MAP Medical Technologies Oy, Tikkakoski, Finland) the first single-photon emission tomography (SPECT) scan was carried out starting at 30 min and the second 3 h from the ligand administration, as the highest uptake in extrastriatal regions peaks at 45–60 min after injection of tracer, and apparent steady-state conditions are achieved within 3–4 h (Kuikka et al., 1997). Both scans continued for approximately 30 min using a dedicated MultiSPECT 3 gamma camera with fan-beam collimators (Siemens Medical Systems Inc., Hoffman Estates, IL, USA). The energy window was centered on the photo peak of [123I] (i.e., 148–170 keV). During 360° rotation (120° per camera head), 40 view/head scans were acquired in a 128 by 128 matrix (with a pixel size of 2.8 mm). The radius of rotation was 13 cm. The imaging resolution was 9–10 mm and a soft filter (Butterworth: cut-off frequency 0.4 cm^{-1} and order 5) was used in the reconstruction to yield images of low-density receptors.

This SPECT imaging procedure has been described in detail by Kuikka et al. (1997). Following the SPECT scans, transaxial slices (6 mm thick) were reconstructed and corrected for attenuation. At the time of performing these imaging studies, proper scatter correction methods were lacking. The imaging data was corrected by using cut-off level of 60% in the regional count density values, which was assumed to correct scatter and partial volume effect in part.

4.2.1 Studies on drug-naïve schizophrenic patients (I–II)

Studies with drug-naïve schizophrenic patients used the imaging data from the first SPECT scan (30–60 min). Regions of interest (ROI) were manually drawn onto the cerebellum (as a reference region = free + non-specific binding), and the temporal pole (I), the thalamus (II) and the midbrain (II) (= free + non-specific + specific binding) with the help of MRI data (as templates of 5 MRI control subjects) and a reference atlas (Talairach and Tournoux, 1993). The operator did not know whether or not the individual scan was from a patient or from a control. Specific binding (SB) of [123I]epidepride in the ROI was calculated from the average count density from each region as (ROI – cerebellum) / cerebellum. The vermis was excluded from the cerebellar ROI. Cerebellar count rates between patients and controls did not differ significantly ($p = 0.39$). The intra-class

correlation co-efficients calculated on the basis of two repeated determinations (in temporal pole) in 11 subjects (6 patients and 5 controls) were 0.85 on the left and 0.95 on the right. The anterior cingulate cortex was excluded from further analysis, since the specific binding values were too low, resulting in a low intra-class correlation co-efficient (0.4). When the frontal cortex was measured as a whole, the specific binding values were even lower than for the anterior cingulate cortex. The high affinity of [123I]epidepride is optimal for imaging the relative low density of D2/3 receptors in extrastriatal regions. In basal ganglia, which have high D2/3 receptor density, the ligand binding does not reach equilibrium, thus making it difficult to measure the striatal D2/3 binding reliably.

4.2.2 Studies on medicated schizophrenic patients (III–IV)

ROIs in the reconstructed images were manually drawn onto the cerebellum (as a reference region = free + non-specific binding), the temporal poles and the midbrain (= free + non-specific + specific binding) with the help of MRI data (as templates of 5 MRI control subjects). For example, the total volume of substantia nigra (both sides combined) was approximately 0.7 ml. No significant difference in ROI area was found between control and patient groups in any of the regions studied. In all cases, the operator was blind to the medication

status of the participant. Measurements of the striatum were excluded, as the ultra high-affinity D2/3 ligand [123I]epidepride does not reach equilibrium in high-density regions.

Dopamine D2/3 receptor apparent binding potential (BP_{app}) of [123I]epidepride corresponds with the BP_{ND} (ratio of specific to non-displaceable binding) defined in consensus nomenclature for in vivo imaging of reversibly binding radioligands (Innis et al., 2007). BP_{app} in the ROI was calculated according to Equation 1, as the ratio between radioactivity in the ROI (C_r) and in the cerebellum (C_c) minus 1 (Figure 1). The time activity curves were integrated for the time interval of 0-210 minutes after tracer injection:

Equation 1. $$BP_{app} = \int_0^{210} C_r(t)dt \Big/ \int_0^{210} C_c(t)dt - 1$$

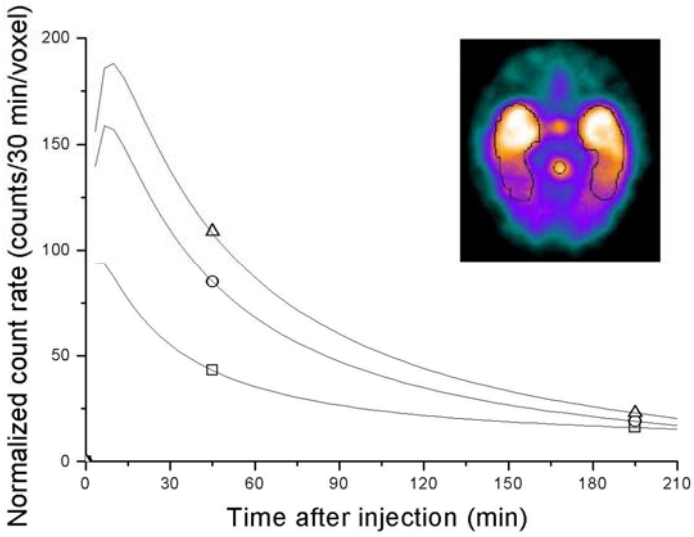

Figure 1. Time activity curves (TACs) for regional radioactivity in the cerebellum (square), in the right temporal pole (circle) and in the midbrain (up triangle). Log-normal function (Origin, Microcal Software Inc., Northampton, MA, USA) was used to calculate the areas under the time activity curves (Bassingthwaighte, 1970). Colour-coded SPECT image illustrates the regions of interest.

Several post-mortem and neuroreceptor-specific imaging studies have estimated the dopamine D2/3 receptor decline of approximately to be 10% per decade in the striatal and extrastriatal brain regions of healthy subjects (Seeman et al., 1987; Ichise et al., 1998; Kaasinen et al., 2000). Some previous neuroimaging studies on drug-naïve patients with schizophrenia have reported an age-effect in the striatum as well as in some extrastriatal areas, i.e., the frontal and temporal cortices (Farde et al., 1990; Talvik et al., 2003). No difference in the age-related reduction in striatal D2/3 receptor density has

been found between schizophrenic patients and healthy subjects (Wong et al., 1997). Age-related alterations in dopamine D2/3 binding were taken into account by using Equation 2 to exclude the possible influence of the different mean ages seen in the present studies:

Equation 2. $BP_{app\text{-}a} = [1 + 0.01 \times (age - 35)] \times BP_{app\text{-}p}$, where $BP_{app\text{-}a}$ is the age-adjusted apparent binding potential and $BP_{app\text{-}p}$ is the apparent binding potential for each patient.

For the calculation of drug occupancy (III), we used the age-adjusted mean D2/3 receptor density value of the drug-naïve schizophrenic patients because recent in vivo neuroimaging studies have revealed a significantly reduced number of dopamine $D_{2/3}$ receptors in the extrastriatal brain regions of these patients, especially in the temporal and anterior cingulate cortices, thalamus and midbrain regions compared to healthy controls (Suhara et al., 2002; Talvik et al., 2003; Yasuno et al., 2004). We also cross-checked the drug occupancy levels by using the age-adjusted mean values obtained from healthy volunteers. D2/3 receptor occupancy, O, was calculated according to Equation 3:

Equation 3. O (%) = [1 – ($BP_{app\text{-}ap}$ / $BP_{app\text{-}ad/ac}$)] x 100, where $BP_{app\text{-}ap}$ is the age-adjusted apparent binding potential for drug-treated patient and $BP_{app\text{-}ad/ac}$ is the age-adjusted mean apparent binding potential of the comparison group obtained from previously collected sample of six drug-naïve schizophrenic patients or the healthy control group.

4.3 MRI ACQUISITION

Patients with schizophrenia underwent a tilted T_1-weighted magnetic resonance scan (MRI) of the brain with a 1.5 T Siemens Vision camera (Erlangen, Germany) using a standard head coil and coronal 3D gradient echo sequence (MPRAGE: TR 10 ms, TE 4 ms, TI 250 ms, flip angle 12°, FOV 250 mm, matrix 256 by 192, 1 acquisition). MRI was used to exclude any neurostructural abnormalities.

4.4 STATISTICAL ANALYSIS

A univariate analysis of covariance (ANCOVA) with age as a covariate was performed to compare the differences in specific binding (SB) values between drug-naïve patients with schizophrenia and healthy controls in order to exclude the

possibility that the slight difference in mean ages might influence the results (I–II). Non-parametric tests were used to compare differences between drug groups in age-adjusted dopamine D2/3 receptor binding values (BP_{app}) (Kruskal-Wallis test for all test groups and Mann-Whitney test to compare olanzapine and clozapine groups), receptor occupancies and clinical scores (Kruskal-Wallis test), and for right-left hemispheric differences of dopamine D2/3 binding within medicated patients (Wilcoxon Rank-Sum test) (III).

Relationships between temporal, thalamic and nigral D2/3 densities, adjusted for age, and the different dimensions of PANSS scores of the drug-naïve patients were assessed using Pearson`s 2-tailed correlation method, as were the age-adjusted cerebellar count rates between drug-naïve schizophrenics and healthy controls (I–II). A Spearman's two-tailed correlation was used for assessing the significance of relationships between D2/3 receptor occupancy (age-adjusted) and various dimensions of PANSS scores among drug-treated patients (III). Pearson's two-tailed correlation was also used to evaluate associations between apparent binding potential values and extrapyramidal symptom scores (SAS), and apparent binding potential values or SAS scores and age (IV). We used the Kruskal-Wallis test to compare differences in SAS scores and age between drug groups (IV). The Mann-Whitney test was performed to compare difference in age between drug-treated and drug-naïve patients (IV). The

level of statistical significance was defined as $p < 0.05$ in all studies.

In studies with drug-naïve schizophrenic patients (I–II), a power analysis of binding values between groups was performed according to the methods of Cohen (1977). The effect size (ES) is a sample-based descriptive estimate of quantity of the strength of the relationship between two variables in a study population. ES presents the average difference between two groups without noticing the variability within the groups.

5 RESULTS

5.1 EXTRASTRIATAL DOPAMINE D2/3 RECEPTOR DENSITY AND DISTRIBUTION IN DRUG-NAÏVE SCHIZOPHRENIC PATIENTS (I)

We found a statistically significant difference in [123I]epidepride specific binding between patients with schizophrenia and control subjects in the temporal cortex (Figure 2). The binding values (ml/ml; mean ± SD) were lower among patients than healthy controls in the left temporal cortex (0.76 ± 0.12 vs. 1.07 ± 0.14, effect size = 2.3, F = 18.4, p = 0.001, ANCOVA) and in the right temporal cortex (0.78 ± 0.12 vs. 1.10 ± 0.19, effect size = 2.0, F = 16.1, p = 0.002). Without age-adjustment the statistical parameters remained almost the same (F = 18.8, p = 0.001 on the left; F = 14.2, p = 0.003 on the right). There was a substantial negative correlation between age and epidepride binding among controls (r = –0.77, p = 0.04 on the left; r = –0.71, p = 0.07 on the right, Pearson's 2-tailed correlation) but not among the patients (r = 0.11, p = NS on the left; r = –0.28, p = NS on the right). We observed prominent negative correlations (Pearson´s 2-tailed correlation, age-adjusted) between PANSS general psychopathological score and dopamine D2/3 receptor binding (r = –0.90, p = 0.014 on the left; r = –0.86, p = 0.028 on the right). The correlations between epidepride binding and PANSS

negative symptom score (r = –0.55, p = NS on the left; r = –0.37, p = NS on the right) and positive symptom score (r = –0.08, p = NS on the left, r = –0.18, p = NS on the right) were smaller. In both hemispheres, D2/3 density explained a large proportion of the variance of the general psychopathological symptom score (r^2 = 81% on the left, r^2 = 74% on the right).

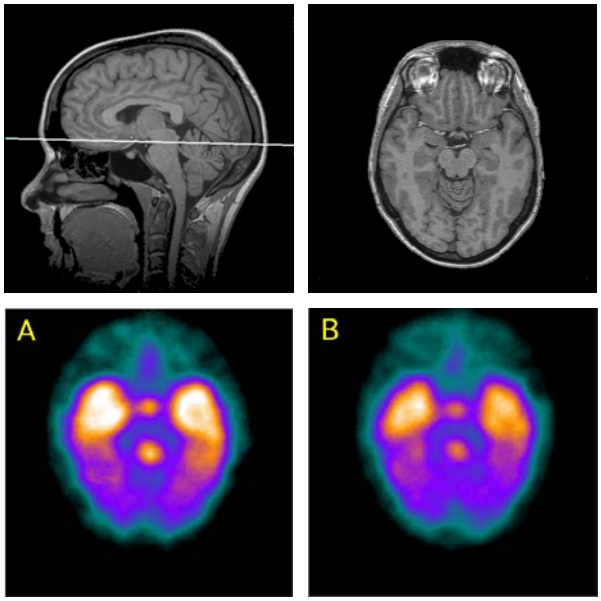

Figure 2. The summarized transaxial image of [123I] epidepride binding of 7 controls (A) and 7 patients (B). The MRI scans demonstrate the level of the summed SPECT slices. The highest ligand uptake is seen in temporal lobes. Note the reduced uptake in patients compared with controls.

5.2 MIDBRAIN DOPAMINE D2/3 RECEPTOR BINDING IN SCHIZOPHRENIA (II)

We observed a statistically significant difference in dopamine D2/3 receptor binding between schizophrenic patients and healthy controls in the midbrain. The binding values (ml/ml; mean ± SD) in the midbrain were lower in patients compared with controls (1.73 ± 0.13 vs. 2.07 ± 0.24, effect size = 1.71, F = 8.34, p = 0.016, ANCOVA). No statistically significant differences were found in the thalamic D2/3 receptor densities between patients with schizophrenia and healthy subjects (1.59 ± 0.23 vs. 1.74 ± 0.32, effect size = 0.51, F = 0.73, p = NS on the right; 1.66 ± 0.20 vs. 1.66 ± 0.25, effect size = 0.01, F = 0.00, p = NS on the left), although a trend-level reduction in the thalamic D2/3 binding of patients was seen on the right. No statistical differences were found between the variance of D2/3 receptor density, either in the thalamus or in the midbrain among schizophrenic patients relative to controls. The binding values did not differ in any ROI between male and female patients (p = 0.19–0.33) or control individuals (p = 0.26–0.82).

The clinical symptoms were assessed within the patient group where obvious negative correlations were found in the thalamus between the PANSS general psychopathological score and [123I]epidepride binding (r = –0.78, p = NS on the right; r = –0.92, p = 0.03 on the left). The correlations between [123I]epidepride binding in the thalamus and the PANSS

negative symptom scores (r = –0.48, p = NS on the right; r = –0.63, p = NS on the left) and positive symptom scores (r = –0.38, p = NS on the right; r = –0.41, p = NS on the left) were weaker. In the left thalamus, the D2/3 receptor density explained a substantial proportion of the variance in the general psychopathological score (r^2 = 85%), whereas the effect on the right side was lower (r^2 = 60%). There were no evident correlations in the midbrain between [123I]epidepride binding and different dimensions of the PANSS scores (positive symptom score: r = 0.66, negative symptom score: r = –0.31 and general psychopathological score: r = 0.28). Neuroanatomical anomalies or atrophy were not observed in any of the MRI scans among schizophrenic patients.

5.3 DOPAMINE D2/3 RECEPTOR BINDING POTENTIAL AND OCCUPANCY IN MIDBRAIN AND TEMPORAL CORTEX BY HALOPERIDOL, OLANZAPINE AND CLOZAPINE (III)

There was a significant difference in midbrain age-adjusted binding values (ml/ml; mean $\pm$ SD) between the medicated groups (1.00 $\pm$ 0.16 for haloperidol, 1.22 $\pm$ 0.10 for olanzapine and 1.59 $\pm$ 0.29 for clozapine, χ^2 = 8.44, df = 2, p = 0.015, Kruskal-Wallis test). In a re-analysis of the results between olanzapine- and clozapine-treated patients, a statistical significance was further observed (Z = –2.27, p = 0.023, Mann-Whitney test). We found no statistically significant differences in age-adjusted dopamine D2/3 BP_{app} between medicated groups in the temporal

pole (0.45 ± 0.03 for haloperidol, 0.63 ± 0.09 for olanzapine and 0.67 ± 0.24 for clozapine, $\chi^2 = 4.00$, df = 2, p = 0.136 on the right; 0.41 ± 0.08 for haloperidol, 0.66 ± 0.08 for olanzapine and 0.76 ± 0.27 for clozapine, $\chi^2 = 4.71$, df = 2, p = 0.095 on the left, Kruskal-Wallis test).

We observed no general lateralization effect in the binding values within the temporal pole (p = 0.18–0.72), except for clozapine-treated patients (Z = –2.20, p = 0.03, Wilcoxon Rank-Sum test). There were no statistical differences in BP_{app} between male and female participants in either the temporal poles or in the midbrain (p = 0.11–0.43, Kruskal-Wallis test). The midbrain ROIs were similar among patients and controls. The free + non-specific tracer uptake (area under the cerebellar time activity curve) did not significantly differ between the control and patient groups. The mean scores of various PANSS items did not differ statistically between the study groups (p = 0.23–0.27, Kruskal-Wallis test).

The Kruskal-Wallis test revealed statistically significant group differences in age-adjusted D2/3 receptor occupancy in relation to antipsychotic-naïve schizophrenics in the midbrain between the medicated groups (Table 6). We did not detect statistically significant differences in temporal lobe occupancy between the medicated groups. When using healthy subjects as a comparison group, drug occupancy levels (mean ± SD; age-adjusted) were notably altered in the temporal pole (67 ± 2% for

haloperidol, 53 ± 7% for olanzapine and 49 ± 18% for clozapine on the right; 71 ± 6% for haloperidol, 53 ± 5% for olanzapine and 45 ± 19% for clozapine on the left), and in the midbrain (53 ± 6% for haloperidol, 44 ± 4% for olanzapine and 27 ± 13 % for clozapine), thus showing substantially overestimated values for all antipsychotics in all brain regions. There was a statistically significant difference between occupancy values (age-adjusted) depending on the comparison group used in all examined brain areas ($Z = -3.20$, $p = 0.001$ in right temporal pole; $Z = -3.19$, $p = 0.001$ in the left temporal pole; $Z = -3.19$, $p = 0.001$ in the midbrain, Wilcoxon Rank-Sum test). We found no correlations between age-adjusted dopamine D2/3 receptor occupancy and PANSS items in any brain regions ($p = 0.20–0.84$, Spearman's correlation).

Table 6. Mean (range) age-corrected D2/3 percentage occupancy (O%)†.

Drug	O% in right TP‡	O% in left TP‡	O% in MB*
haloperidol	61 (59–63)	66 (61–71)	40 (33–46)
olanzapine	46 (35–53)	45 (37–51)	28 (19–33)
clozapine	42 (11–62)	37 (3–59)	5 (-21–28)

*p = 0.016, ‡p = 0.095 – 0.162 (NS)
†Calculated in comparison with drug-naïve patients' mean apparent binding potential.
MB, midbrain; TP, temporal pole.

5.4 EXTRAPYRAMIDAL SIDE-EFFECTS AND DOPAMINE D2/3 RECEPTOR BINDING IN SUBSTANTIA NIGRA (IV)

The demographic and clinical data of the 13 medicated patients are presented in Table 7. Mean ages or extrapyramidal symptom scores did not differ statistically between medication groups (p = 0.20–0.10, Kruskal-Wallis test). In the temporal pole, the BP_{app} values (ml/ml; mean ± SD) were 0.61 ± 0.19 on the right and 0.65 ± 0.20 on the left, and in substantia nigra 1.36 ± 0.35, respectively. We found no statistically significant correlation (Pearson's correlation) between age and BP_{app} values in any ROI (r = –0.42–0.01, p = 0.15–0.98), or age and extrapyramidal signs (r = 0.43, p = 0.14).

Table 7. The demographic and clinical data (mean ± SD) of antipsychotic-medicated patients.

Drug	n	Age*	Gender (f / m)	SAS†
haloperidol	2	51 ± 8	1 / 1	8.5 ± 5.0
olanzapine	4	35 ± 7	1 / 3	3.8 ± 2.2
clozapine	7	35 ± 13	0 / 7	2.4 ± 1.3

*p = 0.20, †p = 0.10, Kruskal-Wallis test

A statistically significant negative correlation was observed between apparent binding potential in the substantia nigra and Simpson and Angus score (r = –0.62, p = 0.024, Pearson's correlation) (Figure 3). In the temporal poles, statistically significant correlations were not detected between BP_{app} values

and extrapyramidal symptoms score (r = –0.36, p = 0.232 on the right; r = –0.42, p = 0.151 on the left, Pearson's correlation).

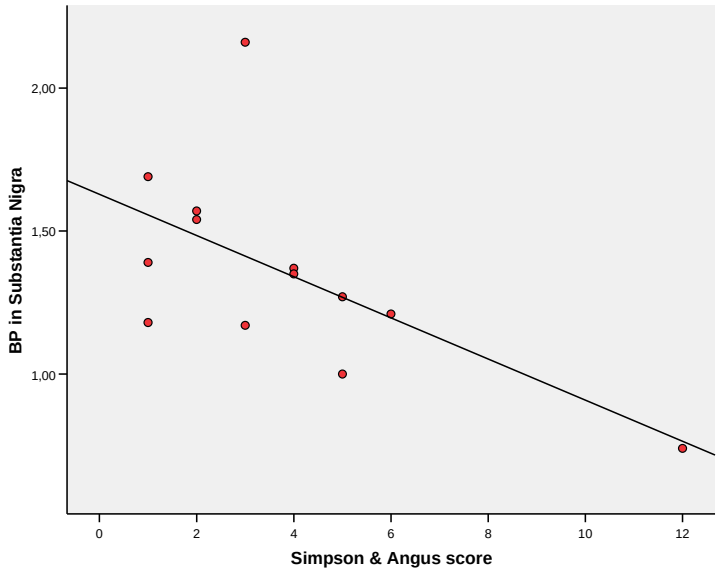

Figure 3. The relation of dopamine D2/3 receptor apparent binding potential (BP_{app}) and Simpson and Angus score in substantia nigra (r = –0.62, p = 0.024).

6 DISCUSSION

6.1 EXTRASTRIATAL DOPAMINE D2/3 RECEPTOR BINDING IN DRUG-NAÏVE PATIENTS WITH SCHIZOPHRENIA (I–II)

6.1.1 Lower dopamine D2/3 receptor densities in temporal cortex (I)

Our findings indicated that dopamine D2/3 receptor binding in the temporal cortex is markedly decreased among drug-naïve schizophrenic patients than in controls. These results on extrastriatal binding are consistent with a previous [11C]FLB PET study demonstrating fewer D2/3 receptors in the anterior cingulate cortex of schizophrenic patients (Suhara et al., 2002).

[123I]Epidepride and the [11C]FLB were the first radioligands which enabled visualization of extrastriatal D2/3 binding in vivo. The extremely high affinity of these tracers is optimal for studying the relatively low density of D2/3 receptors in extrastriatal regions, whereas measuring the striatal D2/3 binding reliably is very difficult, since the ligand binding does not reach equilibrium in high receptor density regions such as the basal ganglia. Therefore, this study focused on measuring the extrastriatal epidepride binding in the temporal cortex, with results from striatum being excluded. The specific binding values in the frontal cortex were less than half of those in the

temporal cortex and were thus too low for reliable evaluation. Due to small sample size and limited spatial resolution, we did not do any further detailed analysis on the subregions of the temporal cortex.

According to a previous quantitative autoradiography study, a disrupted pattern of D2 receptors in the temporal cortex has been shown among patients with schizophrenia compared to matched controls (Goldsmith et al., 1997). In that study, schizophrenic patients exhibited reduced dopamine D2 receptor density in the supragranular layers and increased D2 density in the granular layers in auditory and auditory-visual association cortices of temporal lobe suggesting an aberrant cortical development in these regions. These abnormally organized temporocortical D2 receptors may result in decreased levels of D2 receptors observed in the present study.

6.1.2 Reduced dopamine D2/3 binding in substantia nigra (II)

We observed lower D2/3 values in the substantia nigra of patients with schizophrenia compared to controls. Differences in the thalamic D2/3 densities did not reach statistical significance because of the relatively small sample sizes. A slight trend towards decreased binding values on the right thalamus of schizophrenic patients was observed relative to controls, which

is in line with previous PET studies (Talvik et al., 2003; Yasuno et al., 2004).

To our knowledge, this was the first study on dopamine D2/3 binding in the midbrain of living schizophrenic patients. Our results on D2/3 density in the substantia nigra are in accordance with previous neuroimaging studies that indicate decreased dopamine D2/3 binding sites in other extrastriatal areas, such as the anterior cingulate cortex and thalamus, in patients with schizophrenia (Suhara et al., 2002; Talvik et al., 2003; Yasuno et al., 2004).

In the substantia nigra, dopamine D2 receptors have been suggested to serve as autoreceptors that regulate the nigrostriatal dopamine pathway (Meador-Woodruff et al., 1994; Hurd et al., 2001). On the other hand, the distribution of dopamine D3 receptors in the striatum and substantia nigra is also fairly abundant and overlaps with D2 receptors, whereas D3 receptors are thought to be located postsynaptically (Murray et al., 1994; Gurevich and Joyce, 1999). Distribution of [123I]epidepride in extrastriatal regions is mainly comprised of the dopamine D2 receptor subtype, according to previous findings (Hall et al., 1996). Thus, our finding suggests a reduced number of D2 autoreceptors in the substantia nigra of schizophrenic patients relative to healthy subjects. This may contribute to the dysregulation of the dopamine function in the

striatum of patients with schizophrenia (Laruelle et al., 1999; Moore et al., 1999).

6.1.3 Association between extrastriatal D2/3 receptor parameters and schizophrenic symptoms

We observed negative correlations between D2/3 density in temporal cortex and PANSS negative and, especially, general psychopathological symptom scores among patients. Suhara et al. (2002) observed the strongest negative correlations between the BPRS positive symptoms (rather than general psychopathological symptoms) and D2/3 binding in the anterior cingulate cortex. In that PET study, the correlations were stronger for the binding in the anterior cingulate cortex than in the temporal cortex. These results showed far stronger correlations for epidepride binding in the temporal cortex vs. PANSS symptoms than the corresponding correlations (in the temporal cortex) between [11C]FLB binding vs. BPRS symptoms in the study by Suhara et al. (2002). We were unable to study the binding in the frontal cortex due to low spesific binding in that region. Despite the relatively small sample size, our findings on patients vs. controls in the temporal cortex met statistically the level of significance in both hemispheres, with the same tendency being shown by the results in the [11C]FLB study (Suhara et al., 2002). These results support the previous

hypothesis on the dysfunction of the mesocortical dopamine function underlying the cognitive and negative symptoms in schizophrenia (Finlay, 2001; Okubo et al., 1997).

We observed distinct negative correlations in both sides of the thalamus (although the correlations did not reach statistical significance on the right due to the small number of patients) between D2/3 receptor density and general psychopathological symptom scores. Some functional studies previously reported a connection between decreased metabolic activity in the thalamus and both cognitive functions and negative symptoms in schizophrenic patients (Sabri et al., 1997; Crespo-Facorro et al., 1999; Heckers et al., 2000). This is in line with the experimental study of Melchitzky and Lewis (2001) that relates informational processing and cognitive function to dopaminergic transmission in the thalamus. The present findings agree with these observations and emphasize the significance of thalamo-cortical dopaminergic transmission in the pathophysiology of schizophrenia.

6.1.4 Comparison of imaging studies on extrastriatal D2/3 receptor densities among drug-naïve patients with schizophrenia

The results indicated statistically significant differences in D2/3 receptor sites between unmedicated schizophrenic patients and

healthy subjects in the temporal cortex and substantia nigra. Hitherto only a limited number of studies have focused on extrastriatal D2/3 density among drug-naïve schizophrenic patients. The majority of the PET studies have found low D2/3 receptor binding mostly in medial parts of thalamus. After dividing the thalamus into medial and lateral subregions, decreased D2/3 density in the right medial thalamus was detected in 9 drug-naïve patients (Talvik et al., 2003), which is in line with the present findings. A distinct age-related decline of D2/3 density in the frontal and temporal cortex was observed for both groups, which was not found in the thalamus or anterior cingulate cortex. In the present study, a substantial negative correlation between age and epidepride binding was detected in the temporal cortex of control subjects but not among patients. The discrepancy between findings in the age-related effect on D2/3 density among patients may arise from the slightly higher spatial resolution of PET compared to SPECT, as well as the small sample-size seen in both studies.

Studying the five major subregions of the thalamus separately and using automated percentage-based operational method, Yasuno et al. (2004) found lower FLB 457 binding in averaged central medial and posterior thalamic subregions among 10 never-medicated patients, while no differences between groups were seen in the whole thalamus. Utilizing [18F]fallypride PET for imaging anatomically traced major

nuclei of the thalamus, left medial dorsal nucleus and left pulvinar of 15 drug-naïve schizophrenic patients demonstrated reduced D2/3 density compared to matched controls (Buchsbaum et al., 2006). Moreover, one [11C]raclopride study applying high resolution 3D PET reported decreased D2 binding in the right thalamus of 18 never-medicated schizophrenics (Talvik et al., 2006).

A SPECT study by Glenthoj et al. (2006) using [123I]epidepride with the bolus/infusion method found no changes in D2/3 binding parameters in either the frontal cortex, temporal cortex, or thalamus of 25 never-medicated patients with schizophrenia compared with age-matched controls. The results implicated a right-sided asymmetry in thalamic D2/3 receptor levels among patients which was not found in controls. Frontal D2/3 binding was found to associate positively with positive symptoms, and a gender analysis showed higher D2/3 density and PANSS-positive scores among male patients. Using the simple ratio method for quantification of D2/3 receptors and adjusting the binding values for age, we found no differences in binding values between male and female patients or control individuals with our smaller sample size.

Thalamic D2/3 binding parameters have been demonstrated to associate with schizophrenic symptoms in two PET studies showing a negative correlation between D2/3 density in centromedial parts of the thalamus and BPRS positive symptom

scores (Yasuno et al., 2004; Buchsbaum et al., 2006). However, using a different clinical symptom scale (PANSS), we found a statistically significant correlation between thalamic D2/3 binding and general psychopathological score, but not with positive symptoms, which may partly reflect discrepancies between these two rating scales.

A recent imaging study with [18F]fallypride PET detected a decrease in dopamine D2/3 receptor sites in the left medial thalamus, while finding an increase in D2/3 density of substantia nigra (Kessler et al., 2009). The results also indicated that total positive symptoms, delusions and bizarre behavior correlate positively with D2/3 binding in the lateral and anterior temporal cortex as assessed with BPRS, the Scale for the Assessment of Positive Symtoms (SAPS) and the Scale for the Assessment of Negative Symtoms (SANS). Only four out of 11 patients had been previously antipsychotic-naïve, and among drug-free patients off-medication period varied from 3 to 40 weeks. Previous antipsychotic medication may have an effect on central D2 density by up-regulating D2 receptor levels, as observed in transmitter-specific imaging and experimental animal studies (Burt et al., 1977; Clow et al., 1980; Mackay et al., 1980).

On the basis of studies examining the distribution of D2/3 receptors in the human brain, it is probable that binding in the midbrain is attributable to the substantia nigra (Hall et al., 1996;

Hurd et al., 2001). Although the dopaminergic projections originating from the ventral tegmental area are located close to the substantia nigra, D2 receptors are nearly absent in the ventral tegmental area as compared to the substantia nigra (Meador-Woodruff et al., 1994; Meador-Woodruff et al., 1996). This suggests that the observed signal originates mainly from the substantia nigra. Despite the slightly weaker spatial resolution of SPECT compared to that of PET, these results on substantia nigra can be considered reliable.

6.1.5 Strengths and limitations

The strengths of our studies were that all patients were antipsychotic-naïve, none of the patients suffered comorbid substance abuse or other neuropsychiatric disorders, and we performed analysis of the results using age-corrected D2/3 binding values to exclude the possible influence of minor differences in mean ages between study groups.

Despite the relatively small sample size, our findings on extrastriatal D2/3 receptors in the temporal cortex and substantia nigra reached a statistical level of significance. The small size of the substantia nigra region and the relatively low receptor density compared to that of the striatum make in vivo dopamine receptor studies difficult. A partial volume effect for explaining the results from the substantia nigra cannot

completely be excluded, as it has not been possible to measure the volume of the substantia nigra untill recently (Ahsan et al., 2007).

An experimental imaging study has compared quantitative measures of radioactive uptake between [11C]epidepride PET and [123I]epidepride SPECT in primate brain (Almeida et al., 1999). The results showed that attenuation correction is the largest source of bias in the quantification of D2 receptor binding with SPECT. Attenuation correction alone induced twofold increase in uptake levels, though the remaining differences exceeded 24% compared to PET. When additional scatter correction was applied these differences decreased to 17%. Collimator blurring correction performed jointly with attenuation and scatter corrections provided accurate uptake values in striatum, but did not affect the measurements in cerebellum, where the overall uptake level with SPECT was higher than with PET. In the current study the SPECT images were corrected for attenuation.

Recently, it has been demonstrated that scatter correction significantly improves the exactness of measurements of distribution volumes of receptor ligands studied with [123I]epidepride SPECT (Fujita et al., 2004). The amount and the course of errors were found significantly different between high-density, low-density and receptor-poor regions, making the comparison of uptake values between these areas inaccurate

without scatter correction. During the current patient studies no proper scatter, partial volume and collimator response correction was available. To minimize these errors and to keep the reproducibility at a reasonable level (+/- 7%), the cut-off level of 60% was used.

Although [123I]epidepride binding in the striatum has been reported to be sensitive to endogenous dopamine levels in the short term (Gatley et al., 2000), amphetamine challenged dopamine release did not displace binding of [123I]epidepride (Kessler et al., 1993b). In addition, a recent study with primates showed no change in extrastriatal binding by endogenous dopamine with high-affinity radioligand [11C]FLB 457 (the bromo analogue of epidepride) (Okauchi et al., 2001).

There is still some evidence for the competitive effects of endogenous dopamine on epidepride binding in the temporal cortex (but not in the thalamus) after dopamine depletion (Fujita et al., 2000). Few recent studies with [11C]FLB 457 have indicated that high-affinity ligand binding may be sensitive to dopamine competition after provocation by a cognitive task or medication (Hagelberg et al., 2004; Aalto et al., 2005). However, a newly published randomized, double-blind, placebo-controlled [11C]FLB 457 PET study failed to detect amfetamine-induced alterations in extrastriatal dopamine D2/3 receptor density among healthy subjects, implying that binding of [11C]FLB 457 is not sensitive to cortical dopamine release (Aalto

et al., 2009). This is most propably the case with other ultra-high affinity D2/3 tracers, including [123I]epidepride.

The effect of endogenous dopamine on results from the temporal cortex, substantia nigra or thalamus cannot totally be ruled out. In addition, our results are based on a semi-quantitative analysis in which the specific to non-specific binding ratio is calculated by assuming that the cerebellar count rates (= reference region) do not differ between the groups.

6.2 EXTRASTRIATAL DOPAMINE D2/3 RECEPTOR BINDING AND OCCUPANCY, AND EXTRAPYRAMIDAL SIDE-EFFECTS AFFECTED BY ANTIPSYCHOTIC MEDICATION (III–IV)

6.2.1 Differential extrastriatal dopamine D2/3 blockade by haloperidol, olanzapine and clozapine (III)

We demonstrated a significant difference in the apparent binding potential and occupancy of the midbrain dopamine D2/3 receptors between different antipsychotic compounds. The lowest occupancy was observed in clozapine-treated patients (5%), followed by olanzapine-treated patients (28%), when compared with haloperidol-treated patients (40%). This was the first study to show a statistically significant difference in midbrain dopamine D2/3 receptor binding between two atypical antipsychotics, clozapine and olanzapine. Our results agree with two separate [18F]fallypride PET studies that produced the

same rank order in the substantia nigra/VTA occupancies for clozapine-, olanzapine- and haloperidol-treated patients (Kessler et al., 2005; Kessler et al., 2006).

In our study, the group differences did not reach statistical significance in the temporal cortex, due to the low number of participants. The second-generation antipsychotics clozapine and olanzapine had similar mean D2/3 receptor occupancy values (42% vs. 46% on the right and 37% vs. 45% on the left) in the temporal poles (although the variance in occupancy values were larger within the clozapine group), while haloperidol showed a higher occupancy (61% on the right and 66% on the left). Similarly, two previous PET studies with [11C]FLB 457 showed lower occupancy levels for clozapine than for haloperidol in the temporal cortex (Farde et al., 1997b; Talvik et al., 2001). Conversely, Xiberas et al. (2001a) found no difference in FLB 457 binding indices between haloperidol and clozapine in the temporal cortex, as was also the case with a recent [18F]fallypride PET study reporting similarly high occupancy values between haloperidol and olanzapine (Kessler et al., 2005).

We found that occupancy values changed substantially depending on the comparison group used (either drug-naïve vs. healthy controls) in the examined brain areas, showing an overestimation with all antipsychotics when using the healthy control group. Most occupancy studies have used baseline values of normal controls in the calculation of D2/3 occupancies,

postulating that dopamine D2/3 densities do not differ between schizophrenic patients and healthy subjects. Few studies have calculated drug occupancies using regional D2/3 binding values obtained either from study subjects during as off-medication period or from a control group of drug-free schizophrenic patients (Yasuno et al., 2001b; Kessler et al., 2005; Takano et al., 2006; Kessler et al., 2006; Gründer et al., 2008; Vernaleken et al., 2008). Of these studies, only two defined occupancies using previously entirely unmedicated, i.e., drug-naïve, schizophrenic patients as comparison group (Yasuno et al., 2001b; Takano et al., 2006). In light of the most recent imaging studies, the reduction observed in the extrastriatal dopamine D2/3 receptor density among drug-naïve schizophrenic patients challenges the relevance of using healthy controls for calculating drug occupancy. Extrapolation of the occupancy results obtained using the baseline values of previously drug-treated patients in an off-medication state should be done with caution due to the possible up-regulation of D2 receptors produced by prior antipsychotic treatment.

6.2.2 Regional selectivity of antipsychotics in extrastriatal brain regions (III)

We observed no regional selectivity regarding the high-affinity drug haloperidol. In contrast, clozapine and olanzapine showed

more preferential D2/3 blockade in the temporal cortex than in the substantia nigra, supporting the findings of Kessler and coworkers (2005; 2006). Some of the newer antipsychotic drugs dissociate rapidly from the dopamine receptors, particularly in areas of high receptor density with high levels of endogenous dopamine. However, their mechanism of action in extrastriatal areas has remained unclear (Seeman and Tallerico, 1999). Electrophysiological and experimental animal studies have revealed substantial differences in the modulation and overall level of dopaminergic transmission between mesocortical and nigrostriatal dopamine tracks (Cubeddu et al., 1990; Garris and Wightman, 1994). In the cortex, a lower extracellular dopamine level also enables low-affinity drugs to block dopamine D2/3 receptors at transiently high or moderate levels (Abi-Dargham and Laruelle, 2005).

The present findings underline the importance of cortical drug occupancy for both typical and second-generation antipsychotics, which agrees with the assumption that extrastriatal dopamine receptors are the primary target of antipsychotic drugs (Lidow et al., 1998, Takahashi et al., 2006). Nigrostriatal dopamine transmission also plays an important role in the pathophysiology of schizophrenia. We previously reported a reduced number of nigral dopamine D2/3 receptors (suggested to serve as autoreceptors that regulate dopamine transmission in the striatum) in schizophrenic patients,

compared to healthy controls (II). Differences in the blockade of nigral dopamine D2/3 autoreceptors during elevated nigrostriatal dopamine transmission (observed in the acute phase of schizophrenia) may partly explain the superiority of clozapine in clinical efficacy compared to typical antipsychotics (Kane et al., 2001; Davis et al., 2003).

6.2.3 Association between extrapyramidal side-effects and D2/3 binding in substantia nigra (IV)

The present findings suggest that extrapyramidal side-effects correlate negatively with the D2/3 blockade in the substantia nigra observed in medicated patients with schizophrenia. These results are in line with previous experimental and electrophysiological animal studies that have demonstrated a significant role for nigral dopamine D2 receptors in the control of muscle tone (Double and Crocker, 1995; Hemsley and Crocker, 1998; Hemsley and Crocker, 1999; Crocker and Hemsley, 2001). According to the results from previous in vivo neuroimaging studies, striatal dopamine D2 receptor blockade by both conventional and second-generation antipsychotics has been found to be associated with extrapyramidal symptoms (Farde et al., 1992; Scherer et al., 1994; Kapur et al., 1995; Kapur et al., 2000a; Agid et al., 2007), though a previous PET study did not detect a linear correlation between motor side-effects and

striatal D2 occupancy by the atypical antipsychotic amisulpride (Vernaleken et al., 2004). Furthermore, striatal D2 occupancy of risperidone (with recommended dose range) has been demonstrated to be comparable to that of classical antipsychotics, yet generating extrapyramidal symptoms to a lesser degree (Kapur et al., 1995). Thus, it is evident that there may also be other mechanisms than D2 occupancy in the striatum that may cause extrapyramidal symptoms. Since the present study does not provide data on striatal D2/3 receptor binding, comparison of the possible associations between striatal and nigral binding, or between striatal binding and motor side-effects cannot be performed. Thus, it is not ruled out that these results could mirror the findings in striatal dopamine D2 occupancy.

The nigral dopamine receptors are mostly D2 –like autoreceptors, which have been suggested to participate in the regulation of the nigrostriatal dopamine pathway (Meador-Woodruff et al., 1994; Hurd et al., 2001). Antipsychotic drugs have been shown to increase baseline dopamine cell activity within nigrostriatal, mesolimbic and mesocortical dopaminergic systems with acute administration (Chiodo and Bunney, 1983). An observed increase in dopamine turnover has been related to the blockade of presynaptic dopamine autoreceptors, and it is considered to counteract the antipsychotic drug effect (Carlsson and Lindqvist, 1963; Pucak and Grace, 1994). On the other hand,

repeated treatment with dopamine D2 receptor antagonists may result in a time-dependent decrease in dopamine synthesis and neuronal activity, a condition known as a depolarization block (Chiodo and Bunney, 1983; Grace and Bunney, 1986; Grace, 1992; Gründer et al., 2003). The effects of classical and atypical antipsychotics on the activity of nigral dopamine neurons differ substantially. It has been illustrated that atypical antipsychotics are unable to display depolarization inactivation in nigral presynaptic dopamine cells, consequently sparing from motor side-effects (Chiodo and Bunney, 1983; White and Wang, 1983; Timmerman et al., 1999). While the exact mechanism underlying this difference remains unknown, the involvement of presynaptic dopamine D2 receptors has been suggested as being one important component (Grace, 1992). Thus, the present findings provide in vivo evidence for the involvement of dopamine D2 autoreceptors in the substantia nigra with regard to antipsychotic drug-induced movement disorders. These results support previous findings obtained from pharmacological and rodent studies.

6.2.4 Strengths and limitations

The strengths of these studies were that we used baseline values obtained from drug-naïve patients for calculating occupancy values, and that we used the Simpson and Angus Scale for the

assessment of motor side-effects, which has been demonstrated to be a reliable and valid instrument for estimating drug-induced parkinsonism (Janno et al., 2005).

The limitation of these studies was the small total number of study subjects, which decreases its statistical power. Nevertheless, despite the small sample-size, these results describing differences in the midbrain dopamine D2/3 receptor apparent binding potential and occupancy between different antipsychotic compounds, as well as on the correlation between dopamine D2/3 apparent binding potential in the substantia nigra and the Simpson and Angus score (illustrating parkinsonian symptoms) reached a statistically significant level.

Due to the small size of the substantia nigra, a partial volume correction would have been advisable, but thus far impossible to perform (Kessler et al., 1984). Usage of a simple ROI analysis may affect the sensitivity of the imaging procedure by merging together smaller structures or missing minor abnormalities (Fox et al., 1988). In the present study, ROI areas that were measured from SPECT images did not differ between any of the medicated study groups. The graphical analysis of [123I]epidepride binding used in Studies III and IV have previously shown overall errors less than 10% (relative to the metabolite-accounted kinetic analysis) among healthy subjects, that were caused mostly by intersubject variability (Ichise et al., 1999). Owing to the lack of an externally independent gold SPECT

standard, evaluation of any methodological bias regarding our studies was unfeasible.

The present results were based on a semi-quantitative method that assumes the reference region (cerebellum) count rates to be equal among study groups. Pinborg et al. (2007) have shown the presence of "non-negligible" specific [123I]epidepride binding to dopamine D2/3 receptors in the cerebellum which may affect antipsychotic drug binding potential. In that SPECT study, the cerebellar distribution volume was decreased by 22 $\pm$ 15 % after antipsychotic treatment. The same research group has previously demonstrated that in the absence of cerebellar disease, the use of the cerebellum as a reference region produces solid estimates of [123I]epidepride binding (Pinborg et al., 2000). Although this phenomenon may have influenced the binding values observed in the present studies, it is unlikely that it would have changed the results concerning differences between D2/3 binding of different antipsychotics in the substantia nigra, or regarding the correlation between apparent binding potential in the substantia nigra and extrapyramidal symptom scores.

The overall level of these occupancy results in the examined brain areas was moderate or low compared to that determined in former imaging studies. Such discrepancies in drug occupancy findings between research groups may be caused by many factors. The radioligand and acquisition time used in

addition to drug dosage and physicochemical properties, for example, could substantially affect the results (Seeman and Tallerico, 1999). The molecular interplay between endogenous dopamine, antipsychotic agent and radio-tracer in different brain areas in vivo is not yet fully understood. We used a time interval of 0–210 minutes for the analyses of each ROI, which increases the reliability of the present findings in extrastriatal regions.

Study subjects were treated within ordinary clinical settings, and the medication was optimized by their own doctors. Chlorpromazine-equivalent doses for haloperidol and olanzapine were at corresponding level, while the clozapine dose was three–fourfold compared to other medication groups. Drug dosage has previously been demonstrated to influence the drug occupancy in a dose-dependent manner (Talbot and Laruelle, 2002; Kapur and Mamo, 2003). The observed discrepancy in chlorpromazine-equivalent mean doses between different medication groups does not explain these results in apparent binding potential or occupancy. According to a freshly published article, chlorpromazine-equivalent dose for clozapine is defined to be double, ranging from 108 mg to 140 mg, compared to the previously determined value used in our study (Andreasen et al., 2010). Consequently, this would result in equivalent mean doses for all medication groups in the present study.

Since there is evidence for age-related decline in striatal and extrastriatal dopamine D2/3 receptor density among healthy subjects, as well as among patients with schizophrenia, we adjusted the results concerning apparent binding and occupancy for age in Study III. Confounding factors related to age correction may arise from possible regional differences in ROI size and increasing cortical atrophy during normal aging (Coffey et al., 1992). None of the present study subjects suffered from brain atrophy, and the ROI areas measured from SPECT images did not differ between any of the study groups. Although an age-induced decrease in brain dopamine transmission has been shown to be associated with reduced motor performance in healthy elderly subjects, a correlation between the dopaminergic system and motor function has been suggested to be independent of age (Volkow et al., 1998). We did not find an age-dependent effect on dopamine D2/3 receptor binding or extrapyramidal symptoms, and hence age-correction was not performed in Study IV.

7 SUMMARY AND CONCLUSIONS

The major findings of the study were:

I. Never-medicated patients with schizophrenia had lower D2/3 receptor density in the temporal cortex than did healthy subjects, and the decrease in D2/3 receptor level was associated with general psychopathological schizophrenic symptoms.

II. Drug-naïve schizophrenic patients had a reduced number of D2 autoreceptors in the substantia nigra compared to controls.

III. Thalamic D2/3 density correlated negatively with general psychopathological symptoms of schizophrenia, although D2/3 binding values in thalamus were at the same level as those found in healthy subjects.

IV. In the temporal cortex, D2/3 receptor blockade did not differ significantly between typical and second-generation antipsychotics.

V. Dopamine D2/3 binding and drug occupancy in the substantia nigra differed between antipsychotic compounds. The lowest drug occupancy was for clozapine, followed by olanzapine, when compared to haloperidol.

VI. Extrapyramidal side-effects were associated with nigral D2/3 blockade by antipsychotic drugs in patients with schizophrenia.

In conclusion, the results of the present study were the first to suggest that the density of dopamine D2/3 receptors is reduced in the temporal cortex and substantia nigra of unmedicated schizophrenic patients. A decrease in temporal cortical D2/3 receptor levels is strongly associated with general psychopathological symptoms of schizophrenia, thus supporting the previous hypothesis on the dysfunction of mesocortical dopamine function underlying the cognitive symptoms in schizophrenia. These findings also show that D2/3 density in the thalamus correlate inversely with the cognitive symptoms of schizophrenia, thereby emphasizing the significance of thalamo-cortical dopaminergic function in the pathophysiology of schizophrenia. The observed decrease in nigral D2/3 autoreceptors may contribute to the dysregulation of dopamine transmission in the striatum of schizophrenic patients. These findings implicate marked extrastriatal dopamine D2/3 receptor deficits that may have a neurodevelopmental origin among schizophrenic patients, as well as a connection between the symptomatology of schizophrenia and alterations in limbic and cortical dopamine D2/3 receptors.

In addition, the present results demonstrate that both atypical and conventional antipsychotic drugs occupy similarly cortical dopamine D2/3 receptors, though in the substantia nigra, D2/3 receptor blockade is divergent between different antipsychotic agents. This was the first study to show a

significant difference in dopamine D2/3 binding between the atypical antipsychotics clozapine and olanzapine. These findings suggest a contribution to the differences in clinical profile and therapeutic efficacy, as well as side-effects, between different antipsychotic drugs. The noted association between nigral D2/3 receptor blockade by antipsychotic compounds and extrapyramidal symptoms, observed for the first time in vivo, agrees with previous results from pharmacological and animal studies.

The neurobiological basis of schizophrenia highlights the importance of in vivo neuroimaging studies for helping to gain a deeper understanding of receptor level abnormalities in the pathophysiology of this complex disease. Further studies with accuracy in patient sampling, diagnostics and medication status, as well as solid imaging methods with larger study population are needed to attain this goal.

8 REFERENCES

Aalto S, Brück A, Laine M, Någren K, Rinne JO. Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D_2 receptor ligand [^{11}C]FLB 457. J Neurosci 2005;25:2471-2477.

Aalto S, Hirvonen J, Kaasinen V, Hagelberg N, Kajander J, Någren K, Seppälä T, Rinne JO, Scheinin H, Hietala J. The effects of d-amphetamine on extrastriatal dopamine D2/D3 receptors: a randomized, double-blind, placebo-controlled PET study with [11C]FLB 457 in healthy subjects. Eur J Nucl Med Mol Imaging 2009;36:475-483.

Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, van Dyck CH, Charney DS, Innis RB, Laruelle M. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am J Psychiatry 1998;155:761-767.

Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, Weiss R, Cooper TB, Mann JJ, Van Heertum RL, Gorman JM, Laruelle M. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc Natl Acad Sci U S A 2000;97:8104-8109.

Abi-Dargham A, Laruelle M. Mechanism of action of second generation antipsychotic drugs in schizophrenia: insight from brain imaging studies. Eur Psychiatry 2005;20:15-27.

Abi-Dargham A, van de Giessen E, Slifstein M, Kegeles LS, Laruelle M. Baseline and amphetamine-stimulated dopamine activity are related in drug-naïve schizophrenic subjects. Biol Psychiatry 2009;65:1091-1093.

Abi-Saab WM, Bubser M, Roth RH, Deutch AY. 5-HT2 receptor regulation of extracellular GABA levels in the prefrontal cortex. Neuropsychopharmacology 1999;20:92-96.

Agid O, Mamo D, Ginovart N, Vitcu I, Wilson AA, Zipursky RB, Kapur S. Striatal vs. extrastriatal dopamine D_2 receptors in antipsychotic response – a double-blind PET study in schizophrenia. Neuropsychopharmacology 2007;32:1209-1215.

Ahsan RL, Allom R, Gousias IS, Habib H, Turkheimer FE, Free S, Lemieux L, Myers R, Duncan JS, Brooks DJ, Koepp MJ, Hammers A. Volumes, spatial extents and a probabilistic atlas of the human basal ganglia and thalamus. NeuroImage 2007;38:261-270.

Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psychiatry 2003;60:565-571.

Almeida P, Ribeiro MJ, Bottlaender M, Loc'h C, Langer O, Strul D, Hugonnard P, Grangeat P, Mazière B, Bendriem B. Absolute quantitation of iodine-123 epidepride kinetics using single-photon emission tomography: comparison with carbon-11 epidepride and positron emission tomography. Eur J Nucl Med 1999;26:1580-1588.

Alzheimer A. Beiträge zur pathologischen Anatomie der Hirnrinde und zur anatomischen Grundlage der Psychosen. Monatsschrift für Psychiatrie und Neurologie 1897;2:82-120.

American Psychiatric Association. DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, 3rd ed., revised, Washington, 1987.

American Psychiatric Association. Practice guidelines for the treatment of patients with schizophrenia, 2nd ed. Washington, DC: APA, 2004.

Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry 2010;67:255-262.

Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res 2004;70:117-145.

Arakawa R, Ito H, Okumura M, Takano A, Takahashi H, Takano H, Okubo Y, Suhara T. Extrastriatal dopamine D(2) receptor occupancy in olanzapine-treated patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci 2009 Oct 23. [Epub ahead of print]

Arana GW. An overview of side effects caused by typical antipsychotics. J Clin Psychiatry 2000;61(S8):5-11.

Bassingthwaighte JB. Blood flow and diffusion through mammalian organs. Science 1970;167:1347-1353.

Beer HF, Bläuenstein PA, Hasler PH, Delaloye B, Riccabona G, Bangerl I, Hunkeler W, Bonetti EP, Pieri L, Richards JG, Schubiger PA. In vitro and in vivo evaluation of iodine-123-Ro 16-0154: a new imaging agent for SPECT investigations of benzodiazepine receptors. J Nucl Med 1990;31:1007-1014.

Beer HF, Lin S, Bläuenstein P, Hasler P, Schubiger PA, Maier A, Lichtensteiger W, Oettli R, Bekier A, Weder B. In vitro and in vivo testing of the dopamine D1 ligand [123I]SCH 23982 with respect to its potential application in SPET investigations. Nucl Med Biol 1993;20:607-616.

Benwell ME, Balfour DJ. The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol 1992;105:849-856.

Bergström KA, Halldin C, Yu M, Swahn C-G, Åkerman KK, Hiltunen J, Tiihonen J, Kuikka JT, Lassen N, Widbeck C, Farde L. The metabolite pattern of [123I]epidepride in human plasma determined with a gradient HPLC method. J Labelled Compd Rad 1997;40:151-153.

Bergström KA, Yu M, Kuikka JT, Akerman KK, Hiltunen J, Lehtonen J, Halldin C, Tiihonen J. Metabolism of [123I]epidepride may affect brain dopamine D2 receptor imaging with single-photon emission tomography. Eur J Nucl Med 2000;27:206-208.

Bernardo M, Parellada E, Lomeña F, Catafau AM, Font M, Gómez JC, López-Carrero C, Gutiérrez F, Pavía J, Salamero M. Double-blind olanzapine vs. haloperidol D2 dopamine receptor blockade in schizophrenic patients: a baseline-endpoint. Psychiatry Res 2001;107:87-97.

Bigliani V, Mulligan RS, Acton PD, Visvikis D, Ell PJ, Stephenson C, Kerwin RW, Pilowsky LS. In vivo occupancy of striatal and temporal cortical D2/D3 dopamine receptors by typical antipsychotic drugs. [123I]epidepride single photon emission tomography (SPET) study. Br J Psychiatry 1999;175:231-238.

Bigliani V, Mulligan RS, Acton PD, Ohlsen RI, Pike VW, Ell PJ, Gacinovic S, Kerwin RW, Pilowsky LS. Striatal and temporal cortical D2/D3 receptor occupancy by olanzapine and sertindole in vivo: a [123I]epidepride single photon emission tomography (SPET) study. Psychopharmacology 2000;150:132-140.

Bird ED, Spokes EG, Barnes J, MacKay AV, Iversen LL, Shepherd M. Increased brain dopamine and reduced glutamic acid decarboxylase and choline acetyl transferase activity in schizophrenia and related psychoses. Lancet 1977;2:1157-1158.

Björklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. Trends Neurosci 2007;30:194-202.

Bleuler E. Dementia Praecox or the group of schizophrenias. New York: International Universities Press, 1950.

Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Comings DE. Dopamine D2 receptor gene variants: association and linkage studies in impulsive-addictive-compulsive behaviour. Pharmacogenetics 1995;5:121-141.

Bogerts B. Recent advances in the neuropathology of schizophrenia. Schizophr Bull 1993;19:431-445.

Bourne JA. SCH 23390: the first selective dopamine D1-like receptor antagonist. CNS Drug Rev 2001;7:399-414.

Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. Proc Natl Acad Sci USA 1997;94:2569-2574.

Bressan RA, Erlandsson K, Jones HM, Mulligan RS, Ell PJ, Pilowsky LS. Optimizing limbic selective D2/D3 receptor occupancy by risperidone: a [123I]-epidepride SPET study. J Clin Psychopharmacol 2003a;23:5-14.

Bressan RA, Erlandsson K, Jones HM, Mulligan R, Flanagan RJ, Ell PJ, Pilowsky LS. Is regionally selective D2/D3 dopamine occupancy sufficient for atypical antipsychotic effect? an in vivo quantitative [123I]epidepride SPET study of amisulpride-treated patients. Am J Psychiatry 2003b;160:1413-1420.

Buchsbaum MS, Christian BT, Lehrer DS, Narayanan TK, Shi B, Mantil J, Kemether E, Oakes TR, Mukherjee J. D2/D3 dopamine receptor binding with [F-18]fallypride in thalamus and cortex of patients with schizophrenia. Schizophr Res 2006;85:232-244.

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH. Dopaminergic network differences in human impulsivity. Science 2010;329:532.

Burt DR, Creese I, Snyder SH. Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in brain. Science 1977;196:326-328.

Busatto GF, Pilowsky LS, Costa DC, Mertens J, Terriere D, Ell PJ, Mulligan R, Travis MJ, Leysen JE, Lui D, Gacinovic S, Waddington W, Lingford-Hughes A, Kerwin RW. Initial evaluation of 123I-5-I-R91150, a selective 5-HT2A ligand for single-photon emission tomography, in healthy human subjects. Eur J Nucl Med 1997;24:119-124.

Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, Venturi P, Jones LA, Lewis SW, Sham PC, Gottesman II, Farmer AE, McGuffin P, Reveley AM, Murray RM. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 1999;56:162-168.

Carlsson A. The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1988;1:179-186.

Carlsson A, Linqvist M. Effect of chlorpromazine or haloperidol on formation of 3methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol Toxicol (Copenh) 1963;20:140-144.

Carlsson A, Winblad B. Influence of age and time interval between death and autopsy on dopamine and 3-methoxytyramine levels in human basal ganglia. J Neural Transm 1976;38:271-276.

Carr KD. Chronic food restriction: enhancing effects on drug reward and striatal cell signaling. Physiol Behav 2007;91:459-472.

Casey DE. Pathophysiology of antipsychotic drug-induced movement disorders. J Clin Psychiatry 2004;65(S9):25-28.

Chiodo LA, Bunney BS. Typical and atypical neuroleptics: Differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. J Neurosci 1983;3:1607-1619.

Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993;50:975-990.

Clow A, Theodorou A, Jenner P, Marsden CD. Changes in rat striatal dopamine turnover and receptor activity during one years neuroleptic administration. Eur J Pharmacol 1980;63:135-144.

Coffey CE, Wilkinson WE, Parashos IA, Soady SA, Sullivan RJ, Patterson LJ, Figiel GS, Webb MC, Spritzer CE, Djang WT. Quantitative cerebral anatomy of the aging human brain: cross-sectional study using magnetic resonance imaging. Neurology 1992;42:527-536.

Cohen BD, Rosenbaum G, Luby ED, Gottlieb JS. Comparison of phencyclidine hydrochloride (Sernyl) with other drugs. Simulation of schizophrenic performance with phencyclidine hydrochloride (Sernyl), lysergic acid diethylamide (LSD-25), and amobarbital (Amytal) sodium; II. Symbolic and sequential thinking. Arch Gen Psychiatry 1962;6:395-401.

Cohen J. Statistical power analysis for the behavioral sciences. Academic Press Inc: Orlando, Fla, USA, 1977.

Compton PA, Anglin MD, Khalsa-Denison ME, Paredes A. The D2 dopamine receptor gene, addiction, and personality: clinical correlates in cocaine abusers. Biol Psychiatry 1996;39:302-304.

Conell PH. Amphetamine psychosis. Maudsley Monographs no. 5, Oxford Univ Press, London, Great Britain, 1958.

Conley RR, Kelly DL. Current status of antipsychotic treatment. Curr Drug Targets CNS Neurol Disord 2002;1:123-128.

Cordes M, Snow BJ, Cooper S, Schulzer M, Pate BD, Ruth TJ, Calne DB. Age-dependent decline of nigrostriatal dopaminergic function: a positron emission tomographic study of grandparents and their grandchildren. Ann Neurol 1994;36:667-670.

Corrigall WA, Franklin KB, Coen KM, Clarke PB. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology 1992;107:285-289.

Corripio I, Pérez V, Catafau AM, Mena E, Carrió I, Alvarez E. Striatal D2 receptor binding as a marker of prognosis and outcome in untreated first-episode psychosis. Neuroimage 2006;29:662-666.

Court JA, Lloyd S, Thomas N, Piggott MA, Marshall EF, Morris CM, Lamb H, Perry RH, Johnson M, Perry EK. Dopamine and nicotinic receptor binding and the levels of dopamine and homovanillic acid in human brain related to tobacco use. Neuroscience 1998;87:63-78.

Crawley JC, Crow TJ, Johnstone EC, Oldland SR, Owen F, Owens DG, Smith T, Veall N, Zanelli GD. Uptake of 77Br-spiperone in the striata of schizophrenic patients and controls. Nucl Med Commun 1986;7:599-607.

Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 1976;192:481-483.

Crespo-Facorro B, Paradiso S, Andreasen NC, O'Leary DS, Watkins GL, Boles Ponto LL, Hichwa RD. Recalling word lists reveals

"cognitive dysmetria" in schizophrenia: a positron emission tomography study. Am J Psychiatry 1999;156:386-392.

Crespo-Facorro B, Barbadillo L, Pelayo-Terán JM, Rodríguez-Sánchez JM. Neuropsychological functioning and brain structure in schizophrenia. Int Rev Psychiatry 2007;19:325-336.

Crocker AD, Hemsley KM. An animal model of extrastriatal side effects induced by antipsychotic drugs: relationship with D2 dopamine receptor occupancy. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:573-590.

Crow TJ, Baker HF, Cross AJ, Joseph MH, Lofthouse R, Longden A, Owen F, Riley GJ, Glover V, Killpack WS. Monoamine mechanisms in chronic schizophrenia: post-mortem neurochemical findings. Br J Psychiatry 1979;134:249-256.

Cubeddu LX, Hoffmann IS, Talmaciu RK. Is the release of dopamine from medial prefrontal cortex modulated by presynaptic receptors? Comparison with nigrostriatal and mesolimbic terminals. Ann NY Acad Sci 1990;604:452-461.

Dahlström A, Fuxe K. Localization of monoamines in the lower brain stem. Experientia 1964;20:398-399.

Dao-Castellana MH, Paillère-Martinot ML, Hantraye P, Attar-Lévy D, Rémy P, Crouzel C, Artiges E, Féline A, Syrota A, Martinot JL. Presynaptic dopaminergic function in the striatum of schizophrenic patients. Schizophr Res 1997;23:167-174.

Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003; 60: 553-564.

Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 1991;148:1474-1486.

de Courten-Myers GM. The human cerebral cortex: gender differences in structure and function. J Neuropathol Exp Neurol 1999;58:217-226.

de Haan L, van Bruggen M, Lavalaye J, Booij J, Dingemans PM, Linszen D. Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. Am J Psychiatry 2003;160:303-309.

de Paulis T. The discovery of epidepride and its analogs as high-affinity radioligands for imaging extrastriatal dopamine D(2) receptors in human brain. Curr Pharm Des 2003;9:673-696.

Di Paolo T. Modulation of brain dopamine transmission by sex steroids. Rev Neurosci 1994;5:27-41.

Dingledine R, Borges K, Bowie D, Traynelis SF. The glutamate receptor ion channels. Pharmacol Rev 1999;51:7-61.

Double KL, Crocker AD. Dopamine receptors in the substantia nigra are involved in the regulation of muscle tone. Proc Natl Acad Sci USA 1995;92:1669-1673.

Dresel S, Mager T, Rossmüller B, Meisenzahl E, Hahn K, Möller HJ, Tatsch K. In vivo effects of olanzapine on striatal dopamine D(2)/D(3) receptor binding in schizophrenic patients: an iodine-123 iodobenzamide single-photon emission tomography study. Eur J Nucl Med 1999;26:862-868.

Eidelberg D, Takikawa S, Dhawan V, Chaly T, Robeson W, Dahl R, Margouleff D, Moeller JR, Patlak CS, Fahn S. Striatal 18F-dopa uptake: absence of an aging effect. J Cereb Blood Flow Metab 1993;13:881-888.

Elkashef AM, Doudet D, Bryant T, Cohen RM, Li SH, Wyatt RJ. 6-(18)F-DOPA PET study in patients with schizophrenia. Positron emission tomography. Psychiatry Res 2000;100:1-11.

Elsworth JD, Roth RH. Dopamine synthesis, uptake, metabolism, and receptors: relevance to gene therapy of Parkinson's disease. Exp Neurol 1997;144:4-9.

Emsley R, Oosthuizen P. Evidence-based pharmacotherapy of schizophrenia. Int J Neuropsychopharmacol 2004;7:219-238.

Farde L, Hall H, Ehrin E, Sedvall G. Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. Science 1986;231:258-261.

Farde L, Wiesel FA, Halldin C, Sedvall G. Central D2-dopamine receptor occupancy in schizophrenic patients treated with antipsychotic drugs. Arch Gen Psychiatry 1988;45:71-76.

Farde L, Wiesel FA, Stone-Elander S, Halldin C, Nordström AL, Hall H, Sedvall G. D2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [11C]raclopride. Arch Gen Psychiatry 1990;47:213-219.

Farde L, Nordström AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Arch Gen Psychiatry 1992;49:538-544.

Farde L, Halldin C, Müller L, Suhara T, Karlsson P, Hall H. PET study of [11C]beta-CIT binding to monoamine transporters in the monkey and human brain. Synapse 1994;16:93-103.

Farde L, Hall H, Pauli S, Halldin C. Variability in D2-dopamine receptor density and affinity: a PET study with [11C]raclopride in man. Synapse 1995;20:200-208.

Farde L, Gustavsson JP, Jönsson E. D2 dopamine receptors and personality traits. Nature 1997a;385:590.

Farde L, Suhara T, Nyberg S, Karlsson P, Nakashima Y, Hietala J, Halldin C. A PET-study of [11C]FLB 457 binding to extrastriatal D2-dopamine receptors in healthy subjects and antipsychotic drug-treated patients. Psychopharmacology 1997b;133:396-404.

Fehr C, Yakushev I, Hohmann N, Buchholz H-G, Landvogt C, Deckers H, Eberhardt A, Kläger M, Smolka MN, Scheurich A, Dielentheis T, Schmidt LG, Rösch F, Bartenstein P, Gründer G, Schreckenberger M. Association of Low Striatal Dopamine D_2 Receptor Availability With Nicotine Dependence Similar to That Seen With Other Drugs of Abuse. Am J Psychiatry 2008;165:507-514.

Finlay JM. Mesoprefrontal dopamine neurons and schizophrenia: role of developmental abnormalities. Schizophr Bull 2001;27:431-442.

Flaum M, Andreasen NC. Diagnostic criteria for schizophrenia and related disorders: options for DSM-IV. Schizophr Bull 1991;17:133-142.

Fox PT, Mintun MA, Reiman EM, Raichle ME. Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. J Cereb Blood Flow Metab 1988;8:642-653.

Frankle WG, Gil R, Hackett E, Mawlawi O, Zea-Ponce Y, Zhu Z, Kochan LD, Cangiano C, Slifstein M, Gorman JM, Laruelle M, Abi-Dargham A. Occupancy of dopamine D2 receptors by the atypical antipsychotic drugs risperidone and olanzapine: theoretical implications. Psychopharmacology 2004;175:473-480.

Fujita M, Seibyl JP, Verhoeff NP, Ichise M, Baldwin RM, Zoghbi SS, Burger C, Staley JK, Rajeevan N, Charney DS, Innis RB. Kinetic and equilibrium analyses of [(123)I]epidepride binding to striatal and extrastriatal dopamine D(2) receptors. Synapse 1999;34:290-304.

Fujita M, Verhoeff NP, Varrone A, Zoghbi SS, Baldwin RM, Jatlow PA, Anderson GM, Seibyl JP, Innis RB. Imaging extrastriatal dopamine D(2) receptor occupancy by endogenous dopamine in healthy humans. Eur J Pharmacol 2000;387:179-188.

Fujita M, Varrone A, Kim KM, Watabe H, Zoghbi SS, Seneca N, Tipre D, Seibyl JP, Innis RB, Iida H. Effect of scatter correction on the compartmental measurement of striatal and extrastriatal dopamine D2 receptors using [123I]epidepride SPET. Eur J Nucl Med Mol Imaging 2004;31:644-654.

Fujita M, Kugaya A, Innis RB. Radiotracer imaging: basic principles and exemplary findings in neuropsychiatric disorders. In: Comprehensive Textbook of Psychiatry, ed. BJ Sadock, VA Sadock, pp. 1-3. Lippincott Williams & Wilkins, 8th ed., Philadelphia, Pennsylvania, USA, 2005.

Garnett ES, Firnau G, Nahmias C. Dopamine visualized in the basal ganglia of living man. Nature 1983;305:137-138.

Garris PA, Wightman RM. Different kinetics govern dopaminergic transmission in the amygdala, prefrontal cortex, and striatum: an *in vivo* voltammetric study. J Neurosci 1994;14:442-450.

Gatley SJ, Gifford AN, Carroll FI, Volkow ND. Sensitivity of binding of high-affinity dopamine receptor radioligands to increased synaptic dopamine. Synapse 2000;38:483-488.

Gefvert O, Lundberg T, Wieselgren IM, Bergström M, Långström B, Wiesel F, Lindström L. D(2) and 5HT(2A) receptor occupancy of different doses of quetiapine in schizophrenia: a PET study. Eur Neuropsychopharmacol 2001;11:105-110.

Gerfen CR, Herkenham M, Thibault J. The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. J Neurosci 1987;7:3915-3934.

Glenthoj BY, Mackeprang T, Svarer C, Rasmussen H, Pinborg LH, Friberg L, Baaré W, Hemmingsen R, Videbaek C. Frontal dopamine D(2/3) receptor binding in drug-naive first-episode schizophrenic patients correlates with positive psychotic symptoms and gender. Biol Psychiatry 2006;60:621-629.

Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 2001;158:1367-1377.

Goldsmith SK, Shapiro RM, Joyce JN. Disrupted pattern of D2 dopamine receptors in the temporal lobe in schizophrenia. A postmortem study. Arch Gen Psychiatry 1997;54:649-658.

Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 1991;41:1-24.

Grace AA. The depolarization block hypothesis of neuroleptic action: implications for the etiology and treatment of schizophrenia. J Neural Transm Suppl 1992;36:91-131.

Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: single spike firing. J Neurosci 1984a;4:2866-2876.

Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: burst firing. J Neurosci 1984b;4:2877-2890.

Grace AA, Bunney BS. Induction of depolarization block in midbrain dopamine neurons by repeated administration of haloperidol: analysis using *in vivo* intracellular recording. J Pharmacol Exp Ther 1986;238:1092-1100.

Grebb JA. Neural Sciences: Introduction and Overview. In: Comprehensive Textbook of Psychiatry, ed. BJ Sadock, VA Sadock, pp. 1-3. Lippincott Williams & Wilkins, 8th ed., Philadelphia, Pennsylvania, USA, 2005.

Gründer G, Vernaleken I, Müller MJ, Davids E, Heydari N, Buchholz HG, Bartenstein P, Munk OL, Stoeter P, Wong DF, Gjedde A, Cumming P. Subchronic haloperidol downregulates dopamine synthesis capacity in the brain of schizophrenic patients *in vivo.* Neuropsychopharmacology 2003;28:787-794.

Gründer G, Landvogt C, Vernaleken I, Buchholz HG, Ondracek J, Siessmeier T, Härtter S, Schreckenberger M, Stoeter P, Hiemke C, Rösch F, Wong DF, Bartenstein P. The striatal and extrastriatal D2/D3 receptor-binding profile of clozapine in patients with schizophrenia. Neuropsychopharmacology 2006;31:1027-1035.

Gründer G, Fellows C, Janouschek H, Veselinovic T, Boy C, Bröcheler A, Kirschbaum KM, Hellmann S, Spreckelmeyer KM, Hiemke C, Rösch F, Schaefer WM, Vernaleken I. Brain and plasma pharmacokinetics of aripiprazole in patients with schizophrenia: an [18F]fallypride PET study. Am J Psychiatry 2008;165:988-995.

Gurevich E, Joyce JN. Distribution of dopamine D_3 receptor expressing neurons in the human forebrain: comparison with D_2 receptor expressing neurons. Neuropsychopharmacology 1999;20:60-80.

Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. CNS Drugs 2007;21:911-936.

Hagelberg N, Aalto S, Kajander J, Oikonen V, Hinkka S, Någren K, Hietala J, Scheinin H. Alfentanil increases cortical dopamine D2/D3 receptor binding in healthy humans. Pain 2004;109:86-93.

Hall H, Farde L, Halldin C Hurd YL, Pauli S, Sedvall G. Autoradiographic localization of extrastriatal D_2-dopamine receptors in the human brain using [^{125}I]epidepride. Synapse 1996;23:115-123.

Halldin C, Farde L, Högberg T, Mohell N, Hall H, Suhara T, Karlsson P, Nakashima Y, Swahn CG. Carbon-11-FLB 457: a radioligand for extrastriatal D2 dopamine receptors. J Nucl Med 1995;36:1275-1281.

Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 2003;361:417-419.

Haycock JW, Becker L, Ang L, Furukawa Y, Hornykiewicz O, Kish SJ. Marked disparity between age-related changes in dopamine and other presynaptic dopaminergic markers in human striatum. J Neurochem 2003;87:574-585.

Heckers S, Curran T, Goff D, Rauch SL, Fischman AJ, Alpert NM, Schacter DL. Abnormalities in the thalamus and prefrontal cortex during episodic object recognition in schizophrenia. Biol Psychiatry 2000;48:651-657.

Heiss WD, Herholz K. Brain receptor imaging. J Nucl Med 2006;47:302-312.

Hemsley KM, Crocker AD. The effect of an irreversible dopamine receptor antagonist, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), on the regulation of muscle tone in the rat: the role of the substantia nigra. Neurosci Lett 1998;251:77-80.

Hemsley KM, Crocker AD. Raclopride and chlorpromazine, but not clozapine, increase muscle rigidity in the rat: relationship with D_2 dopamine receptor occupancy. Neuropsychopharmacology 1999;21:101-109.

Hietala J, West C, Syvälahti E, Någren K, Lehikoinen P, Sonninen P, Ruotsalainen U. Striatal D2 dopamine receptor binding characteristics in vivo in patients with alcohol dependence. Psychopharmacology 1994;116:285-290.

Hietala J, Syvälahti E, Vuorio K, Räkköläinen V, Bergman J, Haaparanta M, Solin O, Kuoppamäki M, Kirvelä O, Ruotsalainen U, Salokangas RK. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 1995;346:1130-1131.

Hietala J, Syvälahti E, Vilkman H, Vuorio K, Räkköläinen V, Bergman J, Haaparanta M, Solin O, Kuoppamäki M, Eronen E, Ruotsalainen U, Salokangas RK. Depressive symptoms and presynaptic dopamine function in neuroleptic-naïve schizophrenia. Schizophr Res 1999;35:41-50.

Hippius H. A historical perspective of clozapine. J Clin Psychiatry 1999;60(S12):22-3.

Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 2005;162:2233-2245.

Howes OD, McDonald C, Cannon M, Arseneault L, Boydell J, Murray RM. Pathways to schizophrenia: the impact of environmental factors. Int J Neuropsychopharmacol 2004;7(S1):S7-S13.

Hsiao MC, Lin KJ, Liu CY, Tzen KY, Yen TC. Dopamine transporter change in drug-naive schizophrenia: an imaging study with 99mTc-TRODAT-1. Schizophr Res 2003;65:39-46.

Hurd YL, Suzuki M, Sedvall GC. D1 and D2 dopamine receptor mRNA expression in whole hemisphere sectons of the human brain. J Chem Neuroanat 2001;22:127-137.

Ichise M, Ballinger JR, Tanaka F, Moscovitch M, St. George-Hyslop PH, Raphael D, Freedman M. Age-related changes in D2 receptor binding with iodine-123-iodobenzofuran SPECT. J Nucl Med 1998;39:1511-1518.

Ichise M, Fujita M, Seibyl JP, Verhoeff NP, Baldwin RM, Zoghbi SS, Rajeevan N, Charney DS, Innis RB. Graphical analysis and simplified quantification of striatal and extrastriatal dopamine D2 receptor binding with [123I]epidepride SPECT. J Nucl Med 1999;40:1902-1912.

Innis RB, Seibyl JP, Scanley BE, Laruelle M, Abi-Dargham A, Wallace E, Baldwin RM, Zea-Ponce Y, Zoghbi S, Wang S, Gao Y, Neumeyer JL, Charney DS, Hoffer PB, Marek KL. Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in Parkinson disease. Proc Natl Acad Sci USA 1993;90:11965-11969.

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 2007;27:1533-1539.

Inoue M, Suhara T, Sudo Y, Okubo Y, Yasuno F, Kishimoto T, Yoshikawa K, Tanada S. Age-related reduction of extrastriatal dopamine D2 receptor measured by PET. Life Sci 2001;69:1079-1084.

Jaber M, Jones S, Giros B, Caron MG. The dopamine transporter: a crucial component regulating dopamine transmission. Mov Disord 1997;12:629-633.

Jackson DM, Westlind-Danielsson A. Dopamine receptors: molecular biology, biochemistry and behavioural aspects. Pharmacol Ther 1994;64:291-370.

Jacobs BL, Trulson ME. Mechanisms of action of LSD. Am Sci 1979;67:396-404.

Jakab RL, Goldman-Rakic PS. 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. Proc Natl Acad Sci USA 1998;95:735-740.

Janno S, Holi MM, Tuisku K, Wahlbeck K. Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenic population. BMC Neurology 2005;5:5.

Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991;148:1301-1308.

Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 1976;2:924-926.

Jones AK, Cunningham VJ, Ha-Kawa SK, Fujiwara T, Liyii Q, Luthra SK, Ashburner J, Osman S, Jones T. Quantitation of [11C]diprenorphine cerebral kinetics in man acquired by PET using presaturation, pulse-chase and tracer-only protocols. J Neurosci Methods 1994;51:123-134.

Joyce JN, Janowsky A, Neve KA. Characterization and distribution of [125I]epidepride binding to dopamine D2 receptors in basal ganglia and cortex of human brain. J Pharmacol Exp Ther 1991;257:1253-1263.

Jäger M, Bottlender R, Strauss A, Möller HJ. On the descriptive validity of ICD-10 schizophrenia: empirical analyses in the spectrum of non-affective functional psychoses. Psychopathology 2003;36:152-159.

Jönsson EG, Cichon S, Gustavsson JP, Grünhage F, Forslund K, Mattila-Evenden M, Rylander G, Asberg M, Farde L, Propping P, Nöthen MM. Association between a promoter dopamine D2 receptor gene variant and the personality trait detachment. Biol Psychiatry 2003;53:577-584.

Kaasinen V, Vilkman H, Hietala J, Någren K, Helenius H, Olsson H, Farde L, Rinne JO. Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. Neurobiol Aging 2000;21:683-688.

Kaasinen V, Någren K, Hietala J, Farde L, Rinne JO. Sex differences in extrastriatal dopamine d(2)-like receptors in the human brain. Am J Psychiatry 2001;158:308-311.

Kane JM. Schizophrenia. N Engl J Med 1996;334:34-41.

Kane JM, Marder SR, Schooler NR, Wirshing WC, Umbricht D, Baker RW, Wirshing DA, Safferman A, Ganguli R, McMeniman M, Borenstein M. Clozapine and haloperidol in moderately refractory schizophrenia: A 6-month randomized and double-blind comparison. Arch Gen Psychiatry 2001;58: 965-972.

Kapur S, Remington G, Zipursky RB, Wilson AA, Houle S. The D_2 dopamine receptor occupancy of risperidone and its relationship to extrapyramidal symptoms: a PET study. Life Sci 1995;57:PL 103-107.

Kapur S, Zipursky RB, Remington G, Jones C, DaSilva J, Wilson AA, Houle S. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. Am J Psychiatry 1998;155:921-928.

Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. Am J Psychiatry 1999;156:286-293.

Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D_2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000a;157:514-520.

Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. Arch Gen Psychiatry 2000b;57:553-559.

Kapur S, Seeman P. Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics?: a new hypothesis. Am J Psychiatry 2001;158:360-369.

Kapur S, Mamo D. Half century of antipsychotics and still a central role for dopamine D_2 receptors. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1081-1090.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-276.

Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res 1988;23:99-110.

Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, Hwang DR, Huang Y, Haber SN, Laruelle M. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Arch Gen Psychiatry 2010;67:231-239.

Kessler RM, Ellis JR, Eden M. Analysis of emission tomographic scan data: limitations imposed by resolution and background. J Comput Assist Tomogr 1984;8:514-522.

Kessler RM, Ansari MS, de Paulis T, Schmidt DE, Clanton JA, Smith HE, Manning RG, Gillespie D, Ebert MH. High affinity dopamine D2 receptor radioligands. 1. Regional rat brain distribution of iodinated benzamides. J Nucl Med 1991;32:1593-1600.

Kessler RM, Mason NS, Votaw JR, De Paulis T, Clanton JA, Ansari MS, Schmidt DE, Manning RG, Bell RL. Visualization of extrastriatal dopamine D2 receptors in the human brain. Eur J Pharmacol 1992;223:105-107.

Kessler RM, Whetsell WO, Ansari MS, Votaw JR, de Paulis T, Clanton JA, Schmidt DE, Mason NS, Manning RG. Identification of extrastriatal dopamine D2 receptors in post mortem human brain with [125I]epidepride. Brain Res 1993a;609:237-243.

Kessler RM, Votaw JR, Schmidt DE, Ansari MS, Holdeman KP, de Paulis T, Clanton JA, Pfeffer R, Manning RG, Ebert MH. High affinity dopamine D2 receptor radioligands. 3. [123I] and [125I]epidepride: in vivo studies in rhesus monkey brain and comparison with in vitro pharmacokinetics in rat brain. Life Sci 1993b;53:241-250.

Kessler RM, Ansari MS, Riccardi P, Li R, Jayathilake K, Dawant B, Meltzer HY. Occupancy of striatal and extrastriatal dopamine D2/D3 receptors by olanzapine and haloperidol. Neuropsychopharmacology 2005;30:2283-2289.

Kessler RM, Ansari MS, Riccardi P, Li R, Jayathilake K, Dawant B, Meltzer HY. Occupancy of striatal and extrastriatal dopamine D2 receptors by clozapine and quetiapine. Neuropsychopharmacology 2006;31:1991-2001.

Kessler RM, Woodward ND, Riccardi P, Li R, Ansari MS, Anderson S, Dawant B, Zald D, Meltzer HY. Dopamine D2 receptor levels in striatum, thalamus, substantia nigra, limbic regions, and cortex in schizophrenic subjects. Biol Psychiatry 2009;65:1024-1031.

Kestler LP, Malhotra AK, Finch C, Adler C, Breier A. The relation between dopamine D2 receptor density and personality: preliminary evidence from the NEO personality inventory-revised. Neuropsychiatry Neuropsychol Behav Neurol 2000;13:48-52.

Kirch DG, Taylor TR, Creese I, Xu SX, Wyatt RJ. Effect of chronic nicotine treatment and withdrawal on rat striatal D1 and D2 dopamine receptors. J Pharm Pharmacol 1992;44:89-92.

Knable MB, Egan MF, Heinz A, Gorey J, Lee KS, Coppola R, Weinberger DR. Altered dopaminergic function and negative symptoms in drug-free patients with schizophrenia. [123I]-iodobenzamide SPECT study. Br J Psychiatry 1997a;171:574-577.

Knable MB, Heinz A, Raedler T, Weinberger DR. Extrapyramidal side effects with risperidone and haloperidol at comparable D2 receptor occupancy levels. Psychiatry Res 1997b;75:91-101.

Koeppe RA, Frey KA, Mulholland GK, Kilbourn MR, Buck A, Lee KS, Kuhl DE. [11C]tropanyl benzilate-binding to muscarinic cholinergic receptors: methodology and kinetic modeling alternatives. J Cereb Blood Flow Metab 1994;14:85-99.

Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 1992;13:177-184.

Kornhuber J, Brücke T, Angelberger P, Asenbaum S, Podreka I. SPECT imaging of dopamine receptors with [123I]epidepride: characterization of uptake in the human brain. J Neural Transm Gen Sect 1995;101:95-103.

Kraepelin E. Dementia praecox and paraphrenia. New York: Krieger, 1971.

Küfferle B, Tauscher J, Asenbaum S, Vesely C, Podreka I, Brücke T, Kasper S. IBZM SPECT imaging of striatal dopamine-2 receptors in psychotic patients treatedwith the novel antipsychotic substance quetiapine in comparison to clozapine and haloperidol. Psychopharmacology 1997;133:323-328.

Kuikka JT, Åkerman KK, Hiltunen J, Bergström KA, Räsänen P, Vanninen E, Halldin C, Tiihonen J. Striatal and extrastriatal imaging of dopamine D_2 receptors in the living human brain with [^{123}I]epidepride single-photon emission tomography. Eur J Nucl Med 1997;24:483-487.

Kuikka JT, Repo E, Bergström KA, Tupala E, Tiihonen J. Specific binding and laterality of human extrastriatal dopamine D2/D3 receptors in late onset type 1 alcoholic patients. Neurosci Lett 2000;292:57-59.

Kumakura Y, Cumming P, Vernaleken I, Buchholz HG, Siessmeier T, Heinz A, Kienast T, Bartenstein P, Gründer G. Elevated [18F]fluorodopamine turnover in brain of patients with schizophrenia: an [18F]fluorodopa/positron emission tomography study. J Neurosci 2007;27:8080-8087.

Kumamoto N, Matsuzaki S, Inoue K, Hattori T, Shimizu S, Hashimoto R, Yamatodani A, Katayama T, Tohyama M. Hyperactivation of midbrain dopaminergic system in schizophrenia could be attributed to the down-regulation of dysbindin. Biochem Biophys Res Commun 2006;345:904-909.

Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S. Diffusion tensor imaging in schizophrenia. Eur Psychiatry 2008;23:255-273.

Laakso A, Vilkman H, Kajander J, Bergman J, Paranta M, Solin O, Hietala J. Prediction of detached personality in healthy subjects by low dopamine transporter binding. Am J Psychiatry 2000a;157:290-292.

Laakso A, Vilkman H, Alakare B, Haaparanta M, Bergman J, Solin O, Peurasaari J, Räkköläinen V, Syvälahti E, Hietala J. Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. Am J Psychiatry 2000b;157:269-271.

Laakso A, Bergman J, Haaparanta M, Vilkman H, Solin O, Syvälahti E, Hietala J. Decreased striatal dopamine transporter binding in vivo in chronic schizophrenia. Schizophr Res 2001;52:115-120.

Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 1995;13:9-19.

Laine TP, Ahonen A, Torniainen P, Heikkilä J, Pyhtinen J, Räsänen P, Niemelä O, Hillbom M. Dopamine transporters increase in human brain after alcohol withdrawal. Mol Psychiatry 1999;4:189-191,104-105.

Laruelle M, van Dyck C, Abi-Dargham A, Zea-Ponce Y, Zoghbi SS, Charney DS, Baldwin RM, Hoffer PB, Kung HF, Innis RB. Compartmental modeling of iodine-123-iodobenzofuran binding to dopamine D2 receptors in healthy subjects. J Nucl Med 1994;35:743-754.

Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci USA 1996;93:9235-9240.

Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol Psychiatry 1999;46:56-72.

Laruelle M, Abi-Dargham A, van Dyck C, Gil R, D'Souza DC, Krystal J, Seibyl J, Baldwin R, Innis R. Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [(123)I]beta-CIT. Biol Psychiatry 2000;47:371-379.

Lee T, Seeman P. Elevation of brain neuroleptic/dopamine receptors in schizophrenia. Am J Psychiatry 1980;137:191-197.

Liddle PF. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. Br J Psychiatry 1987;151:145-151.

Lidow MS, Williams GV, Goldman-Rakic PS. The cerebral cortex: a case for a common site of action of antipsychotics. Trends Pharmacol Sci 1998;19:136-140.

Lieberman JA, Kane JM, Alvir J. Provocative tests with psychostimulant drugs in schizophrenia. Psychopharmacology 1987;91:415-433.

Lindström LH, Gefvert O, Hagberg G, Lundberg T, Bergström M, Hartvig P, Långström B. Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. Biol Psychiatry 1999;46:681-688.

Lynd-Balta E, Haber SN. The organization of midbrain projections to the striatum in the primate: sensorimotor-related striatum versus ventral striatum. Neuroscience 1994;59:625-640.

Mackay AV, Bird ED, Spokes EG, Rossor M, Iversen LL, Creese I, Snyder SH. Dopamine receptors and schizophrenia: drug effect or illness? Lancet 1980;2:915-916.

Mamo D, Kapur S, Shammi CM, Papatheodorou G, Mann S, Therrien F, Remington G. A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. Am J Psychiatry 2004;161:818-825.

Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F, Kapur S. Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: a triple tracer PET study. Am J Psychiatry 2007;164:1411-1417.

Martel P, Fantino M. Mesolimbic dopaminergic system activity as a function of food reward: a microdialysis study. Pharmacol Biochem Behav 1996;53:221-226.

Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang DR, Huang Y, Cooper T, Kegeles L, Zarahn E, Abi-Dargham A, Haber SN, Laruelle M. Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. J Cereb Blood Flow Metab 2003;23:285-300.

Martinot JL, Peron-Magnan P, Huret JD, Mazoyer B, Baron JC, Boulenger JP, Loc'h C, Maziere B, Caillard V, Loo H, Syrota A. Striatal D2 dopaminergic receptors assessed with positron emission tomography and [76Br]bromospiperone in untreated schizophrenic patients. Am J Psychiatry 1990;147:44-50.

Martinot JL, Paillère-Martinot ML, Loc'h C, Hardy P, Poirier MF, Mazoyer B, Beaufils B, Mazière B, Allilaire JF, Syrota A. The estimated density of D2 striatal receptors in schizophrenia. A study with positron emission tomography and 76Br-bromolisuride. Br J Psychiatry 1991;158:346-350.

Martinot JL, Paillère-Martinot ML, Loc'h C, Lecrubier Y, Dao-Castellana MH, Aubin F, Allilaire JF, Mazoyer B, Mazière B, Syrota A. Central D2 receptors and negative symptoms of schizophrenia. Br J Psychiatry 1994;164:27-34.

Mateos JJ, Lomeña F, Parellada E, Font M, Fernandez E, Pavia J, Prats A, Pons F, Bernardo M. Decreased striatal dopamine transporter binding assessed with [123I] FP-CIT in first-episode schizophrenic patients with and without short-term antipsychotic-induced parkinsonism. Psychopharmacology 2005;181:401-406.

Mateos JJ, Lomeña F, Parellada E, Mireia F, Fernandez-Egea E, Pavia J, Prats A, Pons F, Bernardo M. Lower striatal dopamine transporter binding in neuroleptic-naive schizophrenic patients is not related to antipsychotic treatment but it suggests an illness trait. Psychopharmacology 2007;191:805-811.

McBride WJ, Chernet E, Dyr W, Lumeng L, Li TK. Densities of dopamine D2 receptors are reduced in CNS regions of alcohol-preferring P rats. Alcohol 1993;10:387-390.

McBride WJ, Chernet E, Russell RN, Chamberlain JK, Lumeng L, Li TK. Regional CNS densities of serotonin and dopamine receptors in high alcohol-drinking (HAD) and low alcohol-drinking (LAD) rats. Alcohol 1997;14:603-609.

McGowan S, Lawrence AD, Sales T, Quested D, Grasby P. Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [18F]fluorodopa study. Arch Gen Psychiatry 2004;61:134-142.

Meador-Woodruff JH, Damask SP, Watson SJ Jr. Differential expression of auroreceptors in the ascending dopamine systems of the human brain. Proc Natl Acad Sci USA 1994;91:8297-8301.

Meador-Woodruff JH, Damask SP, Wang J, Haroutunian V, Davis KL, Watson SJ. Dopamine receptor mRNA expression in human striatum and neocortex. Neuropsychopharmacology 1996;15:17-29.

Meador-Woodruff JH, Healy DJ. Glutamate receptor expression in schizophrenic brain. Brain Res Brain Res Rev 2000;31:288-294.

Melchitzky DS, Lewis DA. Dopamine transporter-immunoreactive axons in the mediodorsal thalamic nucleus of the macaque monkey. Neuroscience 2001;103:1033-1042.

Meltzer HY, Li Z, Kaneda Y, Ichikawa J. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1159-1172.

Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, Weinberger DR, Berman KF. Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nat Neurosci 2002;5:267-271.

Miller CH, Mohr F, Umbricht D, Woerner M, Fleischhacker WW, Lieberman JA. The prevalence of acute extrapyramidal signs and symptoms in patients treated with clozapine, risperidone, and conventional antipsychotics. J Clin Psychiatry 1998;59:69-75.

Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. Physiol Rev 1998;78:189-225.

Moore H, West AR, Grace A. The regulation of forebrain dopamine transmission: relevance to the pathophysiology and psychopathology of schizophrenia. Biol Psychiatry 1999;46:40-55.

Mueser KT, McGurk SR. Schizophrenia. Lancet 2004;363:2063-2072.

Mukherjee J, Yang ZY, Das MK, Brown T. Fluorinated benzamide neuroleptics--III. Development of (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-[18F]fluoropropyl)-2, 3-dimethoxybenzamide as an improved dopamine D-2 receptor tracer. Nucl Med Biol 1995;22:283-296.

Murray AM, Ryoo HL, Gurevich E, Joyce JN. Localization of dopamine D_3 receptors to mesolimbic and D_2 receptors to mesostriatal regions of human forebrain. Proc Natl Acad Sci USA 1994;91:11271-11275.

Mäki P, Veijola J, Jones PB, Murray GK, Koponen H, Tienari P, Miettunen J, Tanskanen P, Wahlberg KE, Koskinen J, Lauronen E, Isohanni M. Predictors of schizophrenia--a review. Br Med Bull 2005;73-74:1-15.

Nakajima S. Subtypes of dopamine receptors involved in the mechanism of reinforcement. Neurosci Biobehav Rev 1989;13:123-128.

Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brücke T. Imaging the pre- and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using [123I] epidepride and [123I] beta-CIT. Mov Disord 1998;13:319-323.

Nocjar C, Roth BL, Pehek EA. Localization of 5-HT(2A) receptors on dopamine cells in subnuclei of the midbrain A10 cell group. Neuroscience 2002;111:163-176.

Nordström AL, Farde L, Wiesel FA, Forslund K, Pauli S, Halldin C, Uppfeldt G. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biol Psychiatry 1993;33:227-235.

Nordström AL, Farde L, Eriksson L, Halldin C. No elevated D2 dopamine receptors in neuroleptic-naive schizophrenic patients revealed by positron emission tomography and [11C]N-methylspiperone. Psychiatry Res 1995a;61:67-83.

Nordström AL, Farde L, Nyberg S, Karlsson P, Halldin C, Sedvall G. D1, D2, and 5-HT2 receptor occupancy in relation to clozapine serum concentration: a PET study of schizophrenic patients. Am J Psychiatry 1995b;152:1444-1449.

Nordström AL, Olsson H, Halldin C. A PET study of D2 dopamine receptor density at different phases of the menstrual cycle. Psychiatry Res 1998a;83:1-6.

Nordström AL, Nyberg S, Olsson H, Farde L. Positron emission tomography finding of a high striatal D2 receptor occupancy in olanzapine-treated patients. Arch Gen Psychiatry 1998b;55:283-284.

Numakawa T, Yagasaki Y, Ishimoto T, Okada T, Suzuki T, Iwata N, Ozaki N, Taguchi T, Tatsumi M, Kamijima K, Straub RE, Weinberger DR, Kunugi H, Hashimoto R. Evidence of novel neuronal functions of dysbindin, a susceptibility gene for schizophrenia. Hum Mol Genet 2004;13:2699-2708.

Nyberg S, Eriksson B, Oxenstierna G, Halldin C, Farde L. Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. Am J Psychiatry 1999;156:869-875.

Okauchi T, Suhara T, Maeda J, Kawabe K, Ohbayashi S, Suzuki K. Effect of endogenous dopamine on extrastriatal [^{11}C]FLB 457 binding measured by PET. Synapse 2001;41:87-95.

Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M. Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. Nature 1997;385:634-636.

Pappata S, Samson Y, Chavoix C, Prenant C, Mazière M, Baron JC. Regional specific binding of [11C]RO 15 1788 to central type benzodiazepine receptors in human brain: quantitative evaluation by PET. J Cereb Blood Flow Metab. 1988;8:304-313.

Parellada E, Lomeña F, Catafau AM, Bernardo M, Font M, Fernández-Egea E, Pavía J, Gutierrez F. Lack of sex differences in striatal dopamine D2 receptor binding in drug-naive schizophrenic patients: an IBZM-SPECT study. Psychiatry Res 2004;130:79-84.

Peralta V, Cuesta MJ. Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. Psychiatry Res 1994;53:31-40.

Peralta V, Cuesta MJ. The nosology of psychotic disorders: a comparison among competing classification systems. Schizophr Bull 2003;29:413-425.

Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Härkänen T, Koskinen S, Lönnqvist J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 2007;64:19-28.

Pickar D, Su TP, Weinberger DR, Coppola R, Malhotra AK, Knable MB, Lee KS, Gorey J, Bartko JJ, Breier A, Hsiao J. Individual variation in D2 dopamine receptor occupancy in clozapine-treated patients. Am J Psychiatry 1996;153:1571-1578.

Pilowsky LS, Costa DC, Ell PJ, Murray RM, Verhoeff NP, Kerwin RW. Antipsychotic medication, D2 dopamine receptor blockade and clinical response: a 123I IBZM SPET (single photon emission tomography) study. Psychol Med 1993;23:791-797.

Pilowsky LS, Costa DC, Ell PJ, Verhoeff NP, Murray RM, Kerwin RW. D2 dopamine receptor binding in the basal ganglia of antipsychotic-free schizophrenic patients. An 123I-IBZM single photon emission computerised tomography study. Br J Psychiatry 1994;164:16-26.

Pilowsky LS, Mulligan RS, Acton PD, Ell PJ, Costa DC, Kerwin RW. Limbic selectivity of clozapine. Lancet 1997;350:490-491.

Pinborg LH, Videbaek C, Knudsen GM, Swahn CG, Halldin C, Friberg L, Paulson OB, Lassen NA. Dopamine D(2) quantification in extrastriatal brain regions using [(123)I]epidepride with bolus/infusion. Synapse 2000;36:322-329.

Pinborg LH, Videbaek C, Ziebell M, Mackeprang T, Friberg L, Rasmussen H, Knudsen GM, Glenthoj BY. [^{123}I]Epidepride binding to cerebellar dopamine D_2/D_3 receptors is displaceable: Implications for the use of cerebellum as a reference region. NeuroImage 2007;34:1450-1453.

Pirker W, Asenbaum S, Wenger S, Kornhuber J, Angelberger P, Deecke L, Podreka I, Brücke T. Iodine-123-epidepride-SPECT: studies in Parkinson's disease, multiple system atrophy and Huntington's disease. J Nucl Med 1997;38:1711-1717.

Pohjalainen T, Rinne JO, Någren K, Syvälahti E, Hietala J. Sex differences in the striatal dopamine D2 receptor binding characteristics in vivo. Am J Psychiatry 1998;155:768-773.

Pucak ML, Grace AA. Evidence that systemically administered dopamine antagonists activate dopamine neuron firing primarily by blockade of somatodendritic auroreceptors. J Pharmacol Exp Ther 1994;271:1181-1192.

Raedler TJ, Knable MB, Lafargue T, Urbina RA, Egan MF, Pickar D, Weinberger DR. In vivo determination of striatal dopamine D2 receptor occupancy in patients treated with olanzapine. Psychiatry Res 1999;90:81-90.

Randrup A, Munkvad I. Stereotyped activities produced by amphetamine in several animal species and man. Psychopharmacologia 1967;11:300-310.

Reeves SJ, Mehta MA, Montgomery AJ, Amiras D, Egerton A, Howard RJ, Grasby PM. Striatal dopamine (D2) receptor availability predicts socially desirable responding. Neuroimage 2007;34:1782-1789.

Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, Bachneff S, Cumming P, Diksic M, Dyve SE, Etienne P, Evans AC, Lal S, Shevell M, Savard G, Wong DF, Chouinard G, Gjedde A. Elevated dopa decarboxylase activity in living brain of patients with psychosis. Proc Natl Acad Sci USA 1994;91:11651-11654.

Remington G, Kapur S, Zipursky R. The relationship between risperidone plasma levels and dopamine D2 occupancy: a positron emission tomographic study. J Clin Psychopharmacol 1998;18:82-83.

Repo E, Kuikka JT, Bergström KA, Karhu J, Hiltunen J, Tiihonen J. Dopamine transporter and D2-receptor density in late-onset alcoholism. Psychopharmacology 1999;147:314-318.

Sabri O, Erkwoh R, Schreckenberger M, Owega A, Sass H, Buell U. Correlation of positive symptoms exclusively to hyperperfusion or hypoperfusion of cerebral cortex in never-medicated schizophrenics. Lancet 1997;349:1735-1739.

Salokangas RK, Vilkman H, Ilonen T, Taiminen T, Bergman J, Haaparanta M, Solin O, Alanen A, Syvälahti E, Hietala J. High levels of dopamine activity in the basal ganglia of cigarette smokers. Am J Psychiatry 2000;157:632-634.

Santor DA, Ascher-Svanum H, Lindenmayer JP, Obenchain RL. Item response analysis of the Positive and Negative Syndrome Scale. BMC Psychiatry 2007;7:66.

Sartorius N, Jablensky A, Korten A, Ernberg G, Anker M, Cooper JE, Day R. Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders. Psychol Med 1986;16:909-928.

Sawaguchi T, Goldman-Rakic PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 1991;251:947-950.

Scherer J, Tatsch K, Schwarz J, Oertel WH, Konjarczyk M, Albus M. D2-dopamine receptor occupancy differs between patients with and without extrapyramidal side effects. Acta Psychiatr Scand 1994;90:266-268.

Schmitt GJ, Meisenzahl EM, Dresel S, Tatsch K, Rossmüller B, Frodl T, Preuss UW, Hahn K, Möller HJ. Striatal dopamine D2 receptor binding of risperidone in schizophrenic patients as assessed by 123I-iodobenzamide SPECT: a comparative study with olanzapine. J Psychopharmacol 2002;16:200-206.

Schmitt GJ, Frodl T, Dresel S, la Fougère C, Bottlender R, Koutsouleris N, Hahn K, Möller HJ, Meisenzahl EM. Striatal dopamine transporter availability is associated with the productive psychotic state in first episode, drug-naive schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 2006;256:115-121.

Schotte A, Janssen PF, Gommeren W, Luyten WH, Van Gompel P, Lesage AS, De Loore K, Leysen JE. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology 1996;124:57-73.

Schröder J, Bubeck B, Silvestri S, Demisch S, Sauer H. Gender differences in D2 dopamine receptor binding in drug-naive patients with schizophrenia: an [123I]iodobenzamide single photon emission computed tomography study. Psychiatry Res 1997;75:115-123.

Schultz SK, Andreasen NC. Schizophrenia. Lancet 1999;353:1425-1430.

Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol 1998;80:1-27.

Seeman P. Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse 1987;1:133-152.

Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 1976;261:717-719.

Seeman P, Ulpian C, Bergeron C, Riederer P, Jellinger K, Gabriel E, Reynolds GP, Tourtellotte WW. Bimodal distribution of dopamine receptor densities in brains of schizophrenics. Science 1984;225:728-731.

Seeman P, Bzowej NH, Guan HC, Bergeron C, Becker LE, Reynolds GP, Bird ED, Riederer P, Jellinger K, Watanabe S, Tourtellotte WW. Human brain dopamine receptors in children and aging adults. Synapse 1987;1:399-404.

Seeman P, Tallerico T. Rapid release of antipsychotic drugs from dopamine D_2 receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine and quetiapine. Am J Psychiatry 1999;156:876-884.

Segal DL, Hersen M, Van Hasselt VB. Reliability of the Structured Clinical Interview for DSM-III-R: an evaluative review. Compr Psychiatry 1994;35:316-327.

Seibyl JP, Woods SW, Zoghbi SS, Baldwin RM, Dey HM, Goddard AW, Zea-Ponce Y, Zubal G, Germine M, Smith EO, Heninger GR, Charney DS, Kung HF, Alavi A, Hoffer PB, Innis RB. Dynamic SPECT imaging of dopamine D2 receptors in human subjects with iodine-123-IBZM. J Nucl Med 1992;33:1964-1971.

Seibyl JP, Scanley BE, Krystal JH, Innis RB. Neuroimaging methodologies: utilizing radiotracers or nuclear magnetic resonance. In: Neurobiology of Mental Illnesses, ed. DS Charney, EJ Nestler, pp. 190-209. Oxford University Press, 2nd ed., New York, New York, USA, 2004.

Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res 2001;49:1-52.

Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11-19.

Sjøholm H, Bratlid T, Sundsfjord J. 123I-beta-CIT SPECT demonstrates increased presynaptic dopamine transporter binding sites in basal ganglia in vivo in schizophrenia. Psychopharmacology 2004;173:27-31.

Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. Neuroimage 2003;19:1709-1715.

Sokoloff P, Schwartz JC. Novel dopamine receptors half a decade later. Trends Pharmacol Sci 1995;16:270-275.

Spitzer RL, Williams JBW, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID) I: history, rationale and description. Arch Gen Psychiatry 1992;49:624-629.

Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 2006;188:510-518.

Stefanini E, Frau M, Garau MG, Garau B, Fadda F, Gessa GL. Alcohol-preferring rats have fewer dopamine D2 receptors in the limbic system. Alcohol Alcohol 1992;27:127-130.

Stephenson CM, Bigliani V, Jones HM, Mulligan RS, Acton PD, Visvikis D, Ell PJ, Kerwin RW, Pilowsky LS. Striatal and extra-striatal D(2)/D(3) dopamine receptor occupancy by quetiapine in vivo. [(123)I]-epidepride single photon emission tomography(SPET) study. Br J Psychiatry 2000;177:408-415.

Stone JM, Bressan RA, Erlandsson K, Ell PJ, Pilowsky LS. Non-uniform blockade of intrastriatal D2/D3 receptors by risperidone and amisulpride. Psychopharmacology 2005;180:664-669.

Stone JM, Arstad E, Erlandsson K, Waterhouse RN, Ell PJ, Pilowsky LS. [123I]TPCNE--a novel SPET tracer for the sigma-1 receptor: first human studies and in vivo haloperidol challenge. Synapse 2006;60:109-117.

Stone JM, Pilowsky LS. Novel targets for drugs in schizophrenia. CNS Neurol Disord Drug Targets 2007;6:265-672.

Stone JM, Davis JM, Leucht S, Pilowsky LS. Cortical dopamine D2/D3 receptors are a common site of action for antipsychotic drugs--an original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature. Schizophr Bull 2009;35:789-797.

Strange P. Antipsychotic drugs: importance of dopamine receptors for mechanisms of therapeutic actions and side effects. Pharmacol Rev 2001;53:119-133.

Straub RE, Jiang Y, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C, Wormley B, Sadek H, Kadambi B, Cesare AJ, Gibberman A, Wang X, O'Neill FA, Walsh D, Kendler KS. Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am J Hum Genet 2002;71:337-348.

Suhara T, Fukuda H, Inoue O, Itoh T, Suzuki K, Yamasaki T, Tateno Y. Age-related changes in human D1 dopamine receptors measured by positron emission tomography. Psychopharmacology 1991;103:41-45.

Suhara T, Yasuno F, Sudo Y, Yamamoto M, Inoue M, Okubo Y, Suzuki K. Dopamine D2 receptors in the insular cortex and the personality trait of novelty seeking. Neuroimage 2001;13:891-895.

Suhara T, Okubo Y, Yasuno F, Sudo Y, Inoue M, Ichimiya T, Nakashima Y, Nakayama K, Tanada S, Suzuki K, Halldin C, Farde L. Decreased dopamine D_2 receptor binding in the anterior cingulate cortex in schizophrenia. Arch Gen Psychiatry 2002;59:25-30.

Sunahara RK, Guan HC, O'Dowd BF, Seeman P, Laurier LG, Ng G, George SR, Torchia J, Van Tol HH, Niznik HB. Cloning of the gene for a human dopamine D5 receptor with higher affinity for dopamine than D1. Nature 1991;350:614-619.

Szabo Z, Kao PF, Scheffel U, Suehiro M, Mathews WB, Ravert HT, Musachio JL, Marenco S, Kim SE, Ricaurte GA, Wong DF, Wagner HN, Dannals RF. Positron emission tomography imaging of serotonin transporters in the human brain using [11C](+)McN5652. Synapse 1995;20:37-43.

Takahashi H, Higuchi M, Suhara T. The role of extrastriatal dopamine D2 receptors in schizophrenia. Biol Psychiatry 2006;59:919-928.

Takano A, Suhara T, Kusumi I, Takahashi Y, Asai Y, Yasuno F, Ichimiya T, Inoue M, Sudo Y, Koyama T. Time course of dopamine D2 receptor occupancy by clozapine with medium and high plasma concentrations. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:75-81.

Talairach J, Tournoux P. Referentially oriented cerebral MRI anatomy. New York: Thieme Medical Publishers, Inc., 1993.

Talbot PS, Laruelle M. The role of in vivo molecular imaging with PET and SPECT in the elucidation of psychiatric drug action and new drug development. Eur Neuropsychopharmacol 2002;12:503-511.

Talvik M, Nordström AL, Nyberg S, Olsson H, Halldin C, Farde L. No support for regional selectivity in clozapine-treated patients: a PET study with [(11)C]raclopride and [(11)C]FLB 457. Am J Psychiatry 2001;158:926-930.

Talvik M, Nordström AL, Olsson H, Halldin C, Farde L. Decreased thalamic D2/D3 receptor binding in drug-naïve patients with schizophrenia: a PET study with [11C]FLB 457. Int J Neuropsychopharmacol 2003;6:361-370.

Talvik M, Nordström AL, Okubo Y, Olsson H, Borg J, Halldin C, Farde L. Dopamine D2 receptor binding in drug-naïve patients with schizophrenia examined with raclopride-C11 and positron emission tomography. Psychiatry Res 2006;148:165-173.

Tauscher J, Küfferle B, Asenbaum S, Fischer P, Pezawas L, Barnas C, Tauscher-Wisniewski S, Brücke T, Kasper S. In vivo 123I IBZM SPECT imaging of striatal dopamine-2 receptor occupancy in schizophrenic patients treated with olanzapine in comparison to clozapine and haloperidol. Psychopharmacology 1999;141:175-181.

Tauscher J, Hussain T, Agid O, Verhoeff NP, Wilson AA, Houle S, Remington G, Zipursky RB, Kapur S. Equivalent occupancy of dopamine D1 and D2 receptors with clozapine: differentiation from other atypical antipsychotics. Am J Psychiatry 2004;161:1620-1625.

Tibbo P, Silverstone PH, McEwan AJ, Scott J, Joshua A, Golberg K. A single photon emission computed tomography scan study of striatal dopamine D2 receptor binding with 123I-epidepride in patients with schizophrenia and controls. J Psychiatry Neurosci 1997;22:39-45.

Tienari P, Wynne LC, Moring J, Läksy K, Nieminen P, Sorri A, Lahti I, Wahlberg KE, Naarala M, Kurki-Suonio K, Saarento O, Koistinen P, Tarvainen T, Hakko H, Miettunen J. Finnish adoptive family study: sample selection and adoptee DSM-III-R diagnoses. Acta Psychiatr Scand 2000;101:433-443.

Tiihonen J, Kuikka J, Bergström K, Hakola P, Karhu J, Ryynänen OP, Föhr J. Altered striatal dopamine re-uptake site densities in habitually violent and non-violent alcoholics. Nat Med 1995;1:654-657.

Timmerman W, Heijmen M, Westerink BHC, Bruggeman R, den Boer JA. Effects of acute and chronic administration of olanzapine in comparison to clozapine and haloperidol on extracellular recordings of substantia nigra reticulata neurons in the rat brain. Psychopharmacology 1999;144:286-294.

Tomida K, Takahashi N, Saito S, Maeno N, Iwamoto K, Yoshida K, Kimura H, Iidaka T, Ozaki N. Relationship of psychopathological symptoms and cognitive function to subjective quality of life in patients with chronic schizophrenia. Psychiatry Clin Neurosci 2010;64:62-69.

Toru M, Nishikawa T, Mataga N, Takashima M. Dopamine metabolism increases in post-mortem schizophrenic basal ganglia. J Neural Transm 1982;54:181-91.

Trollor JN, Valenzuela MJ. Brain ageing in the new millennium. Aust N Z J Psychiatry 2001;35:788-805.

Tsai G, Yang P, Chung LC, Lange N, Coyle JT. D-serine added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 1998;44:1081-1089.

Tune LE, Wong DF, Pearlson G, Strauss M, Young T, Shaya EK, Dannals RF, Wilson AA, Ravert HT, Sapp J, Cooper T, Chase GA, Wagner HN Jr. Dopamine D2 receptor density estimates in schizophrenia: a positron emission tomography study with 11C-N-methylspiperone. Psychiatry Res 1993;49:219-237.

Tupala E, Hall H, Bergström K, Särkioja T, Räsänen P, Mantere T, Callaway J, Hiltunen J, Tiihonen J. Dopamine D(2)/D(3)-receptor and transporter densities in nucleus accumbens and amygdala of type 1 and 2 alcoholics. Mol Psychiatry 2001;6:261-267.

Tupala E, Hall H, Bergström K, Mantere T, Räsänen P, Särkioja T, Tiihonen J. Dopamine D2 receptors and transporters in type 1 and 2 alcoholics measured with human whole hemisphere autoradiography. Hum Brain Mapp 2003;20:91-102.

Usiello A, Baik JH, Rougé-Pont F, Picetti R, Dierich A, LeMeur M, Piazza PV, Borrelli E. Distinct functions of the two isoforms of dopamine D2 receptors. Nature 2000;408:199-203.

Van den Oord EJ, Rujescu D, Robles JR, Giegling I, Birrell C, Bukszár J, Murrelle L, Möller HJ, Middleton L, Muglia P. Factor structure and external validity of the PANSS revisited. Schizophr Res 2006;82:213-223.

Van Rossum. The significance of dopamine receptor blockade for the action of neuroleptic drug. In: Brill H, Cole JO, Deniker P, Hippius H, Bladley PB, eds. Proceedings of the Fifth Collegium Internationale Neuropsychopharmacologicum; Washington DC; 1967:321-329.

Vares M, Ekholm A, Sedvall GC, Hall H, Jönsson EG. Characterization of patients with schizophrenia and related psychoses: evaluation of different diagnostic procedures. Psychopathology 2006;39:286-295.

Vernaleken I, Siessmeier T, Buchholz HG, Härtter S, Hiemke C, Stoeter P, Rösch F, Bartenstein P, Gründer G. High striatal occupancy of D2-like dopamine receptors by amisulpride in the brain of patients with schizophrenia. Int J Neuropsychopharmacol 2004;7:421-430.

Vernaleken I, Fellows C, Janouschek H, Bröcheler A, Veselinovic T, Landvogt C, Boy C, Buchholz HG, Spreckelmeyer K, Bartenstein P, Cumming P, Hiemke C, Rösch F, Schäfer W, Wong DF, Gründer G. Striatal and extrastriatal D2/D3-receptor-binding properties of ziprasidone: a positron emission tomography study with [18F]Fallypride and [11C]raclopride (D2/D3-receptor occupancy of ziprasidone). J Clin Psychopharmacol 2008;28:608-617.

Volkow ND, Ding YS, Fowler JS, Wang GJ, Logan J, Gatley SJ, Hitzemann R, Smith G, Fields SD, Gur R. Dopamine transporters decrease with age. J Nucl Med 1996a;37:554-559.

Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, MacGregor RR, Schlyer DJ, Hitzemann R, Wolf AP. Measuring age-related changes in dopamine D2 receptors with 11C-raclopride and 18F-N-methylspiroperidol. Psychiatry Res 1996b;67:11-16.

Volkow ND, Wang GJ, Fowler JS, Logan J, Hitzemann R, Ding YS, Pappas N, Shea C, Piscani K. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcohol Clin Exp Res 1996c;20:1594-1598.

Volkow N, Gur RC, Wang GJ, Fowler JS, Moberg PJ, Ding YS, Hitzemann R, Smith G, Logan J. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatry 1998;155:344-49.

Wang GJ, Volkow ND, Fowler JS, Logan J, Gur R, Netusil N, Hitzemann RJ, Pappas NS. Age associated decrements in dopamine D2 receptors in thalamus and in temporal insula of human subjects. Life Sci 1996;59:PL31-35.

Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Brain dopamine and obesity. Lancet 2001;357:354-357.

Watson GB, Bolanowski MA, Baganoff MP, Deppeler CL, Lanthorn TH. D-cycloserine acts as a partial agonist at the glycine modulatory site of the NMDA receptor expressed in Xenopus oocytes. Brain Res 1990;510:158-160.

Weickert CS, Straub RE, McClintock BW, Matsumoto M, Hashimoto R, Hyde TM, Herman MM, Weinberger DR, Kleinman JE. Human dysbindin (DTNBP1) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. Arch Gen Psychiatry 2004;61:544-555.

Weinberger DR, Gibson R, Coppola R, Jones DW, Molchan S, Sunderland T, Berman KF, Reba RC. The distribution of cerebral muscarinic acetylcholine receptors in vivo in patients with dementia. A controlled study with 123IQNB and single photon emission computed tomography. Arch Neurol 1991;48:169-176.

Wernick MN, Aarsvold JN. Introduction to emission tomography. In: Emission Tomography: The Fundamentals of PET and SPECT, ed. MN Wernick, JN Aarsvold, pp. 11-23. Elsevier Academic Press, San Diego, California, USA, 2004.

White FJ, Wang RY. Differential effects of classical and atypical antipsychotic drugs on A9 and A10 dopamine neurons. Science 1983;221:1054-1057.

Williams SM, Goldman-Rakic PS. Widespread origin of the primate mesofrontal dopamine system. Cereb Cortex 1998;8:321-345.

Wirshing WC. Movement disorders associated with neuroleptic treatment. J Clin Psychiatry 2001;62(S21):15-18.

Wong DF, Wagner HN Jr, Dannals RF, Links JM, Frost JJ, Ravert HT, Wilson AA, Rosenbaum AE, Gjedde A, Douglass KH, Petronis JD, Folstein MF, Toung JKT, Burns HD, Kuhar MJ. Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science 1984;226:1393-1396.

Wong DF, Wagner NH Jr, Tune LE, Dannals RF, Pearlson GD, Links JM, Tamminga CA, Broussolle EP, Ravert HT, Wilson AA, Toung JKT, Malat J, Williams JA, O'Tuama LA, Snyder SH, Kuhar MJ, Gjedde A Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. Science 1986;234:1558-1563.

Wong DF, Yung B, Dannals RF, Shaya EK, Ravert HT, Chen CA, Chan B, Folio T, Scheffel U, Ricaurte GA, Neumeyer JL, Wagner HN, Kuhar MJ. In vivo imaging of baboon and human dopamine transporters by positron emission tomography using [11C]WIN 35,428. Synapse 1993;15:130-142.

Wong DF, Pearlson GD, Tune LE, Young LT, Meltzer CC, Dannals RF, Ravert HT, Reith J, Kuhar MJ, Gjedde A. Quantification of neuroreceptors in the living human brain: IV. Effect of aging and elevations of D2-like receptors in schizophrenia and bipolar illness. J Cereb Blood Flow Metab 1997;3:331-341.

Wong DF, Broussolle EP, Wand G, Villemagne V, Dannals RF, Links JM, Zacur HA, Harris J, Naidu S, Braestrup C, Wagner HN Jr, Gjedde A. In vivo measurement of dopamine receptors in human brain by positron emission tomography. Age and sex differences. Ann NY Acad Sci 1988;515:203-214.

Woods S. Chlorpromazine-equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003;64:663-667.

World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: WHO, 1992.

Wolkin A, Barouche F, Wolf AP, Rotrosen J, Fowler JS, Shiue CY, Cooper TB, Brodie JD. Dopamine blockade and clinical response: evidence for two biological subgroups of schizophrenia. Am J Psychiatry 1989;146:905-908.

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 2000;157:16-25.

Xiberas X, Martinot JL, Mallet L, Artiges E, Loc'H C, Mazière B, Paillère-Martinot ML. Extrastriatal and striatal D(2) dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. Br J Psychiatry 2001a;179:503-508.

Xiberas X, Martinot JL, Mallet L, Artiges E, Canal M, Loc'h C, Mazière B, Paillère-Martinot ML. In vivo extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. J Clin Psychopharmacol 2001b;21:207-214.

Yang YK, Yu L, Yeh TL, Chiu NT, Chen PS, Lee IH; SPECT study. Associated alterations of striatal dopamine D2/D3 receptor and transporter binding in drug-naive patients with schizophrenia: a dual-isotope SPECT study. Am J Psychiatry 2004;161:1496-1498.

Yang YK, Yao WJ, McEvoy JP, Chu CL, Lee IH, Chen PS, Yeh TL, Chiu NT. Striatal dopamine D2/D3 receptor availability in male smokers. Psychiatry Res 2006;146:87-90.

Yasuno F, Suhara T, Sudo Y, Yamamoto M, Inoue M, Okubo Y, Suzuki K. Relation among dopamine D(2) receptor binding, obesity and personality in normal human subjects. Neurosci Lett 2001a;300:59-61.

Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T, Tanada S. Dose relationship of limbic-cortical D2-dopamine receptor occupancy with risperidone. Psychopharmacology 2001b;154:112-114.

Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T, Takano A, Nakayama K, Halldin C, Farde L. Low dopamine d(2) receptor binding in subregions of the thalamus in schizophrenia. Am J Psychiatry 2004;161:1016-1022.

Zald DH, Cowan RL, Riccardi P, Baldwin RM, Ansari MS, Li R, Shelby ES, Smith CE, McHugo M, Kessler RM. Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. J Neurosci 2008;28:14372-14378.

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Extrastriatal Dopamine D2/3 Receptors in Schizophrenia

Earlier studies on schizophrenia have suggested abnormalities in central dopamine function. In this study, the densities of D2/3 receptors in extrastriatal brain regions were studied using single-photon emission computed tomography (SPECT) ligand [123I]epidepride. Reduced D2/3 receptor density in temporal cortex and substantia nigra was found among patients compared with controls. In substantia nigra, divergent D2/3 binding by various antipsychotic drugs was observed, and extrapyramidal symptoms correlated negatively with drug-induced nigral D2/3 binding.

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