POSITRON EMISSION TOMOGRAPHY STUDIES OF THE D$_1$ DOPAMINE RECEPTOR IN SCHIZOPHRENIA

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Cover illustration: Positron Emission Tomography (PET) image of a horizontal brain section at the level of striatum of a healthy man. The image show a color-coded concentration of radioactivity accumulated between 9 and 51 minutes after i.v. injection of the D_1 dopamine receptor radioligand [^{11}C]SCH23390.

Positron Emission Tomography studies of the D1 dopamine receptor in schizophrenia

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To Monica and Sven

A hypothesis or theory is clear, decisive, and positive, but it is believed by no one but the man who created it. Experimental findings, on the other hand, are messy, inexact things, which are believed by everyone except the man who did that work.

Harlow Shapley (1885-1972)

ABSTRACT

This thesis is based on investigations of central D1-dopamine receptor (D1R) binding in vivo using positron emission tomography (PET). The aims were i) to examine the antipsychotic effect of a D1R antagonist in schizophrenia and ii) to test the dopamine hypothesis of schizophrenia by comparing D1R binding between patients and healthy subjects.

SCH39166, is the first selective D1R antagonist that was developed both as a PET radioligand for D1R and as an antipsychotic drug. The D1-receptor occupancy of SCH39166 was determined with PET and [11C]SCH39166 in a dose-response fashion after single oral doses in healthy volunteers. The D1R occupancy in the putamen was about 70 % after 100 mg. The conclusion was that this dose would be adequate to investigate potential antipsychotic effect of a D1R antagonist in schizophrenia.

SCH39166 was then given orally in escalating doses to 17 acutely ill drug free schizophrenic patients (DSM-IIIR) in an open 4-week study. The drug had to be withdrawn prematurely in ten patients due to deterioration or refusal to take SCH39166. In the nine patients participating for more than 2 weeks, the drug did not have an apparent antipsychotic effect. After withdrawal of SCH39166, the patients improved when treated with classical neuroleptics or clozapine. The result of the study does not support the prediction that selective D1R antagonism have antipsychotic effect in schizophrenia.

To better inform statistical evaluation of any cross sectional evaluation of D1R binding a test-retest PET study of the D1R selective radioligand [11C]SCH23390 was performed in fifteen healthy subjects to compare different methodologies of image analysis. The binding potential (BP_{ND}) values were compared following manual and automated delineation of regions of interest (ROI's) as well as with and without frame-by-frame realignment. No significant differences were observed for repeatability using automated and manual delineation methods whereas frame-by-frame realignment generated higher BP_{ND} values and improved repeatability. The results suggest that the choice of ROI delineation method is not an important condition for reliability, whereas thorough movement correction is of importance.

A cohort of 18 first-episode neuroleptic-naïve patients with schizophrenia or schizophreniform psychosis and 17 healthy control subjects were examined with PET and [11C]SCH23390. The patients had a statistically significant lower D1R BP_{ND} in frontal cortex with a moderate effect size. This suggests a reduction of prefrontal D1R density in the pathophysiology of schizophrenia. Study II and IV provides indirect support for the hypothesis of frontal hypodopaminergia.

The observation of a low D1R-binding in schizophrenia may explain why a D1R-antagonist (which further reduces the availability of D1R) has no obvious antipsychotic effect. The findings provide support for current developments of D1R-agonists for the treatment of schizophrenia.

LIST OF SCIENTIFIC PAPERS

I. **Karlsson, P.**, Sedvall, G., Halldin, C., Swahn, C. G. and Farde, L. (1995). "Evaluation of SCH 39166 as PET ligand for central D1 dopamine receptor binding and occupancy in man." Psychopharmacology (Berl) 121(3): 300-308. PMID: 8584610

II. **Karlsson, P.**, Smith, L., Farde, L., Harnryd, C., Sedvall, G. and Wiesel, F. A. (1995). "Lack of apparent antipsychotic effect of the D1-dopamine receptor antagonist SCH39166 in acutely ill schizophrenic patients." Psychopharmacology (Berl) 121(3): 309-316. PMID: 8584611

III. **Stenkrona, P.**, Matheson, G. J., Cervenka, S., Sigray, P. P., Halldin, C. and Farde, L. (2018). "[(11)C]SCH23390 binding to the D1-dopamine receptor in the human brain-a comparison of manual and automated methods for image analysis." EJNMMI Res 8(1): 74. PMID: 30069645

IV. **Stenkrona, P.**, Matheson, G. J., Halldin, C., Cervenka, S. and Farde, L. (2019). "D1-Dopamine Receptor Availability in First-Episode Neuroleptic Naïve Psychosis Patients." Int J Neuropsychopharmacol 22(7): 415-425. PMID: 30958880

Comment: The author of this thesis changed his surname in 2011 from Karlsson to Stenkrona.

ADDITIONAL PUBLICATIONS RELATED TO THE THESIS SUBJECT

I.   **Karlsson P**, Farde L, Halldin C, Swahn CG, Sedvall G, Foged C, et al. PET examination of [11C]NNC 687 and [11C]NNC 756 as new radioligands for the D1-dopamine receptor. Psychopharmacology (Berl). 1993;113(2):149-56. PMID: 7855175.

II.   **Karlsson P**, Farde L, Halldin C, Sedvall G, Ynddal L, Sloth-Nielsen M. Oral administration of NNC 756--a placebo controlled PET study of D1-dopamine receptor occupancy and pharmacodynamics in man. Psychopharmacology (Berl). 1995;119(1):1-8. PMID: 7675940.

III.   **Karlsson P**, Farde L, Halldin C, Sedvall G. PET study of D1 dopamine receptor binding in neuroleptic-naïve patients with schizophrenia. Am J Psychiatry. 2002;159(5):761-7. PMID: 11986129.

IV.   Sedvall G, **Karlsson P**, Lundin A, Anvret M, Suhara T, Halldin C, et al. Dopamine D1 receptor number--a sensitive PET marker for early brain degeneration in Huntington's disease. Eur Arch Psychiatry Clin Neurosci. 1994;243(5):249-55. PMID: 8172940.

V.   Plaven-Sigray P, Gustavsson P, Farde L, Borg J, **Stenkrona P**, Nyberg L, Backman L, Cervenka S. Dopamine D1 receptor availability is related to social behavior: a positron emission tomography study. Neuroimage. 2014;102 Pt 2:590-5. PMID: 25134976.

VI.   Matheson GJ, **Stenkrona P**, Cselenyi Z, Plaven-Sigray P, Halldin C, Farde L, Cervenka S. Reliability of volumetric and surface-based normalisation and smoothing techniques for PET analysis of the cortex: A test-retest analysis using [11C]SCH-23390. Neuroimage. 2017;155:344-53. PMID: 28419852.

VII.   Matheson GJ, **Stenkrona P**, Cselenyi Z, Plaven-Sigray P, Halldin C, Farde L, Cervenka S. Reliability of volumetric and surface-based normalisation and smoothing techniques for PET analysis of the cortex: A test-retest analysis using [11C]SCH-23390. Neuroimage. 2017;155:344-53. PMID: 28419852.

CONTENTS

LIST OF ABBREVIATIONS

[11C]	Carbon 11
BP_{ND}	Binding potential, non displaceable
BPRS	Brief Psychiatric Rating Scale
DLPFC	Dorsolateral prefrontal cortex
DR	Dopamine receptors
DSM-IIIR	Diagnostic and Statistical Manual, third edition, revised
D1R	D1-dopamine receptors
D2R	D2-dopamine receptors
FWHM	Full Width at Half Maximum
i.v.	Intra Venous
Ki	Inhibition constant
MBq	Mega Becquerel
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PFC	Prefrontal cortex
ROI	Regions of Interest
WM	Working Memory

1 RATIONAL FOR THIS THESIS

The dopamine hypothesis has since the 1960's had a central role in schizophrenia research. The development of Positron Emission Tomography (PET) and molecular neuroimaging in the early 1980's allowed for studies of the biochemistry of the dopamine system in the living human brain. This is a particular advantage in schizophrenia research since the methodology allows for examination of young drug free first-episode patients. One part of the present thesis work is methodological and includes the development and evaluation of two radioligands for brain imaging of the D_1-dopamine receptor (Study I, III). The methodology was then used to examine the hypothesis on the D_1-dopamine receptor as a potential target for the drug treatment of schizophrenia (Study II), and finally, the hypotheses on altered D_1-dopamine receptor expression in young untreated patients with schizophrenia (Study IV).

The following introduction will position the thesis into the context of schizophrenia research with primary emphasis on molecular imaging.

2 INTRODUCTION

2.1 SCHIZOPHRENIA

Schizophrenia is a heritable psychiatric disorder affecting about 1 % of the world population (McGrath et al. 2008, Kahn et al. 2015). The early onset and often lifelong duration of schizophrenia will accumulate into a considerable burden at the individual, social and economic levels (Salomon et al. 2010).

Schizophrenia is like all psychiatric disorders a clinical syndrome. In the medical field, a syndrome is defined as a "term applied to a group of symptoms occurring regularly and thus constituting a disease to which some particular name is given" (Macpherson, 2004, p. 602). Several classifications of psychiatric disorders have been developed and fine-tuned since the 19th century and they all rely heavily on expert consensus (Kendler and Solomon 2016). In research on schizophrenia the most common classification system is the DSM (Diagnostic and Statistical Manual of Mental Disorders) published by the American Psychiatric Association since 1952. From the DSM-III edition in 1980 and onwards the psychiatric diagnoses were grounded in empirical evidence as opposed to previous theory-bound nosology. The last revision, DSM-5, was published in 2013 (APA 2013).

Schizophrenia is characterized by a wide set of symptoms that can be divided into 'positive', 'negative' and more recently also 'cognitive' categories (for review see (Kahn et al. 2015). Positive symptoms are behaviors and thoughts that are not normally present, such as delusions, hallucinations and disorganized speech. Negative symptoms are rather a loss or diminution of normal functions and include social withdrawal, affective flattening (diminution of emotional expression), anhedonia (the inability to feel pleasure) and abulia (diminished initiative and energy). In addition, it has more recently been demonstrated that impairment of cognitive function is a core feature of schizophrenia, including deficits in attention, memory, working memory, verbal learning, and executive functions (Saykin et al. 1994, Palmer et al. 1997, Hahn et al. 2012). Of interest is that a recent meta-analysis confirms that young antipsychotic drug-naïve patients with schizophrenia perform more poorly than healthy controls in all cognitive domains, with effect sizes comparable to that of chronic, medicated patients (Fatouros-Bergman et al. 2014).

2.2 THE DEVELOPMENT OF THE CONCEPT OF SCHIZOPHRENIA

Historical sources support the view that schizophrenia is not a "new disorder". Written documents describing symptoms that are common in schizophrenia can be traced back to the second millennium B.C. in ancient Egypt. What appears to be mental disorders are described in the Book of Hearts, a chapter of the Ebers Papyrus dating to circa 1550 BC (Ebers 1875). Similarly, a Chinese text written around 1000 BC, describe symptoms of insanity, dementia, and seizures (Ti Nei and Su Wên 1975). Psychotic symptoms were also described in ancient Greek and Roman literature (Evans et al. 2003). It is also likely that medieval Muslim physicians identified and treated many cases of schizophrenia (Youssef and Youssef 1996).

In addition and throughout history, demonic or supernatural possession has been implicated in many cultures as the cause of psychotic behaviors (Littlewood 2004).

The term psychosis was coined in 1845 by the Austrian physician Baron Ernst von Feuchtersleben, to denote a 'mental disorder which affected the personality as a whole' (Feuchtersleben 1847). The earliest detailed description of what later became known as schizophrenia, was of an English patient described in a case-report called "Illustrations of Madness" (Haslam 1810).

The French physician Bénédict Augustin Morel was the first to use the term démence précoce (premature dementia) in his text book Études cliniques (Morel 1852). Later, Arnold Pick (1851–1924), professor of psychiatry in Prague, used dementia praecox to specifically label a deteriorating psychotic disorder from which no one recovered (Pick 1891). Emil Kraepelin, at the time professor of psychiatry in Heidelberg, elaborated further on the term dementia praecox (Kraepein 1919). He included the three contemporary concepts of psychosis, i.e. hebephrenia (bizarre behavior), catatonia (disturbed movements) and paranoia (feeling persecuted). Kraepelin also divided the complex psychiatric taxonomies of the nineteenth century into two classes: manic-depressive psychosis, now termed bipolar disorder, and dementia praecox.

The term 'schizophrenia' was coined in 1908 by the Swiss psychiatrist Paul Eugen Bleuler, and was derived from the Greek words 'schizo' (split) and 'phren' (mind) (Bleuler 1908). Bleuler had intended the term to refer to the dissociation or 'loosening' of thoughts and feelings that he had found to be a prominent feature of the illness. The splitting of different psychological functions "of thinking, feeling, and relation to the external world", resulting in a loss of unity of the personality, was the most important sign of the disease in Bleuler's conception (Stotz-Ingenlath 2000). Importantly, his term was not meant to convey the idea of an actual split of the personality (or multiple personalities), a common and rather entrenched myth regarding schizophrenia that continues to this day.

Several attempts to subcategorize schizophrenia have proven less useful since patients may change between subcategories over time. Schizophrenia subtypes have been abandoned in the DSM-5 because of their "limited diagnostic stability, low reliability, and poor validity," and they didn't appear to help with providing better treatment or predicting treatment response (APA 2013). Worth noting is also that the delineation of schizophrenia by specific symptoms has proven difficult since none of the symptoms of schizophrenia are pathognomonic (unique and sufficient symptom for a diagnosis).

2.3 PATHOPHYSIOLOGY OF SCHIZOPHRENIA

Brain diseases with biomarkers, such as the presence of emboli, protein tangles, or unusual electrical activity patterns, are generally defined as neurological disorders. Most remaining brain diseases that includes behavioral disturbances are generally defined as psychiatric disorders. It follows that for all psychiatric disorders, there is no objective diagnostic test or

validated biological marker. By consequence, the existence of a specific brain disease underlying schizophrenia is a yet an unproven hypothesis (Jablensky 2010).

2.3.1 Early hypotheses of schizophrenia

The biological concept of mental illness has existed since the early days of the establishment of psychiatry as a medical specialty. It is clear that initial hypotheses for schizophrenia and other mental disorders were heavily influenced by the development of other disciplines. The rise of modern medicine in bacteriology, endocrinology and immunology became the basis for a generation of new organic hypotheses in biological psychiatry (Deecke 1874, Noll 2007). However, the application of these disciplines did not bear on schizophrenia research.

In search for an organic cause, Kraepelin recognized that patients with dementia praecox share many of the behavioral abnormalities observed in demented patients with lesions of the frontal lobes (Kraepelin, 1919). However, investigations of brains post mortem of patients with schizophrenia did not reveal any such lesions or gross structural changes (Noll 2011).

In the absence of morphological abnormalities of the brain, psychodynamic views on the origin of dementia praecox began appearing in the literature in the early 1900's following ideas of Sigmund Freud, Carl Jung and Eugene Bleuler, who attributed the disease to deficiencies in specific aspects of parenting. These ideas reached a height in the 1960's with the concept of the "schizophrenogenic mother" (Laing and Esterson 1964). This thinking has subsequently been abandoned (Harrington 2012).

2.3.2 Early pharmacological treatment of schizophrenia

The first marketed and widely used sedatives used for patients with schizophrenia were the barbiturates, of which the first was developed in Germany in 1903. Besides pharmacology, several somatic treatments were invented such as malariotherapy and lobotomy, which were awarded the Nobel prize in Physiology or Medicine in 1927 and 1949 respectively. While these drugs and procedures sedated and calmed the patient they were not really viewed as treatments (Braslow and Marder 2019). The exception was Electro Convulsive Therapy (ECT) that from the beginning in the 1930's was effective in treating some patients with psychosis (Cerletti and Bini 1938, Endler 1988).

2.3.3 Antipsychotic drugs

The first major antipsychotic drug was chlorpromazine. Phenothiazine, the core molecule of chlorpromazine, was synthetized in 1883 and produced as a synthetic dye for the textile industry. Following the early discoveries of neurotransmitters the phenothiazines were in the 1940's recognized to have antihistamine properties. Shortly after, chlorpromazine was synthesized by Paul Charpentier in 1951 to be used for anesthetic post-operative purposes. In the first clinical test the French surgeon Henri Laborit noted a marked calming effect with no obvious sedation (Laborit et al. 1952). In subsequent clinical investigations at Saint-Anne's hospital in Paris it was found that chlorpromazine relieved psychotic symptoms, such as delusions and hallucinations (Delay and Deniker 1952). They coined the word neuroleptic,

originating from the Greek words for "neuron" and "take hold of", to denote the clinical effects of this type of drug (Deniker 1989). Unlike the sedatives and hypnotics, chlorpromazine was the first drug that psychiatrists believed actually treated mental disorders. Worth mentioning is that a drug with different chemical structure but similar clinical properties as chlorpromazine is reserpine, a drug derived from an Indian plant, Rauwola serpentina. Reserpine was used extensively in the 1950s, but disregarded due to its long onset of action as well as side effects of hypotension and depression (Healy and Savage 1998).

A more potent group of antipsychotics are the butyrophenones. They were by-products of the opioid meperidine (pethidine). The most renowned is haloperidol, first synthesized in 1958 in Belgium (Granger and Albu 2005) and one of the most widely used of the first generation of antipsychotic drugs.

2.3.4 The dopamine hypothesis of antipsychotic drug action

Spectrophotofluorimetry was a new technique for measuring drugs in the body developed in Bernard Brodie's Laboratory at the National Institutes of Health, USA (Costa et al. 1989). Among Brodie's coworkers was Arvid Carlsson, who studied reserpine. After returning to Sweden, his further work with reserpine led to the discovery that dopamine is a neurotransmitter (Carlsson et al. 1957, Carlsson 2001). A few years later, Carlsson and his assistant Margit Lindqvist demonstrated that chlorpromazine and haloperidol increases catecholamine metabolites in the mouse brain (Carlsson and Lindqvist 1963). Based on these and other findings it was hypothesized that the antipsychotic effect of neuroleptics is mediated by blocking dopamine receptors (Carlsson and Lindqvist 1963, van Rossum 1966, Nyback and Sedvall 1968). Besides its pharmacological importance, the discovery that antipsychotic drugs act by inhibiting dopamine transmission led to intensified research on the organization and functional role of the dopaminergic neurotransmission systems in brain.

The hypothesis of the mechanism of antipsychotic drug action was further supported by the advent of radioligand binding studies in the 70's. It received support from the demonstration of a correlation between antipsychotic potency and the affinity of antipsychotic drugs to dopamine receptors *in vitro* (Seeman et al. 1976)

2.3.5 The dopamine hypothesis of the pathophysiology of schizophrenia

The dopamine hypothesis of schizophrenia is based on several pharmacological and neurobiological findings where dopamine activity is related to symptoms of schizophrenia. Drugs stimulating dopamine transmission, such as the dopamine-releasing compound amphetamine (Conell 1958, Randrup and Munkvad 1967) were found to induce symptoms that resemble paranoid schizophrenia. Drugs reducing dopamine transmission, such as neuroleptics, ameliorates psychotic symptoms. Hence, based on the psychotomimetic effect of dopamine stimulating drugs and the antipsychotic effect of neuroleptics, Jacques van Rossum postulated the dopamine hypothesis of schizophrenia in 1966 (van Rossum 1966). He proposed that "overstimulation of dopamine receptors could be part of the etiology".

2.4 CURRENT UNDERSTANDING OF THE DOPAMINERGIC SYSTEM IN BRAIN

The dopamine system is the last monoamine system to be laid down in the brain during ontogeny (development of an organism), which suggests that it may have an important stabilizing and integrative influence on brain circuits (Grace 2016). Despite dopaminergic neurons being rare, less than 1/100,000 brain neurons, the dopamine system has shown to be ubiquitous. Separate populations of dopamine neurons have large axonal arborization (branching) that each project to a specific brain region. Dopamine is involved in the regulation of a variety of physiological and brain functions such as voluntary movement, reward, sleep regulation, feeding, affect, attention, cognition, olfaction, vision, smell, hormonal regulation, sympathetic regulation, penile erection, as well as immunological, cardiovascular, renal and gastrointestinal functions (Beaulieu et al. 2015).

Dopamine is a neurotransmitter that belongs to the group of catecholamines (dopamine, norepinephrine and epinephrine). Dopamine is derived from the amino acid tyrosine, which in turn is derived from dietary sources as well as synthesis from the amino acid L-phenylalanine. (Fig. 1).
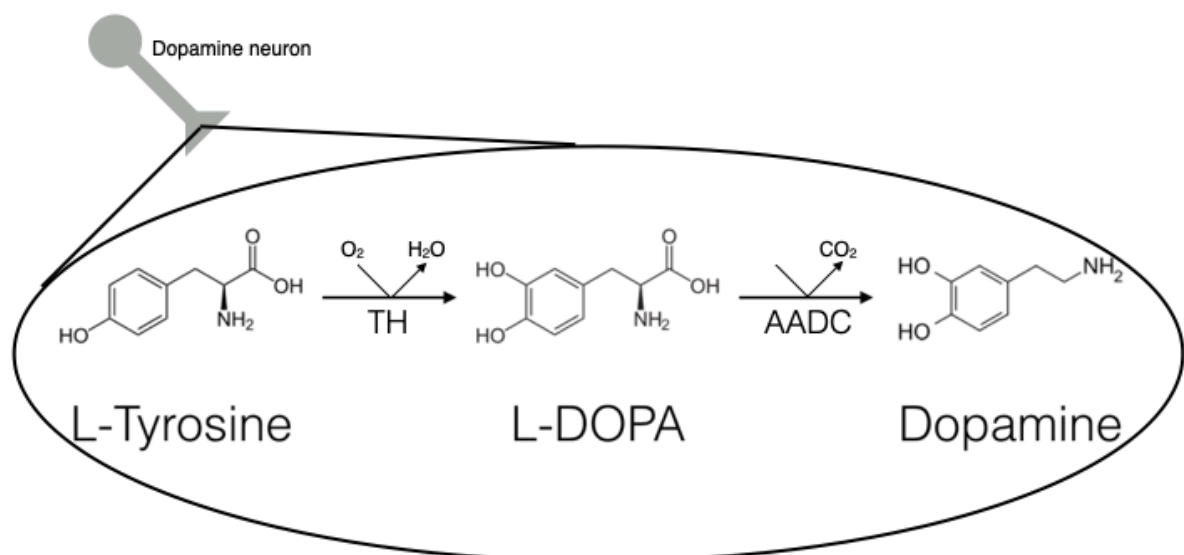
Figure 1. Synthesis of dopamine in the axon terminal of a neuron. In the first rate-determining step, tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase (TH). In the second step, L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (AADC).

2.4.1 Dopamine pathways

Mapping the functional organization of the catecholamine neurons and their pathways in the brain started in the early 1960s with the invention of the fluorescence histochemical method, a.k.a. the Falck-Hillarp method (Falck et al. 1982, Fuxe et al. 2007). The toolbox of molecular imaging techniques has since then expanded with immunocytochemistry, receptor autoradiography and in vivo imaging by Positron Emission Tomography (PET).

The majority of dopamine molecules are synthesized in dopaminergic neurons in the mesencephalon, a.k.a. the midbrain, i.e the upper part of the brainstem (Fig. 2). From there, the three major projections are the nigrostriatal (substantia nigra to dorsal striatum), the mesolimbic (ventral tegmental area (VTA) to the ventral striatum), and the mesocortical (VTA to the prefrontal cortex) (Dahlstroem and Fuxe 1964, Ungerstedt 1973, Bjorklund and Dunnett 2007).

Dopamine Pathways

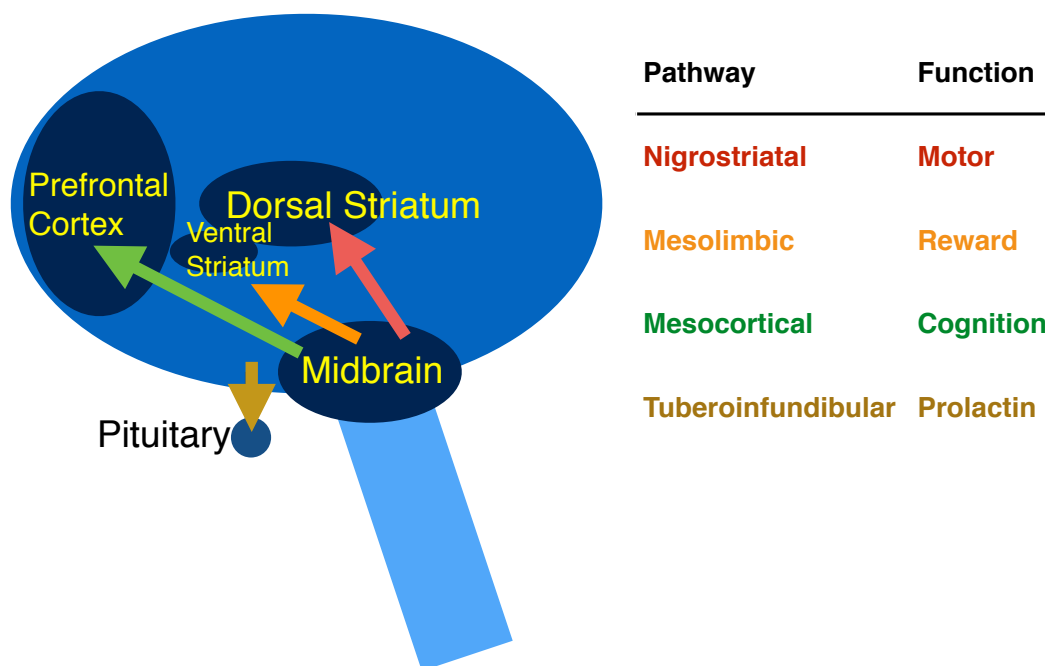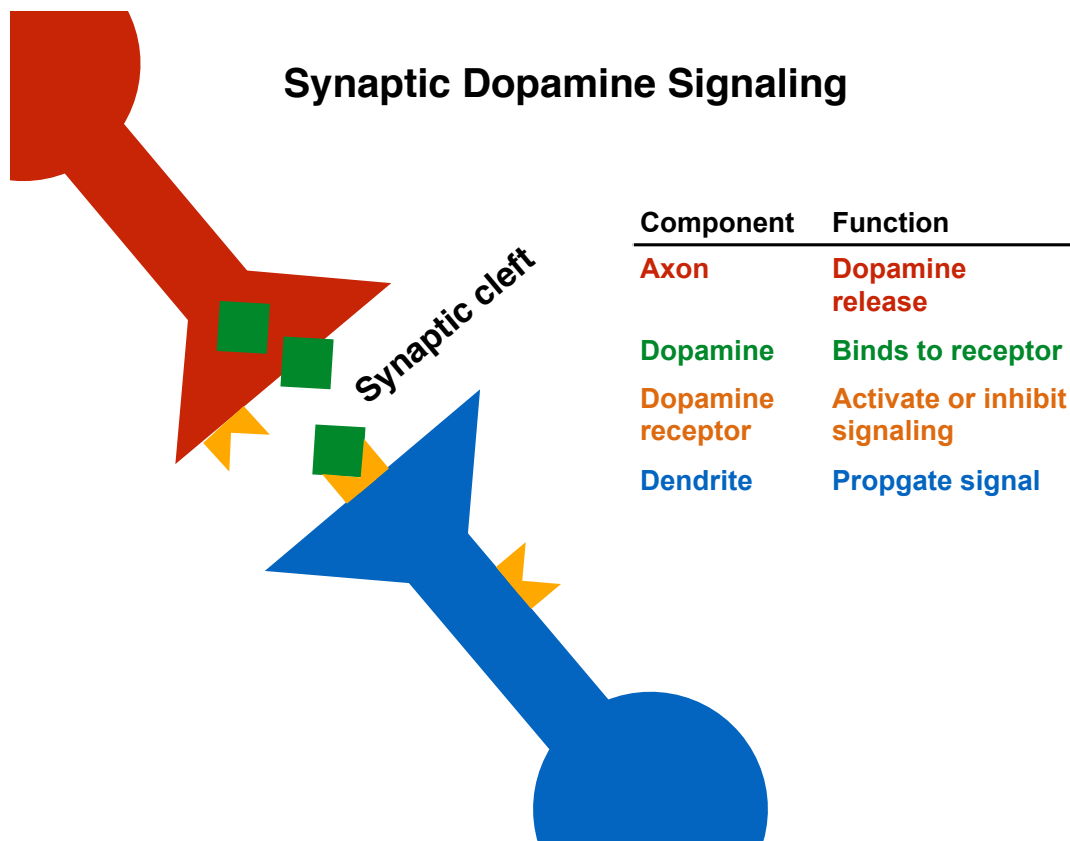| Pathway	Function
Nigrostriatal	**Motor**
Mesolimbic	**Reward**
Mesocortical	**Cognition**
Tuberoinfundibular	**Prolactin**

Figure 2. Illustration of a central sagittal section of the brain showing the major dopamine pathways.

Substantia nigra contains the largest dopamine cell group. It is subdivided into pars compacta, composed of motor-related neurons projecting to the dorsal striatum (caudate and putamen), termed the mesostriatal pathway, and pars reticulata, composed of reward-related neurons to the ventral striatum (nucleus accumbens) termed the mesolimbic pathway (Iversen and Iversen 2007).

2.4.2 Dopamine receptor subtypes

In general, neurotransmitters like DA are released from a neuron projection (axon) into a space (synaptic cleft) linked to the target neutron projection (dendrite) (Fig. 3). The neurotransmitter binds specifically to molecules, neuroreceptors, located in the cell membrane pre-, post- or extra synaptically. The binding activates or inhibits signaling in the target neuron. In addition to synaptic signaling, it is proposed that DA and other neurotransmitters in the CNS participate in volume transmission, i.e. via the transmitter

concentration in the extracellular fluid binding to extrasynaptical receptors (Agnati and Fuxe 2014).

Synaptic Dopamine Signaling

Component	Function
Axon	Dopamine release
Dopamine	Binds to receptor
Dopamine receptor	Activate or inhibit signaling
Dendrite	Propgate signal

Synaptic cleft

Figure 3. Illustration of components of synaptic dopamine transmission.

Five mammalian dopamine receptor(DR) subtypes (D_1 to D_5) have been identified and characterized (for review see (Missale et al. 1998, Beaulieu et al. 2015). They are grouped in two families based on biochemical, pharmacological and molecular characteristics, the D1-like (D_1 and D_5) and D2-like (D_2, D_3, and D_4) family. For simplicity, the present introduction uses the terms D1R and D2R for the D1R- and D2R-like family, respectively.

The original classification of DR was based on biochemical observations where DA modulate adenylyl cyclase (AC) activity through G proteins, the DR – cAMP cascade (Kebabian et al. 1972). Receptors that activate G proteins (G protein coupled receptors (GPCR)) constitute a large family of several hundred receptors in brain.

The D1R and D2R have different distribution in the human brain. The D1R is more abundant than the D2R because of its higher concentration throughout the neocortex (Lidow et al. 1991, Hall et al. 1994). The highest concentrations of D1R and D2R are in the basal ganglia where they have similar concentration levels (Hall et al. 1994).

At a subtype level messengerRNA (mRNA) for the D1-subtype has been found in the striatum, the neocortex, and all limbic regions of the human brain (Meador-Woodruff et al. 1996). The D5-subtype mRNA levels are generally lower throughout the brain and very low in the striatum (Beischlag et al. 1995).

In the striatum, D1R and D2R are expressed on inhibitory GABAergic medium-sized spiny neurons (MSN) (inhibiting neurons) constituting 75 % of the striatal neurons (Perez-Costas et al. 2010). The MSN are about 15 microns in diameter with large dendritic arborization about 0,5 mm in diameter. Most dendrites express either D1R or D2R whereas a few express both (Lester et al. 1993, Aizman et al. 2000). D1R is exclusively post-synaptic. In contrast D2R is expressed both post- and pre-synaptically (Sokoloff et al. 2006, Rankin et al. 2010).

However, the DR may in addition form heterocomplexes (combine with other types of receptors). For instance, a subpopulation of medium spiny neurons contains both D1R and D2R forming a heterodimeric protein complex (Lee et al. 2004). The D1-D2 heterodimer has a unique pharmacological and signaling profile distinct from its constituent monomer receptors. It has been suggested that these differences may have impact on the affinity for antipsychotic drugs and functional implications for neuropsychiatric disorders including schizophrenia (Hasbi et al. 2020). Besides the basal ganglia, D1-D2 heterodimer expression has been found in several cortical regions including the prefrontal cortex (Hasbi et al. 2020).

2.4.3 Dopamine and the prefrontal cortex

Of the many brain regions innervated by dopaminergic neurons, the dorsolateral prefrontal cortex (DLPFC) has attracted considerable interest in schizophrenia research. As the most recently developed brain region, in both phylogeny and ontogeny, the DLPFC has been proposed as the predominant site of mental disorders overall (Ghika 2008).

The DLPFC contains a large number of DR and is highly sensitive to inputs from midbrain dopaminergic neurons (Robbins 2000). The DA innervation of the DLPFC likely arises from salient DA neurons in the midbrain, that increase their firing to aversive as well as rewarding events (Bromberg-Martin et al. 2010, Kodama et al. 2014). This mesocortical input is part of a circuitry of neuronal connections between the cortex, the basal ganglia, the thalamus, and back to the cortex that comprises feedback loops that are of relevance for cognitive function (Fettes et al. 2017).

At a functional level it has been shown that D1R in the DLPFC has a role specifically in working memory (WM), which is the ability to hold mental representations for task solving and abstract thought (Goldman-Rakic 1992). This was early demonstrated in nonhuman primates (NHP) (Brozoski et al. 1979). Depletion of DA from the DLPFC was as detrimental to cognition as removing the cortex itself. These early experimental observations in animals stimulated discussions on the implications for schizophrenia research. Ken Davis and coworkers hypothesized that negative symptoms of schizophrenia results from frontal hypodopaminergia (Davis et al. 1991), This was partly based on the similarities between the behavior exhibited both by animals and humans with frontal lobe lesions and negative symptoms of schizophrenia (Brozoski et al. 1979). Moreover, it was demonstrated that the deficits could be reversed by L-dopa and apomorphine, a non-selective dopamine agonist. Later the findings were reproduced by local injections of selective D1R antagonists in the PFC, indicating that PFC working memory functions are mediated by D1R (Sawaguchi and

Goldman-Rakic 1991). Other experimental studies showed that D1R agonists reverse impaired cognitive function induced by DA depletion in the PFC or by DA antagonists (Murphy et al. 1996). More recent electrophysiological studies in healthy humans further demonstrate that blocking of prefrontal D1R compromises dopamine signals essential for learning and motivation (Gorelova et al. 2002, Hamid et al. 2016) Similarly, impaired working memory in nonhuman primates has been demonstrated by excessive D1R stimulation, e.g. with local D1R agonist infusion into DLPFC (Gamo et al. 2015), or during stress exposure when high levels of DA are released (Murphy et al. 1996), Hence, stimulation of D1Rs in DLPFC produces an 'inverted-U' dose-response on working memory whereby either too little or too much stimulation appears to impair cognitive performance.

DA acts at both D1R and D2R in the DLPFC, but D1R is the most prominent, especially in superficial layers of the brain cortex (Lidow et al. 1991, Smiley et al. 1994) where the receptor is expressed on the distal dendrites of excitatory pyramidal cortico-striatal projection neurons (motor neurons extending to the spinal cord). Modulation via D_1 receptors can influence both excitatory and disinhibitory microcircuits in the PFC (Anastasiades et al. 2019). D1R in layer 3 are preferentially expressed on a subset of spines (neuronal protrusions) of pyramidal cells (Smiley et al. 1994, Paspalas et al. 2013, Arnsten et al. 2015, Gamo et al. 2015). Spine density in patients with schizophrenia is lower in pyramidal neurons located in layer 3, a major site for cortico–cortico and thalamo-cortical integration (Glausier and Lewis 2018). Working memory depends on the activity of excitatory pyramidal cells in DLPFC layer 3 (Goldman-Rakic 1995).

Radiological investigations of the brain in patients with schizophrenia have consistently shown structural abnormalities such as enlarged ventricles, smaller whole-brain and frontal lobe volumes, due to gray matter loss (Lawrie and Abukmeil 1998, Steen et al. 2006, Levitt et al. 2010, Haukvik et al. 2013). Evidence suggests that the anatomical abnormalities are present before the onset of schizophrenia (Lawrie et al. 2001, Pantelis et al. 2003). Moreover, postmortem studies demonstrate that the frontal gray matter loss is not due to neuronal loss but reduced dendritic spine density, primarily in layer 3 pyramidal cells where D1R are abundant (Glantz and Lewis 2000, Thune et al. 2001).

The importance of D1R for negative and cognitive functions suggest that the anatomical and cellular changes in the DLPFC may be neural substrates for impaired D1R signaling in schizophrenia. Hence, at initiation of the present thesis work, it was hypothesized that impaired D1R transmission may underlie the negative and cognitive symptoms in schizophrenia.

2.5   PET STUDIES ON THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

The dopamine hypothesis of schizophrenia has in numerous studies been investigated in vivo with PET at both the presynaptic and postsynaptic level. One approach has been to study radioligand binding to the striatal dopamine transporter protein (DAT), serving as an index of the density of dopaminergic neurons. However a quantitative meta-analysis of 13 Single

Photon Emission Tomography (SPECT) and PET studies of DAT, gave no support for a significant difference between patients and controls (Fusar-Poli and Meyer-Lindenberg 2013).

Another early approach is to use $[^{11}C/^{18}F]$-DOPA to measure the pre-synaptic dopamine synthesis rate and storage in striatal dopamine neurons (Hietala et al. 1995). Here, two quantitative meta-analyses of 15 and 11 studies respectively supports a significant increase in patients compared to controls (d = 0.79 and Hedges' g = 0.867 respectively) (Howes et al. 2012, Fusar-Poli and Meyer-Lindenberg 2013).

The function of the presynaptic dopaminergic neuron has also been studied with SPECT and PET by measuring the reduction in a D2R radioligand binding following administration of amphetamine that releases dopamine from the neuron and elevates the concentration in the synaptic cleft. Four out of five studies using this approach found evidence of higher radioligand displacement in patients with schizophrenia compared with controls, three in the striatum (Laruelle et al. 1996, Breier et al. 1997, Abi-Dargham et al. 1998) and one in the DLPFC (Slifstein et al. 2015). One study using a D2R agonist radioligand did not find any such difference in the striatum (Frankle et al. 2018). Increased striatal dopamine transmission has also been supported by a dopamine depletion study, showing increased striatal baseline occupancy of dopamine at D2R in patients compared to controls (Abi-Dargham et al. 2000, Kegeles et al. 2010). Taken together, the findings of increased striatal dopamine synthesis capacity, release and baseline occupancy supports the dopamine hypothesis of a hyperdopaminergic state in the striatum in patients with schizophrenia.

At the postsynaptic level the D2R availability in the striatum has been examined in numerous studies, providing some evidence for a small increase in patients compared with controls (for review see (Howes et al. 2012). However, after controlling for antipsychotic treatment with D2R blocking drugs, the increase was not significant, but similar effect sizes suggest insufficient statistical power.

There were no PET-studies on D1R binding in patients with schizophrenia published at initiation of the present thesis work in the early 1990s. In an early PET-study in Japan low frontal D1R binding was reported in drug free patients with schizophrenia (Okubo et al. 1997). However, shortly thereafter a study was published showing elevated D1R binding in the DLPFC in patients with schizophrenia (Abi-Dargham et al. 2002). Moreover, the increased DLPFC D1R binding was a strong predictor of poor performance of working memory. In our first study (not included in the present thesis), we found no change in D1R in a small sample of antipsychotic naïve patients (Karlsson et al. 2002). The previous PET studies on frontal D1R are discussed in relation to study IV of the present thesis.

2.6 PET STUDIES ON THE DOPAMINE HYPOTHESIS OF ANTIPSYCHOTIC DRUG ACTION

Molecular imaging is not used in psychiatric practice in general since no imaging marker for any psychiatric disorder has been consistently demonstrated. However, PET has benefitted

the psychiatric practice of psychopharmacology by using well characterized selective PET radioligands showing target engagement and receptor occupancy in drug treated patients (Farde et al. 1988), for review see (Halldin et al. 2001). PET measurement of patients treated with clinically effective doses of antipsychotic drugs and low risk of extrapyramidal side effects (EPS) has consistently shown 75-80 % D2R occupancy (for review see (Ginovart and Kapur 2012). Subsequently, the traditional dosing of older antipsychotics like haloperidol was markedly reduced which has improved treatment compliance and outcome measures by reducing debilitating side effects without diminishing the specific antipsychotic effects.

Subsequently, drug development has benefitted from PET imaging by providing guidance on the optimal dose to be used in clinical trials (Halldin et al. 2001). The plasma concentration corresponding to 50 % occupancy (Ki-plasma), can be calculated from the "plasma concentration – receptor occupancy relationship" in a PET study and implemented to suggest the optimal dose in clinical trials. The present thesis applied this methodology to determine the dosing of the D1R antagonist SCH39166 (Study I) in a clinical trial (Study II).

2.7 THE ROLE OF THE D1 DOPAMINE RECEPTORS IN ANTIPSYCHOTIC DRUG TREATMENT

Even though all antipsychotic drugs are antagonists or partial antagonists at the D2R subtype (Farde et al. 1988, Yokoi et al. 2002), D1R occupancy has also been reported in patients treated with some antipsychotic drugs such as clozapine or flupentixol (Farde et al. 1992). Clozapine is the prototype for atypical antipsychotic drugs, defined as not causing the typical motor side effects of neuroleptics (Essali et al. 2009). The D1R-occupancy of clozapine at clinical treatment is relatively high when compared to other antipsychotic drugs whereas the D2R occupancy is lower (Farde et al. 1992). The mechanism of action of clozapine is not fully understood since this drug binds to a number of other receptors. However, based on the PET-findings mentioned above and an extensive literature on experimental studies (Creese and Chen 1985, Chipkin et al. 1988, Coffin et al. 1989, Farde 1992, Bourne 2001, Salmi et al. 2004, Jardemark et al. 2010, Arnsten et al. 2017), it has been suggested that D1R could be a drug target for antipsychotic effect.

The selective D1R antagonist SCH39166 was synthesized and developed as an antipsychotic drug by Schering-Plough, New Jersey (Chipkin et al. 1988). Preclinical tests in vitro and in vivo indicated potential antipsychotic effect similar to that of D2R antagonists but with reduced liability to produce EPS (Chipkin et al. 1988). The present thesis work was initiated at the time of the initial drug trials with SCH39166 in human subjects. The aim was to use SCH39166 as a test drug to examine the hypothesis that antipsychotic effect can be mediated by D1R blockade.

3 RESEARCH AIMS

The first aim of the present thesis was to use PET to facilitate the development of the potential antipsychotic drug SCH39166 in the human brain. SCH39166 was radiolabeled with carbon-11 and the binding was examined in humans. D1R occupancy of orally administered SCH39166 was estimated in healthy subjects. Finally, the antipsychotic effect and safety of SCH39166 was evaluated in an open study in acutely hospitalized patients with psychosis.

The second aim was to determine the repeatability of [11C]SCH23390 binding parameters in a methodological study using different methods of image analysis.

The third aim was to test aspects of the dopamine hypothesis of schizophrenia by comparison of regional D1R binding between healthy subjects and acutely ill antipsychotic drug-naïve patients with schizophrenia.

4 MATERIALS AND METHODS

4.1 ETHICAL CONSIDERATIONS

Ethical considerations served to identify and ameliorate study related risk factors that could compromise the participants physical and personal integrity. Physical safety issues of the experimental procedures were radiation exposure, pharmacodynamics, cannulation of blood vessels, immobilization, claustrophobia and compliance to the procedures. Personal integrity issues were competence of informed consent, dealing with possible deviant health parameters, collection of sensitive personal information. Amelioration was by weighing the issues against scientific quality of study design and resources. The Guidelines for Good Clinical Practice (GCP) by the European Medicines Agency was used ((ICH E6 (R2) Good clinical practice), which is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

4.2 PARTICIPANTS

The studies were approved by the Regional Ethical Board. The collection of arterial blood in study 1 was approved by the Stockholm County Council Biobank. The clinical trial with SCH39166 was approved by the Swedish Medical Products Agency. All use of the radioligands was approved by the Radiation Safety Committee at the Karolinska University Hospital.

A total of 41 healthy control subjects were included in study 1, 3 and 4. A total of 35 patients with first episode of schizophreniform psychosis were included in study 2 and 4.

All subjects were physically healthy according to history, physical examination, blood and urine chemistry, ECG and MRI or CT examination of the brain. Exclusion criteria were previous intake of any antipsychotic drug, history of drug allergy, alcoholism or drug addiction or significant somatic disorder. Further exclusion criteria for the healthy volunteers were history or presence of any psychiatric disorder and history of a psychiatric disorder in a first-degree relative.

4.3 CLINICAL RATINGS

Patients' clinical symptoms were rated by using the 18-item Brief Psychiatric Rating Scale (BPRS) (each item rated on a 0–6 scale) (Overall and Gorham 1962, Kolakowska 1976). The overall total rating and scores on positive and negative symptom clusters were used (Bech et al. 1986). The positive symptom cluster consists of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content (BPRS items 4, 11, 12, and 15). The negative symptom cluster consists of emotional withdrawal, motor retardation, and blunted affect (BPRS items 3, 13 and 16).

4.4 POSITRON EMISSION TOMOGRAPHY (PET)

PET is the cornerstone methodology utilized in study I, III and IV. It is an in vivo imaging technique that after intravenous injection measure molecules labelled with positron emitting nuclides (radioligands) in the body. An elaborate infrastructure is required to produce a radioligand and conduct the PET measurement (Fig. 4).

Positron Emission Tomography - infrastructure
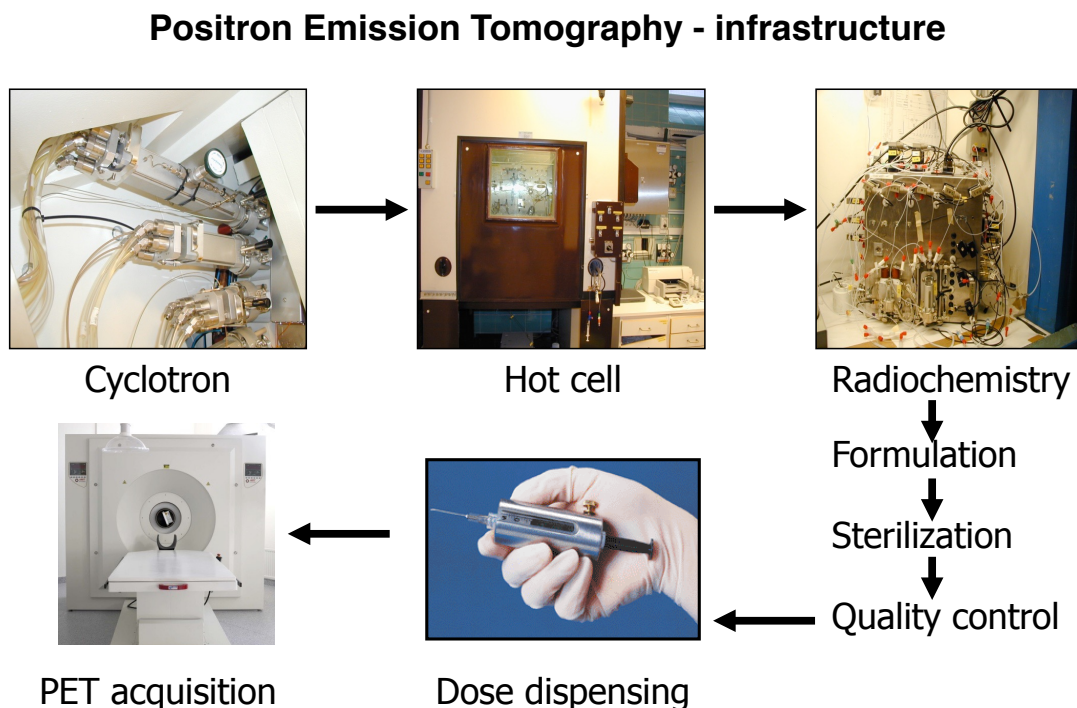
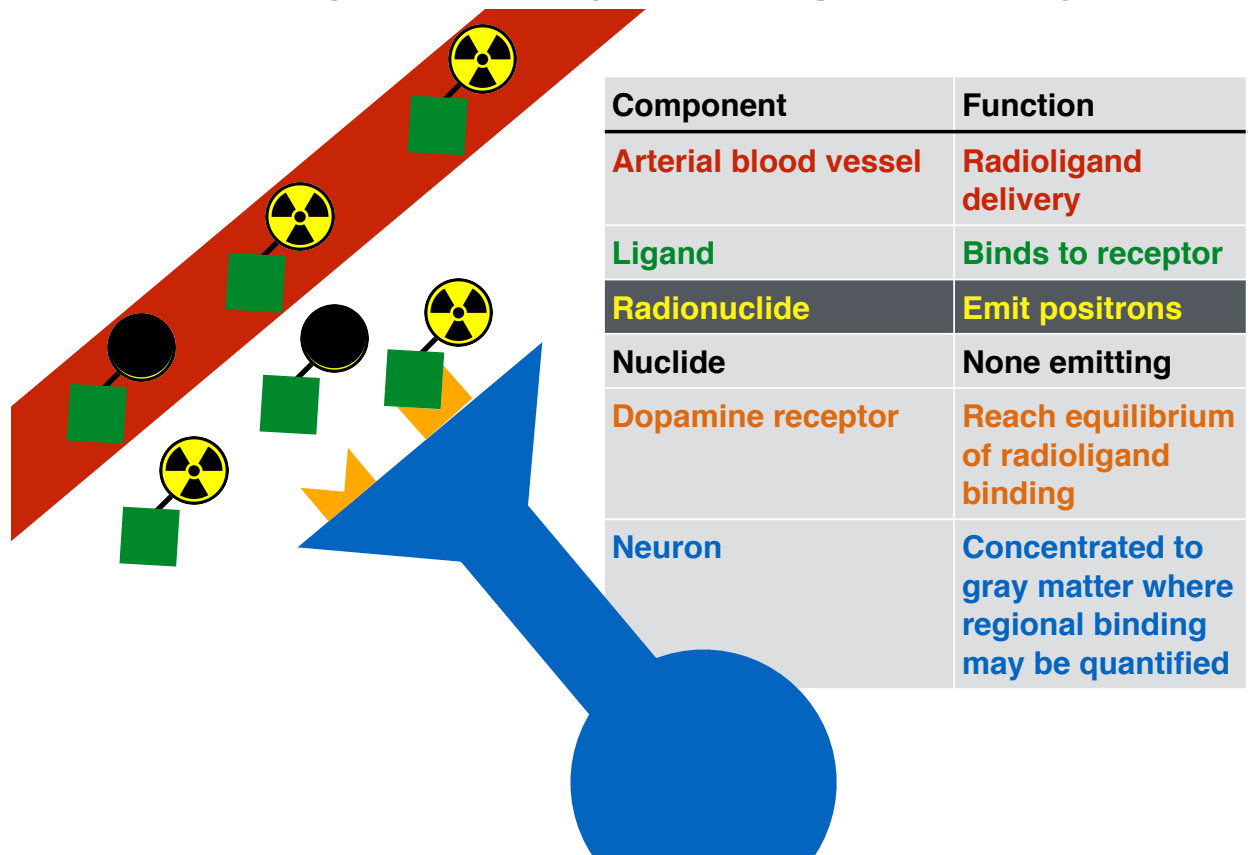**Figure 4.** *The equipment and procedures required to generate a PET-measurement.*

4.4.1 Brief description of principles for PET-imaging

The technology is based on the radiophysical properties of positron-emitting radionuclides. Such radionuclides do not occur naturally and has to be produced in a cyclotron (Fig. 4). Commonly used radionuclides are carbon-11 having a decay half-life of 20.3 min and fluor-18 with a half-life of 110 min.

Following production in a cyclotron the radionuclide is used to radiolabel a molecule of interest. In order to reduce the total mass and avoid pharmacological effects, a high proportion of the molecules are labelled with the radionuclide, termed high specific radioactivity or high molar activity. After quality control the radioligand is injected intravenously and transported via the blood stream to the brain (Fig. 5).
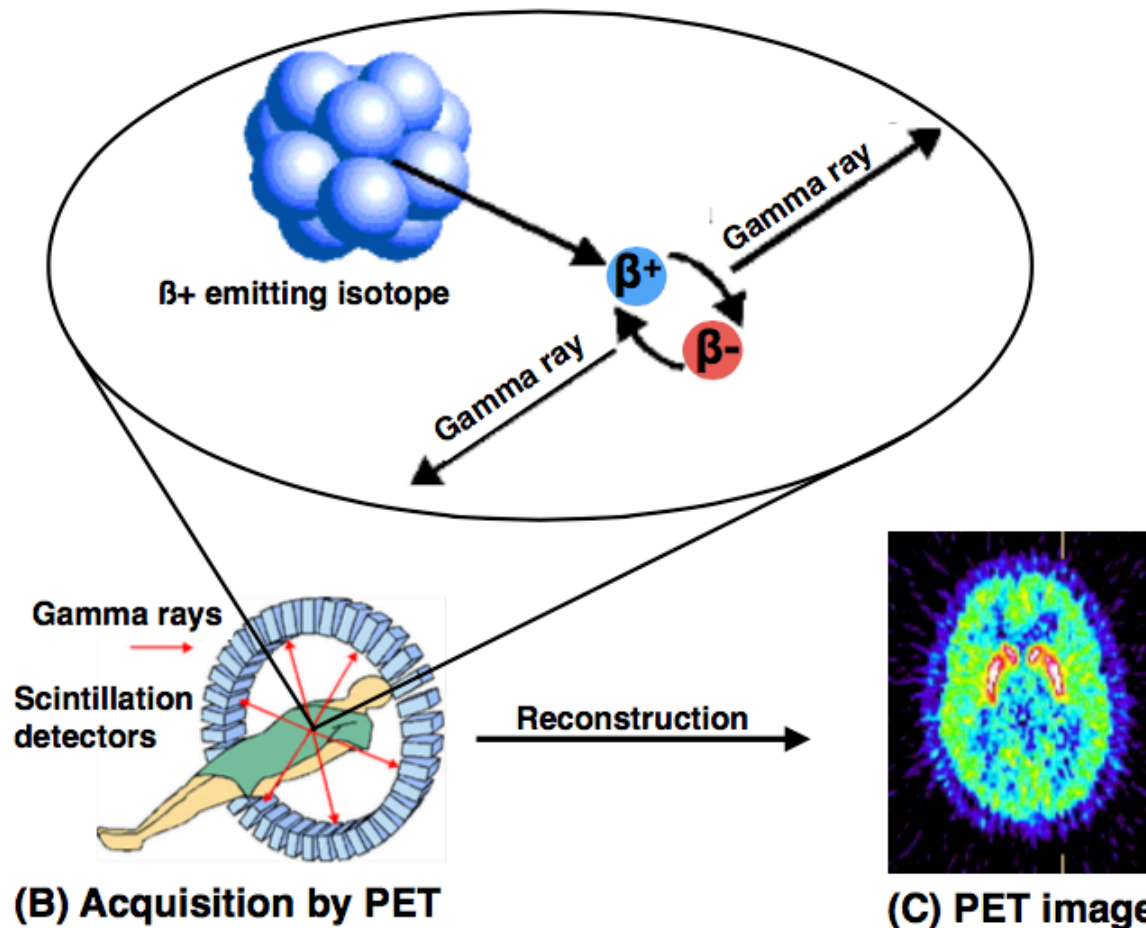
Radioligand delivery and receptor binding

Component	Function
Arterial blood vessel	Radioligand delivery
Ligand	Binds to receptor
Radionuclide	Emit positrons
Nuclide	None emitting
Dopamine receptor	Reach equilibrium of radioligand binding
Neuron	Concentrated to gray matter where regional binding may be quantified

Figure 5. Delivery and binding of a radioligand to a neuroreceptor.

At decay the radionuclide emits a positron which travels a short distance in tissue until it combines with an electron. The two particles annihilate, producing two 511 keV gamma rays that are emitted 180° apart (Fig. 6 A).


Figure 6. A-C Position emission and annihilation (A). Detectors co-registering gamma rays (B). Reconstructed PET image (C).

A PET system is based on a large number of gamma ray sensitive scintillators which are mounted in rings (Fig. 6 B). The subject, whether human or animal, is positioned in the gantry in the middle of the ring system. The pair of photons produced from a single annihilation will register almost simultaneously on opposing pairs of scintillation detectors as a "coincidence event."

The rings of scintillation detectors register thousands of coincidence events per second (Phelps and Mazziotta 1985, Cherry 2001). The multitude of events are then reconstructed in 3D, rendering a volume where each picture element (pixel) has a numerical value for the radioactivity concentration (nCi/cc or kBq/ml) (Fig. 6 C).

The PET images are segmented into anatomical or functional regions of interests (ROI) manually or by the aid of an anatomical atlas, based on information from structural magnetic resonance (MR) images (Fig. 7). In addition to co-registration the processing may entail

movement correction, gray and white matter segmentation, anatomical landmarks and surface-based reconstruction and smoothing.
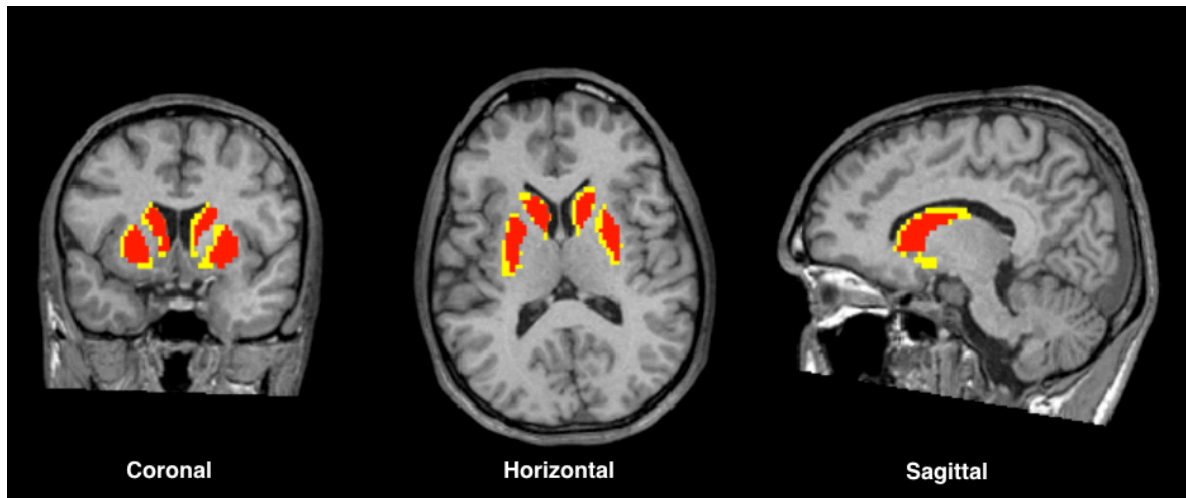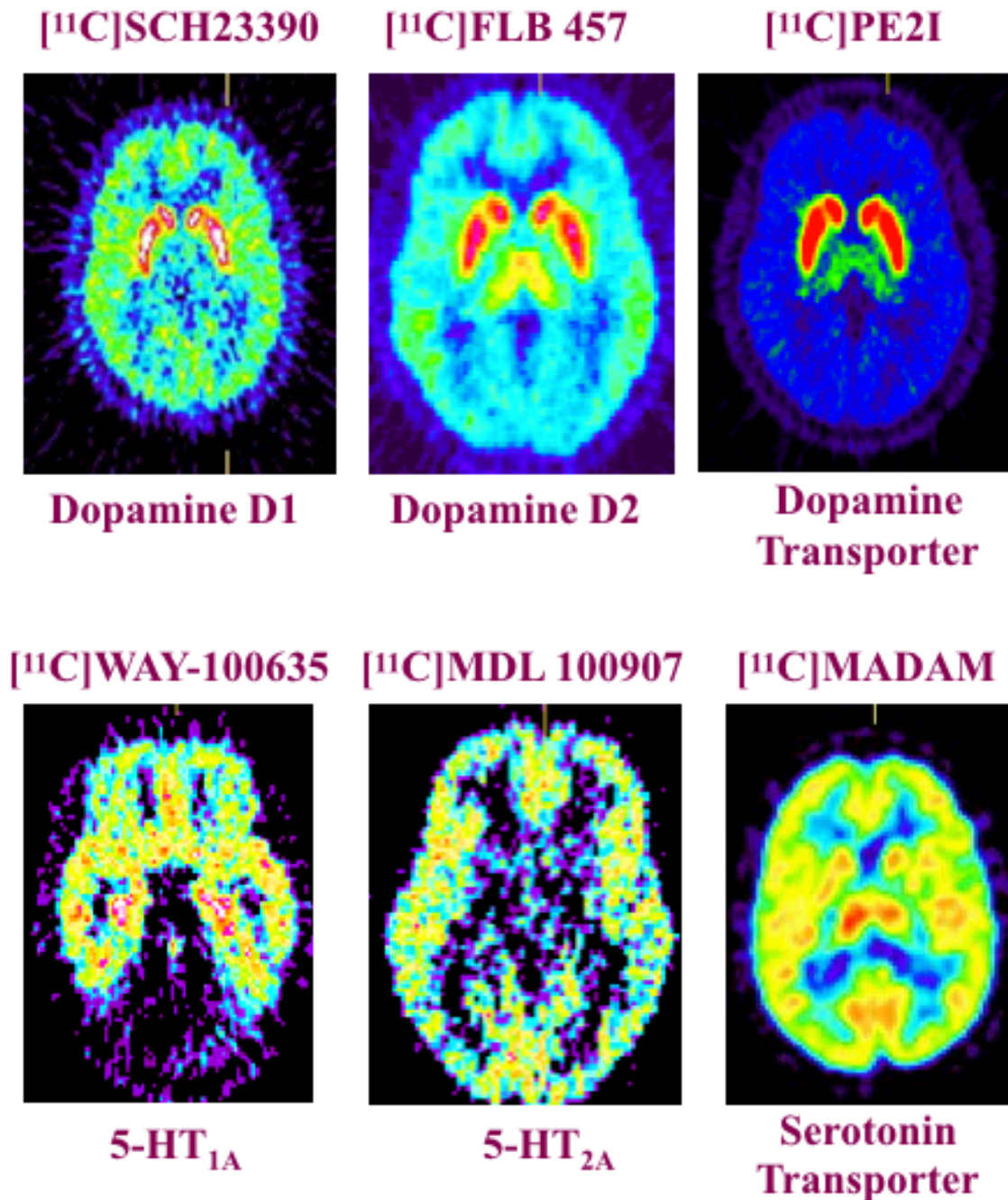

Figure 7. Color coded pixels extracted from Regions of interests (ROI's) of the striatum, superimposed on MRI images. Three orthogonal projections show pixels from manual (red) superimposed on automated (yellow) generated ROI's.

4.4.2 PET - molecular neuroimaging

Molecular neuroimaging is based on the availability of suitable radiolabeled molecules (radioligands) that after i.v. injection rapidly enters the brain and bind to the protein of interests. The target could for instance be a neurotransmitter receptor, a transport protein or an enzyme.

Over the years, several neurotransmitter systems have been studied in animals, healthy subjects and patient populations with psychiatric disorders using PET. The dopaminergic system has been the most extensively investigated in terms of both pre-synaptic and post-synaptic biological markers (Fig. 8) (Halldin et al. 2001).

[¹¹C]SCH23390 — Dopamine D1
[¹¹C]FLB 457 — Dopamine D2
[¹¹C]PE2I — Dopamine Transporter

[¹¹C]WAY-100635 — 5-HT$_{1A}$
[¹¹C]MDL 100907 — 5-HT$_{2A}$
[¹¹C]MADAM — Serotonin Transporter

Figure 8. *Color coded trans axial PET images of the brain of healthy volunteers showing regional distribution of different radioligands developed at Karolinska Institutet.*

The key radioligand used in the present thesis work is [¹¹C]SCH23390. A widely used reference radioligand for neuroreceptor imaging of D1R originally developed (Halldin et al. 1986) and subsequently applied in clinical studies at Karolinska Institutet (Farde et al. 1987, Farde et al. 1989, Wiesel et al. 1990, Farde 1992, Farde et al. 1992, Sedvall et al. 1994, Karlsson et al. 1995, Nordstrom et al. 1995, Ginovart et al. 1997, Karlsson et al. 2002, McNab et al. 2009, Jucaite et al. 2010). The thesis work also includes radiolabeling and PET examination of the potential antipsychotic drug SCH39166 (Chipkin et al. 1988, Halldin et al. 1991).

4.4.3 MR and PET image processing

The processing of the MRI and PET images are described in detail in the PET studies of the thesis. The image processing has developed considerably during the thesis work particularly from manual to automated procedures. A manual procedure was used in Study I whereas automated procedures were used in Study III and IV.

Both the manual and automated methods had the T1-weighted MR images pre-processed to have the brain oriented in a standardized symmetrical manner. In brief, the MR images were reoriented to have the line defined by the anterior and posterior commissures (nerve bundles connecting the brain hemispheres), termed the AC-PC line, parallel to the horizontal plane (divides the brain top and bottom) and the sagittal plane (divides the brain left and right). The MR images were then co-registered to the summation PET image (9-51 min) using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) using the Normalized Mutual Information algorithm (Studholme et al. 1998) and the default 7x7 FWHM smoothing of the 256x256 joint histogram.

Manual ROI's (study I and III): The MR images were used to delineate regions of interest (ROI's) such as the caudate nucleus (CAU), the putamen (PUT), the dorsolateral prefrontal cortex (DLPFC) and the cerebellum (CER). The regions were chosen to represent regions of central interest in schizophrenia research. An in-house software, HBA (Roland et al. 1994), was used where the pre-processed MRI images were loaded for manual delineation of the ROI's on any of the three orthogonal projections. The manual delineation was performed by the author. The CAU and PUT were delineated as described by Mawlawi et al. (Mawlawi et al. 2001), with the modification that the sagittal planes were used instead of the coronal (divides the brain front to back). The DLPFC was traced on all the coronal planes anterior to the genu of the corpus callosum (nerve bundles connecting the brain hemispheres). The cerebellum was drawn on the central six transaxial images of the cerebellum about 1 cm distant from the subarachnoidal space (a liquid filled space surrounding the brain). The ROI's were translated into the PET study space using the inter-modality coregistration matrices.

Automated ROI's (study III, IV): The automated definition of target ROI's was performed using FreeSurfer (FS, version 5.0.0, http://surfer.nmr.mgh.harvard.edu/) (Fischl 2012) to obtain subject-specific anatomical delineation by reconstruction of the cortex and segmentation of subcortical structures as described elsewhere (Dale et al. 1999, Fischl et al. 1999). The FreeSurfer morphometric procedures have been shown to exhibit good reproducibility across scanner manufacturers and across different field strengths (Han et al. 2006, Reuter et al. 2012), and have been validated against histological (Rosas et al. 2002) as well as manual measurements (Kuperberg et al. 2003). In addition, the cortical structures are divided based on individual cortical folding patterns to match cortical geometry across subjects (Fischl et al. 1999).

Time activity curves: The ROI data sets (manual and automated) were applied to extract regional time–activity curves (TAC's) of the radioactivity concentration from the PET images.

Calculation of binding potential values (studies I, III, IV): The regional binding potential (BP) values for radioligand binding to D1R were calculated with the equilibrium method (study I) (Farde et al. 1989) and with the Simplified Reference Tissue Model using the cerebellum curve as estimate for non-specifically bound radioligand (Lammertsma and Hume 1996). Both methods of calculation require TAC's of sufficient duration in order to reach equilibrium, i.e. when the rates of binding and releasing of the radioligand receptor complex is equal. This allows for assumptions needed for the methods to be valid based on the law of mass action (definition). Most radioligands require between 20 and 60 minutes to reach equilibrium. This means that a PET measurement is considerably longer than any radiological investigation.

5 RESULTS

5.1 STUDY I

Background and methods: SCH39166 was the first selective D1-dopamine receptor antagonist developed for clinical trials in schizophrenia. In the present study, SCH39166 and its enantiomer SCH39165 were radiolabeled with ^{11}C and [^{11}C]SCH39166 was evaluated as a radioligand for PET. In addition, D1R occupancy was estimated after single oral doses in healthy subjects.

Results: After intravenous injection of [^{11}C]SCH39166 the distribution of radioactivity in brain grossly reflected D1R density (Fig. 1 B). The putamen to cerebellum ratio at equilibrium was low (1.54 ±0.18 SD)..
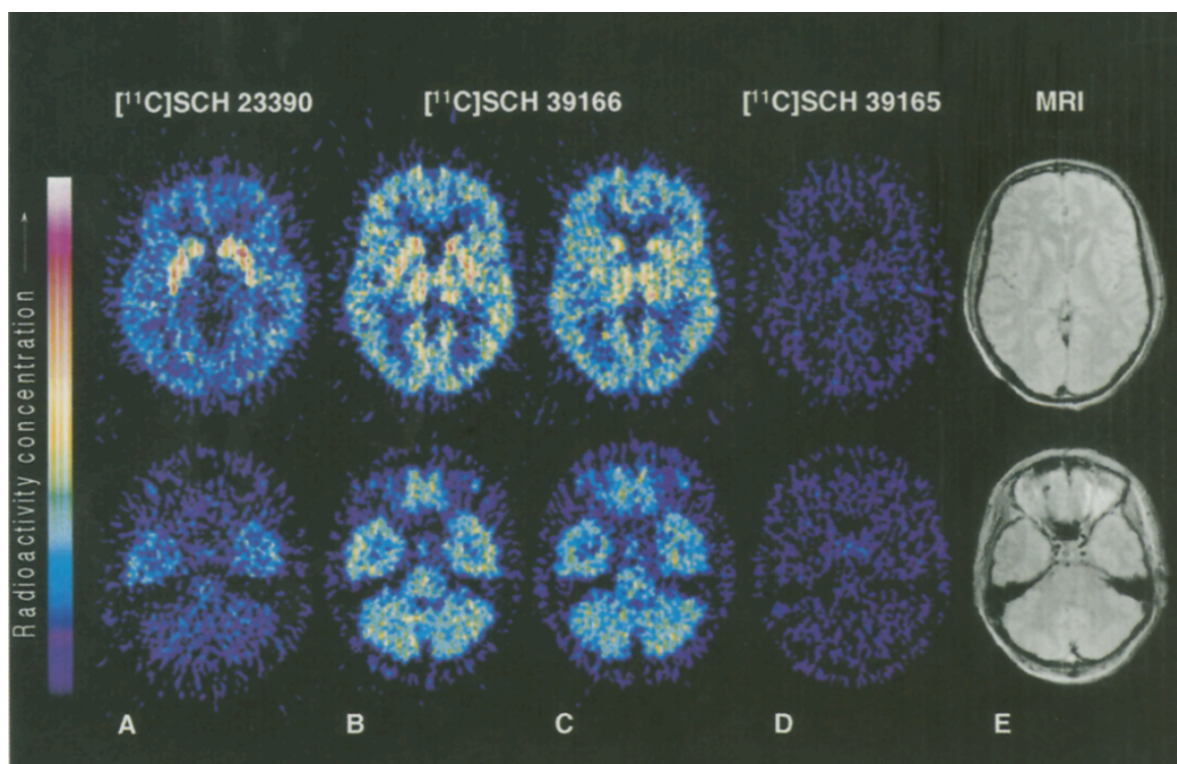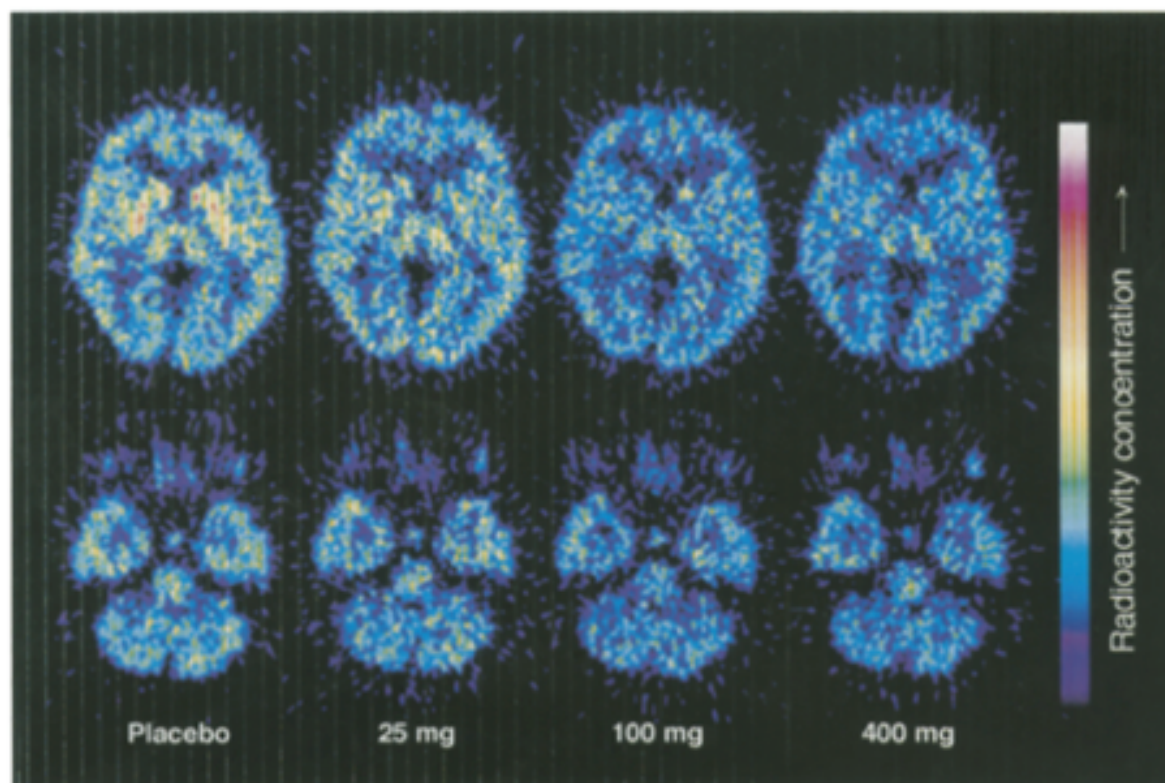

Figure 1. *A-E Horizontal PET images at the level of striatum (upper panels) and cerebellum (lower panels) in healthy males after IV injection of [^{11}C]SCH23390 (A), [^{11}C]SCH39166 high (B) (subject 5) and low (C) (subject 5) specific radioactivity, [^{11}C]SCH 39165 (D) (subject 5). In E a corresponding MR image is shown. PET images show accumulated radioactivity 9-63 minutes normalized to injected dose of radioactivity.*

Saturability of specific binding was demonstrated after IV injection of [^{11}C]SCH39166 with low specific radioactivity (Fig. 2). Stereospecificity of binding was confirmed using the stereoisomer [^{11}C]SCH39165.
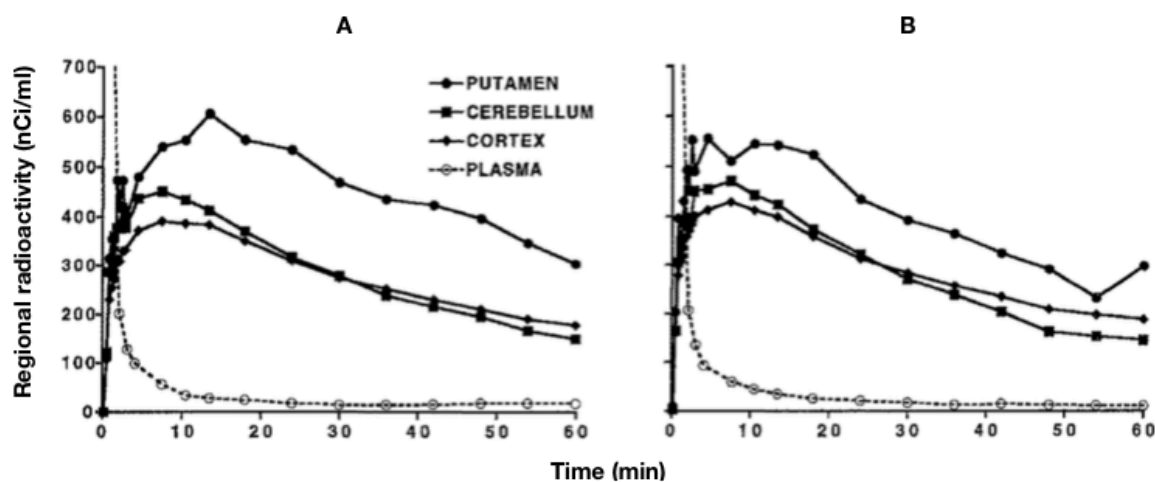
Figure 2. Time activity curves in brain regions and plasma after i.v. injection [^{11}C]SCH39166 with high (A) and low (B) specific radioactivity in a healthy subject (no. 5). Radioactivity in B is normalized to cerebellum in A (AUC 9-45 min).

D1-Receptor occupancy was demonstrated with [^{11}C]SCH39166 after simultaneous administration of intravenous low doses of SCH39166 to six subjects and 2 h after single oral doses of SCH39166 to each of three healthy subjects (25, 100 and 400 mg) (Fig. 3). There was a substantial reduction of specific [^{11}C]SCH39166 uptake in the putamen after all doses.

Figure 3. Horizontal PET images of the brain at the level of striatum (upper panels) and cerebellum (lower panels) after i.v. injection [^{11}C]SCH39166 before and after single oral doses of SCH39166 (25, 100 and 400 mg) in a healthy man (no. 8). PET images show accumulated radioactivity 9-63 min normalized to unchanged [^{11}C]SCH39166 in plasma.

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Single oral doses of 100 mg induced approximately 70 % D1-dopamine receptor occupancy in the putamen (Table 1),

Table 1. DlR occupancy in the putamen, mean plasma concentration and inhibition constant Ki(plasma) after oral doses of SCH39166. Ki(plasma) was estimated using the calculated D1-dopaminereceptor occupancy value and the corresponding plasma concentration of SCH39166.

Subj. no.	SCH 39166 oral dose (mg)	D1R occupancy (%)	Plasma conc. (ng/ml)	$K_{i\ (plasma)}$ (ng/ml)
7	25	60	6.5	4.3
	100	65	25	13
	400	69	110	49
8	25	49	9.8	10
	100	78	28	7.8
	400	78	167	47
9	25	51	9.1	8.8
	100	73	33	12
	400	60	71	48

5.2   STUDY II

Background and aims: SCH39166 is a D1R antagonist with potential as an antipsychotic drug and has previously been examined in healthy subjects. In this first clinical study the potential antipsychotic effect, tolerability and safety of SCH39166 was examined,

Methods: SCH39166 was given orally to 17 acutely ill drug free patients with schizophrenia (DSM-IIIR) in an open 4-week study (Table 1). Doses were escalated from 10 to 100 mg b.i.d. according to a fixed schedule over 17 days and remained at 100 mg b.i.d. for another 11 days.

Table 1 Demographic data for 17 patients with schizophrenia or schizophreniform psychosis participating in an open clinical study of SCH 39166

Patient	Age (years)	Sex (M/F)	Subtype	Duration at admission	Treatment before study	Neuroleptic free before study
1	26	M	Paranoid	<6 months[a]	naive	
2	47	M	Paranoid	31 years	perphenazine	6 months
3	20	M	Undiff.	<6 months[b]	naive	
4	28	M	Catatonic	2 years	naive	
5	26	M	Paranoid	1 year	haloperidol	10 months
6	30	M	Paranoid	9 years	remoxipride	6 months
7	24	M	Paranoid	2 years	haloperidol	1 year
8	38	M	Paranoid	14 years	fluphenazine	11 years
9	36	M	Paranoid	10 years	haloperidol	4 months
10	28	M	Paranoid	3 years	haloperidol	1 year
11	31	M	Undiff.	9 years	melperone	4 days
12	28	M	Disorganized	6 years	perphenazine	8 days
13	29	M	Paranoid	1 year	naive	
14	26	M	Undiff.	2 years	remoxipride	4 days
15	26	M	Disorganized	<6 months[a]	naive	
16	27	M	Paranoid	<6 months[b]	naive	
17	56	F	Disorganized	36 years	clozapine	5 days

[a] Schizoaffective at follow-up
[b] Schizophrenia at follow-up

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Results: The drug was withdrawn prematurely in ten patients because of deterioration or refusal to take SCH39166. In the nine patients participating for more than 2 weeks, none had an apparent reduction of BPRS or CGI scores (Fig. 1 and Table 2 respectively). Side effects were agitation, akathisia and emesis in single patients. After withdrawal of SCH39166 the patients improved clinically when treated with classical neuroleptics or clozapine.
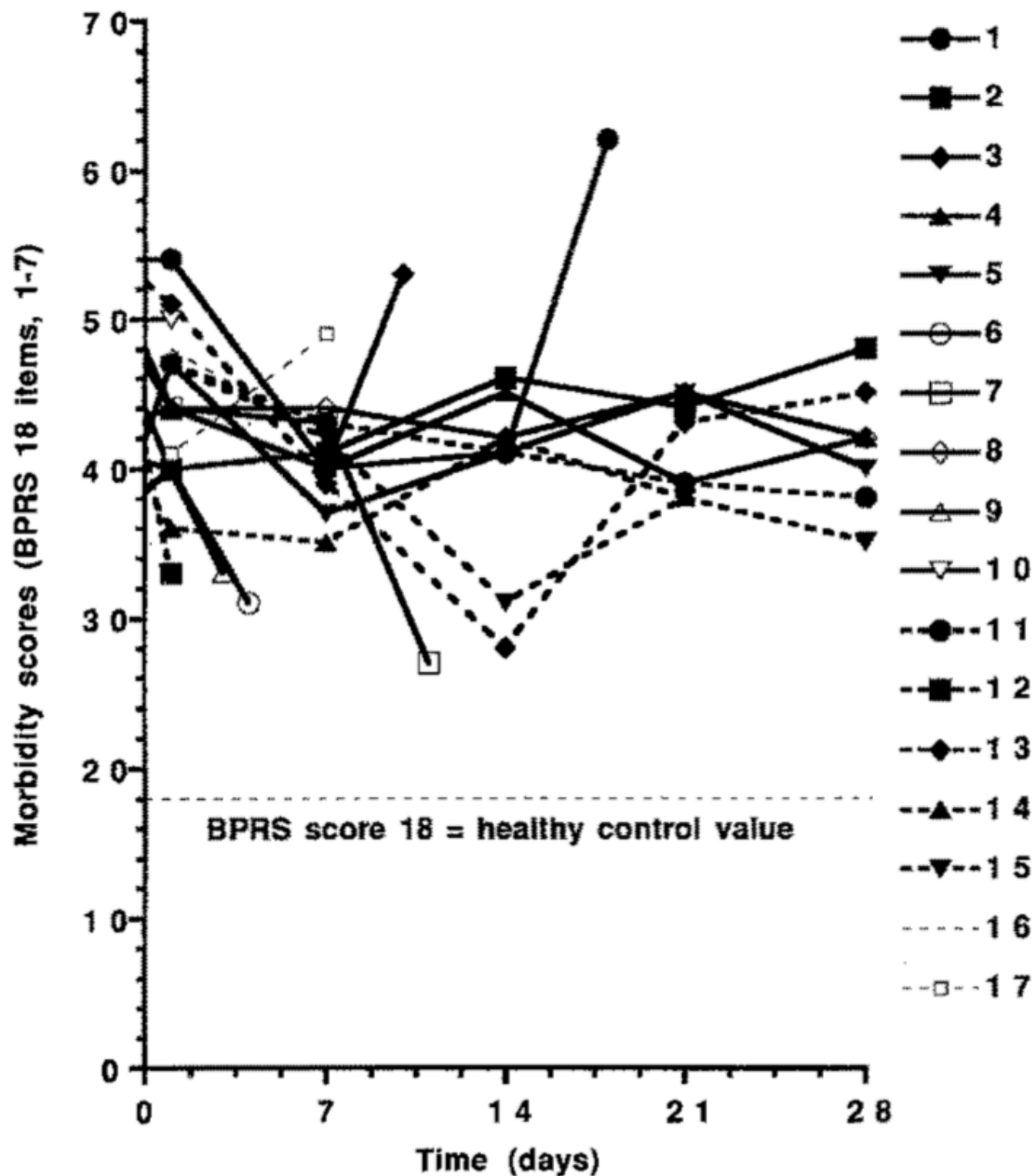
Figure 1. Total BPRS score of 17 acutely ill schizophrenic, schizophreniform or schizoaffective patients before and during oral treatments with SCH39166.

Table 2. Clinical Global Impression scores in patients treated with SCH39166. Last assessment during the SCH39166 study was made at the last day of treatment. Assessment after the study was made at discharge from the hospital, 0 not assessed, / normal, 2 borderline mentally ill, 3 mildly ill, 4 moderately ill, 5 markedly ill, 6 severely ill, 7 extremely ill.

Patient	CGI score (illness severity)						Treatment after	
	Baseline	SCH 39166 treatment						
		1w	2w	3w	4w		SCH 39166	At discharge
1	6	4	4	6	5		haloperidol+Li	1
2	6	5	5	5	5		perphenazine	2
3	6	6	5				zuclopenthixol	2
4	5	5	5	5	5		haloperidol	4
5	5	5	5	5	5		haloperidol	2
6	5	6	6				haloperidol	2
7	5	5	5				zuclopenthixol	3
8	5	5	5				thioridazine	4
9	5	5	5	5	5		haloperidol	1
10	6	5	6				haloperidol	2
11	5	5	5	5	5		flupentixol dec	3
12	3	3	5	5	5		thioridazine	2
13	5	4	3	4	5		remoxipride	2
14	4	3	4	4	5		clozapine	3
15	4	5	3	5	5		haloperidol	2
16	5	5	5				perphenazine	2
17	5	5	5				clozapine	3

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5.3 STUDY III

Background and aims: The D1R radioligand [^{11}C]SCH23390 has been frequently used in PET studies. In drug-naïve patients with schizophrenia, the findings have been inconsistent, with decreases, increases, and no change in the frontal cortex D1R (Cervenka 2018). While these discrepancies are likely primarily due to a lack of statistical power in these studies, we speculated that an additional explanation may be the differences due to methods of image analysis between studies, affecting reliability as well as bias between groups.

Methods: Fifteen healthy subjects underwent two PET measurements with [^{11}C]SCH23390 on the same day. The binding potential (BP$_{ND}$) was compared using a 95 % confidence interval following manual and automated delineation of a region of interest (ROI) as well as with and without frame-by-frame realignment.

Results: Automated target region delineation produced lower BP$_{ND}$ values, while automated delineation of the reference region yielded higher BP$_{ND}$ values (Table). However, no significant differences were observed for repeatability using automated and manual delineation methods. Frame-by-frame realignment generated higher BP$_{ND}$ values and improved repeatability.

Table. ROI volumes and binding potential (BP$_{ND}$) values for [^{11}C]SCH23390 binding obtained by two repeated PET measurements analyzed by three different comparisons of methods: (1) ROI method (manual (Man)/FreeSurfer (FS)), (2) movement correction (no realignment/realignment), and (3) definition of the cerebellum as reference region (manual/modified FSL).

	CAU		PUT		DLPFC		INS		CBL	
ROI volume by ROI method (mL)	Man	FS	Man	FS	Man	FS	Man	FS	Man	FSL
Median	6.5	9.5	8.4	13.0	39.3	53.7	10.8	16.6	7.6	8.1
Interquartile range	5.7–8.8	8.8–9.9	8.0–9.4	12.4–13.8	37.4–43.4	49.2–57.2	10.0–11.1	16.4–18.2	6.3–8.3	6.9–10.1
CoV %	16.4	8.9	12.9	8.4	15.8	10.0	9.1	8.0	19.2	21.1
Mean diff (CI 95%)	−3.1 (−3.4, −2.8)[a]		−4.5 (−5.0, −3.9)[a]		−12 (−15.9, −9.8)[a]		−6.7 (−7.4, −6.0)[a]		−1.0 (−2.0, −0.4)[a]	
BP$_{ND}$ by ROI method	Man	FS	Man	FS	Man	FS	Man	FS		
Median	1.65	1.39	1.85	1.62	0.32	0.26	0.55	0.53		
Interquartile range	1.43–1.76	1.14–1.52	1.72–1.88	1.49–1.68	0.26–0.33	0.21–0.29	0.50–0.58	0.50–0.57		
CoV %	16.1	20.9	7.0	8.9	17.0	19.4	8.8	8.4		
Mean diff (CI 95%)	0.28 (0.24, 0.31)[a]		0.20 (0.17, 0.23)[a]		0.05 (0.04, 0.06)		0.01 (0.01, 0.02)			
BP$_{ND}$ by realignment	No realign	Realign	No realign	Realign	No realign	Realign	No realign	Realign		
Median	1.46	1.57	1.74	1.73	0.27	0.30	0.54	0.53		
Interquartile range	1.24–1.63	1.33–1.65	1.61–1.81	1.61–1.75	0.21–0.29	0.26–0.32	0.50–0.58	0.50–0.58		
CoV %	22.1	14.7	9.0	9.7	21.2	15.4	8.8	8.2		
Mean diff (CI 95%)	−0.10 (−0.16, −0.05)[a]		0.00 (−0.03, 0.03)		−0.04 (−0.05, −0.02)[a]		0.00 (−0.01, 0.01)			
BP$_{ND}$ by reference region	Man CBL	FSL CBL	Man CBL	FSL CBL	Man CBL	FSL CBL	Man CBL	FSL CBL		
Median	1.49	1.53	1.70	1.77	0.28	0.29	0.52	0.55		
Interquartile range	1.26–1.62	1.31–1.67	1.58–1.76	1.63–1.80	0.22–0.30	0.25–0.31	0.49–0.57	0.51–0.58		
CoV %	18.7	17.6	8.3	7.3	18.8	16.9	8.8	8.3		
Mean diff (CI 95%)	−0.04 (−0.06, −0.03)[a]		−0.05 (−0.06, −0.03)[a]		−0.02 (−0.03, −0.01)[a]		−0.03 (−0.03, −0.01)[a]			

The values were obtained from four brain regions in 15 subjects, each value represents the mean of the eight values for that measurement or part of the analysis.

Interquartile range = 25th to 75th percent

CoV coefficient of variation, CI confidence interval

a The confidence interval does not contain zero

5.4 STUDY IV

Background and aims: PET studies examining differences in D1-dopamine receptor binding between control subjects and patients with schizophrenia have been inconsistent, reporting higher, lower, and no difference in the frontal cortex (Cervenka 2018). Exposure to antipsychotic medication has been suggested to be a likely source of this heterogeneity. We hypothesized higher DLPFC D1R availability in patients compared with controls based on the previous literature on D1R in psychosis showing higher frontal D1R primarily in drug-naïve patients and individuals at high risk in the majority of studies (Abi-Dargham et al. 2002, Hirvonen et al. 2006, Abi-Dargham et al. 2012). Hence, there is a need for studies of patients at early stages of the disorder who have not been exposed to such drugs.

Methods: Here, we compared 17 healthy control subjects and 18 first-episode neuroleptic naïve patients with schizophrenia or schizophreniform psychosis (Table 1) using positron emission tomography and the D1-dopamine receptor radioligand [^{11}C]SCH23390. The brain regions selected a priori for comparisons were the striatum and the DLPFC since these regions are frequently implicated in the literature on central D1R and schizophrenia.

Table 1. Demographic characteristics and BPRS scores for 18 patients with schizophrenia or schizoaffective disorder.

Patient no	Age (y)	Sex	BPRS total score	BPRS positive symptoms score	BPRS negative symptoms score	Diagnosis at 1-year follow-up
1	28	F	48	18	9	Schizophrenia
2	21	M	46	15	15	Schizophrenia
3	35	F	52	17	7	Schizoaffective disorder
4	19	F	37	15	10	Schizophrenia
5	22	M	26	11	4	Schizophrenia
6	32	M	50	19	12	Schizoaffective disorder
7	22	M	41	15	11	Schizophrenia
8	39	M	60	24	9	Schizophrenia
9	35	M	59	24	9	Schizophrenia
10	33	F	36	14	9	Schizophrenia
11	32	M	33	16	3	Schizophrenia
12	41	M	27	11	5	Schizophrenia
13	41	M	31	14	5	Schizophrenia
14	36	F	33	18	3	Schizophrenia
15	21	M	41	16	10	Schizophrenia
16	49	M	41	14	13	Schizophrenia
17	51	F	58	24	15	Schizophrenia
18	22	F	35	7	3	Schizophrenia

Results: We observed a statistically significant difference in the dorsolateral prefrontal cortex (Table 2 and 3). Contrary to our expectations, patients had less D1-dopamine receptor availability with a moderate effect size.

Table 2. Group means and SD of BP_{ND} for all presented regions

Region	Control	Patient	Analysis
STR	1.61 (0.24)	1.53 (0.21)	A Priori
DLPFC	0.34 (0.075)	0.28 (0.061)	A Priori
ACC	0.40 (0.067)	0.39 (0.089)	Exploratory
TC	0.41 (0.078)	0.36 (0.063)	Exploratory
MPFC	0.37 (0.076)	0.36 (0.098)	Exploratory
OFC	0.40 (0.089)	0.37 (0.090)	Exploratory

These are the raw BP_{ND} values without any correction for age.

In a Bayesian analysis, we show that the data are over 50 times more likely to have occurred under the decrease as opposed to the increase hypothesis (Table 3). This effect was not global, as our analysis showed that the null hypothesis was preferred over either hypothesis in the striatum.

Table 3. Bayes factors comparing each hypothesis (Rows) against each other hypothesis (Columns) for the test of differences in BP_{ND} between psychosis patients and controls.

Model	Increase	Decrease	Null
DLPFC			
Increase	1	0.02	0.07
Decrease	55.25	1	3.69
Null	14.97	0.27	1
Striatum			
Increase	1	0.41	0.12
Decrease	2.46	1	0.3
Null	8.11	3.29	1

6 DISCUSSION AND CONCLUSIONS

6.1 STUDY I

[^{11}C]SCH39166 binds is a saturable and stereoselective manner to D1R in the human brain. However, the low contrast makes [^{11}C]SCH39166 less suitable for detailed regional mapping of D1R. An oral dose of 100 mg should be appropriate to investigate the antipsychotic potential of D1R antagonism in clinical studies.

The D1R occupancy after the oral doses did not increase with the increased doses as expected. Hence, the Ki-plasma values increased several folds after 400 mg compared to that after 25mg. Theoretically, this could be due to specific binding in the cerebellum, which in figure 2 of one of the subjects seems to be somewhat reduced with the increasing doses. Radioactivity in blood was measured in the experiments with high and low specific radioactivity (Fig. 1 and 2). After low specific radioactivity, the cerebellum to plasma ratio changed on average by -0.2 % (-25 to +29 %, mean ±range) compared to that after high specific radioactivity. However, the doses in the IV experiments were relatively low so that the subsequent Ki-plasma values were more similar among the doses. Hence, most likely the D1R occupancy values after the higher oral doses were underestimated due to specific binding in the cerebellum. Based on the Ki for the low dose the high dose D1R occupancy should have been close to 90 %.

6.2 STUDY II

The result of the study does not support the prediction that selective D1R antagonism will produce antipsychotic effects in schizophrenia. This was an open study but Schering-Plough viewed the results as sufficiently conclusive to withdraw SCH39166 from further development in treating schizophrenia. However, clinical trials with SCH39166 in other disorders with dopamine dysfunction such as Tourette's syndrome, Restless Legs Syndrome, stuttering and gambling disorder, has shown favorable results (Grant et al. 2014, Maguire et al. 2019, Billnitzer and Jankovic 2020, Ondo and Olubajo 2020). D1R active drugs continue to be engaged in both academia and the pharmaceutical industry in order to be translated into clinical practice in schizophrenia (for review see (Arnsten et al. 2017).

6.3 STUDY III

The results suggest that the choice of ROI delineation method is not an important factor for reliability, whereas the improved repeatability following movement correction confirm its importance in PET image analysis. Realignment is therefore especially important for measurements in patient populations such as schizophrenia or Parkinson's disease, where motion artifacts may be more prevalent.

6.4 STUDY IV

This investigation represents the largest single sample of neuroleptic-naïve patients examined for D1-dopamine receptor availability using PET and suggests a reduction of

prefrontal D1-dopamine receptor density in the pathophysiology of schizophrenia. However, further work will be required to reach a consensus.

The comparison of D1R showed considerable overlap. As comparison subjects are defined as "normal" based biomarkers that may have high interindividual variability, a hypothesized pathophysiology may overlap considerably between a group of healthy individuals and patients. Hence, the present results suggest that any differences in D1R binding may only be detectable at the group level and not be useful for individual diagnostic purposes.

Children who eventually develop schizophrenia show negative and cognitive symptoms before overt psychosis such as disturbances in attention and social behavior (Carpenter et al. 1988, Davies et al. 1998, Walker et al. 1999). Such observations have stimulated research on prodromal symptoms of schizophrenia including neurological soft signs (Bachmann et al. 2014). Hence, the postulated D1R dependence of negative symptoms suggest the present reduced frontal D1R binding to be a trait defect in schizophrenia.

A number of early brain imaging studies of patients with schizophrenia suggest that hypofunction of the prefrontal cortex contributes to the cognitive deficits (Ingvar and Franzen 1974, Buchsbaum et al. 1982, Farkas et al. 1984, Liddle et al. 1992). The hypofrontality hypothesis of schizophrenia was coined in the 1970s based on early imaging studies showing reduced frontal blood flow in patients (Ingvar and Franzen 1974). More recent studies in patients with schizophrenia performing working memory tasks has shown reduced DLPFC activation, as measured by functional magnetic resonance imaging (Glahn et al. 2005, Minzenberg et al. 2009, Shimodera et al. 2012, Fryer et al. 2015) and electroencephalography (Minzenberg et al. 2010, Senkowski and Gallinat 2015), as well as reduced cerebral blood flow as measured by PET (Davidson and Heinrichs 2003, Park et al. 2006, Dreher et al. 2012). The occurrence of reduced frontal perfusion and metabolism is seen both during activation and at rest, which indicates a trait defect in schizophrenia (Hill et al. 2004). A recent review of neuroimaging studies on the effects of cognitive remediation therapies in patients with schizophrenia highlights that enhanced brain activation in prefrontal and thalamic regions may be in agreement with the hypofrontality hypothesis (Penades et al. 2017).

The cortical-basal ganglia-thalamic-cortical circuit integrate information across reward, cognitive, and motor functions (for review see (Haber 2016). In 1991, Davis and colleagues postulated that the striatal hyperdopaminergia, causing positive symptoms, is secondary to a frontal hypodopaminergia, causing negative symptoms (Davis et al. 1991). This view is based on preclinical data where lesions in the PFC cortex of rats increased levels of dopamine in the striatum (Haroutunian et al. 1988). The opposite has also been demonstrated, namely that an increased striatal D2R signaling induce cortical hypodopaminergia (Simpson et al. 2010). Transgenic mice selectively overexpressing striatal D2R have persistent abnormalities in prefrontal cortex function and deficits in executive function and working memory, deficits that are often found in experimental schizophrenia models (for review see (Beaulieu et al. 2015). In vivo evidence of skewed striatal-cortical dopamine levels in schizophrenia are

supported by the increased striatal 6-fluorodopa uptake in the striatum and deficient WCST-related activation in PFC (Meyer-Lindenberg et al. 2002). The results in Study II and IV in the present thesis of lack of antipsychotic effect of D1R antagonism and reduced D1R binding in the DLPFC support current versions of the dopamine hypothesis in schizophrenia, i.e. a combination of frontal hypodopaminergia and striatal hyperdopaminergia (Howes et al. 2012, Terrillion et al. 2017, Rao et al. 2018, McCutcheon et al. 2019, Li et al. 2020).

7 FUTURE PERSPECTIVES

The present observation of reduced frontal D1R binding contradicts parts of the previous literature on D1R in psychosis showing higher cortical D1R primarily in drug-naïve patients and individuals at high risk. To reach consensus a possibility is to perform a meta-analysis of the seven studies on D1R binding in schizophrenia reported so far (Okubo et al. 1997, Abi-Dargham et al. 2002, Karlsson et al. 2002, Hirvonen et al. 2006, Kosaka et al. 2010, Abi-Dargham et al. 2012, Stenkrona et al. 2019). However, the total number of drug naïve patients in these studies are likely too few for a rigorous analysis.

The reduced DLPC D1R reported in this thesis may be an underlying neurochemical mechanism for cognitive deficits and mood related symptoms such as the apathy and negative symptoms observed in patients with schizophrenia. This observation is in line with suggestions that D1R agonists may have beneficial effect in schizophrenia (Sedvall and Farde 1995, Arnsten et al. 2017). Preclinical studies showing reversal of dopamine depletion induced cognitive deficits by D1R agonists has inspired the development of selective D1R agonists for the treatment of schizophrenia (Arnsten et al. 2017, Bruns et al. 2018, Hall et al. 2019).

However, efforts to develop D1R agonists have been hampered due to poor drug-like properties, tachyphylaxis, and possibly also inverted U-shaped dose-response curves, whereby increasing doses of D1R agonists may impair cognition, e.g., as occurs with very high levels of endogenous DA release during uncontrollable stress (Zahrt et al. 1997, Arnsten and Goldman-Rakic 1998, Arnsten et al. 2017). An initial clinical trial failed to demonstrate improved cognition in patients with schizophrenia by the full selective D1R agonist DAR-0100A, which may have been due to low dosing and consequently also low D1R occupancy (Girgis et al. 2016). Recently a combined haloperidol and levodopa administration, to achieve high selective D1R agonist effect, was found to improve working memory related brain activation in humans (van Ruitenbeek et al. 2018). Hence, improved D1R agonists which achieve higher levels of D1R occupancy are needed to test the efficacy of this putative mechanism for cognitive enhancement in schizophrenia.

A different approach to orthosteric acting drugs would be to develop a positive allosteric potentiator (PAM) of the D1R that should amplify the response to endogenous dopamine, thus increasing D1R tone when and where dopamine is released (Foster and Conn 2017, Bruns et al. 2018). This mode of action is in contrast to a D1R agonist, which will activate all D1R to which it has access for as long as it is present. Very recently, a placebo controlled clinical trial of D1R PAM suggested improvement in psychomotor function, visual attention and information processing in patients with schizophrenia (Desai et al. 2020).

Additional avenues for D1R drug development are compounds targeting several neuro receptors simultaneously. A recent drug candidate, lumateperone, currently undergoing clinical trials, have a combined D1R and glutamate activating effects that may more effectively ameliorate cognitive impairments in schizophrenia (Vyas et al. 2020).

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