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TOWARDS A NOVEL TREATMENT OF HUNTINGTON'S DISEASE

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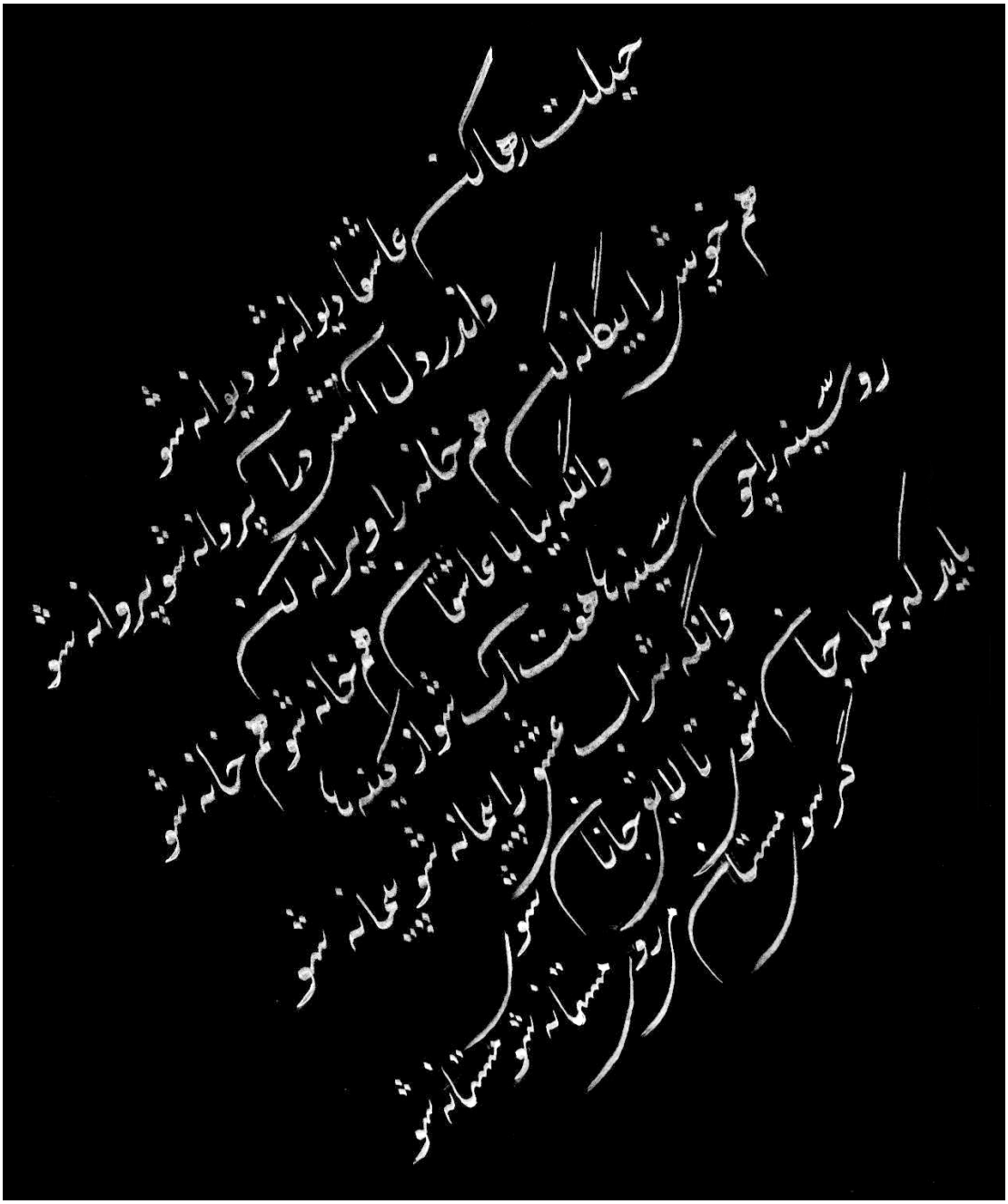
To my brothers
Hamid & Saeid



Poem by Rumi (Molana), Persian 13th century philosopher and Sufi mystic. The written verses relates to love, passion, delusion, truth, madness, wine, drunkenness, liberation, ego, soul, unification, divinity, and transcendence.

ABSTRACT

The function of the human brain is based on complex interactions between billions of neurons. The brain function declines as a result of normal aging, but is also disturbed in neuropsychiatric and neurodegenerative disorders. Huntington's disease is a hereditary autosomal-dominant neurodegenerative disorder that manifests with a complex range of symptoms resulting in severe motor deficiencies, cognitive decline, behavioral disturbances, and premature death. To date, no preventive, disease-modifying, or even symptomatic therapy exists.

Normal function of the brain is maintained by different neurotransmitters, which act through their receptors. One such example is the monoamine neurotransmitter dopamine, which plays a central role in normal brain function. The dopamine system is involved in a wide range of functions such as motor function, reward, cognition and emotion, and is importantly connected to the modulation of glutamate functions in the brain. There is evidence that dopaminergic systems are disturbed in Huntington's disease, and that the delicate balance between dopamine and glutamate interplay is disrupted in the disorder.

Dopaminergic stabilizers belong to a novel class of CNS compounds that can both enhance and counteract psychomotor activity depending on the initial level. Such effects are believed to be mediated by state dependent modulation of monoaminergic and glutamatergic functions. One such compound, pridopidine (ACR16), is currently in development for the treatment of Huntington's disease.

The aim of this thesis was to better understand the physiopharmacology of dopaminergic stabilizers and to investigate their effects in healthy subjects and patients with Huntington's disease. To explore the possibilities for this therapy in Huntington's disease, three experimental studies using positron emission tomography were undertaken. These studies yielded a number of findings. It could be shown that the extrastriatal density of dopamine D_2 receptors is well preserved in patients with Huntington's disease. This finding has implications for pridopidine therapy since the D_2 receptor is believed to be the primary target receptor for the compound. In addition, it was shown that in patients with Huntington's disease, pridopidine treatment induced general state dependent changes in cerebral metabolic activity, and increases in cerebral metabolic activity in brain regions believed to be important for mediating compensatory mechanisms in the disorder. In another study elucidating the mechanisms of action of dopaminergic stabilizers in healthy subjects, it could be shown that a single dose of the compound produced modest reductions in the availability of striatal dopamine D_2 receptors, and more marked fluctuations in the availability of cortical and striatal dopamine D_1 receptors. The results from this mechanistic study suggest that dopaminergic stabilizers exert their glutamate modulating properties via indirect effects of dopamine D_1 receptors. Moreover, in the framework of this thesis, an overview of available imaging biomarkers to study the progression of Huntington's disease is presented, providing guidance for methods to be applied in studies aimed at modifying disease progression.

SAMMANFATTNING

Människohjärnans funktion är baserad på ett komplext samspel mellan flera miljarder nervceller. Hjärnans funktion försämras som en följd av normalt åldrande, men är också störd i neuropsykiatriska och neurodegenerativa sjukdomar. Huntingtons sjukdom en ärftlig autosomalt dominant neurodegenerativ sjukdom som manifesterar sig med svåra motoriska brister, försämring av kognitiva funktioner, beteendestörningar och för tidig död. Än idag finns det för denna sjukdom ingen förebyggande, sjukdomsmodifierande, eller ens symtomlindrande behandling.

Den normala hjärnfunktionen upprätthålls av olika signalsubstanser, vilka verkar genom sina receptorer. Ett sådant exempel är monoaminerga signalsubstansen dopamin, som spelar en avgörande roll i hjärnans normala funktion. Dopaminsystemet är inblandat i en rad olika funktioner såsom motorik, belöning, kognition och emotion och är en viktig modulator av en annan viktig signalsubstans: glutamatfunktionen i hjärnan. Forskning har visat att det dopaminerga systemet är stört vid Huntingtons sjukdom och att den ömtåliga balansen och samspelet mellan dopamin och glutamat har rubbats.

Dopaminerga stabilisatorer tillhör en ny klass av läkemedel för det centrala nervsystemet, som både kan öka och motverka psykomotorisk aktivitet beroende på den ursprungliga aktivitetsnivån. Dessa effekter tros vara orsakade av modulering av monoaminerga och glutamaterga funktioner. En av dessa substanser, pridopidin (ACR16), är för närvarande under utveckling för behandling av Huntingtons sjukdom.

Syftet med denna avhandling var att bättre förstå fysiofarmakologin bakom dopaminerga stabilisatorer och att undersöka deras effekter på friska individer och patienter med Huntingtons sjukdom. Tre experimentella studier genomfördes med hjälp av positronemissionstomografi. Det kunde visas att den extrastriatala distributionen av dopamin D_2-receptorer är välbevarad hos patienter med Huntingtons sjukdom. Detta resultat har konsekvenser för pridopidinbehandling eftersom denna receptor tros vara läkemedlets primära målreceptor. Dessutom visade det sig att pridopidin inducerar generella nivåberoende förändringar i hjärnans metaboliska aktivitet, samt ökar metabolismen i hjärnregioner vilka anses vara viktiga för att förmedla kompensationsmekanismer vid sjukdomen. Vidare belystes verkningsmekanismerna av dopaminerga stabilisatorer på friska individer, där det kunde visas att en enda dos av substansen producerade måttliga minskningar i tillgången på striatala dopamin D_2-receptorer, och mer markanta fluktuationer i tillgången på kortikala och striatala dopamin D_1-receptorer. Resultaten från denna mekanistiska studie indikerar att dopaminerga stabilisatorer utövar sina glutamat-modulerande egenskaper via indirekta effekter av dopamin D_1-receptorer. Inom ramen för denna avhandling genomfördes även en sammanställande studie över tillgängliga imaging-biomarkörer lämpliga för att studera utvecklingen av Huntingtons sjukdom hos patienter. I denna föreslås riktlinjer för metoder som lämpligen kan användas i studier som syftar till att modifiera sjukdomsförloppet.

RÉSUMÉ

La fonction du cerveau humain est basée sur les interactions complexes entre des milliards de neurones. L'altération de la fonction cérébrale sa manifest du vieillissement normal, mais est également perturbé dans les troubles neuropsychiatriques et neurodégénératives. La maladie de Huntington est une maladie neurodégénérative autosomal-dominante qui se manifeste par un ensemble complexe de symptômes résultant de déficiences motrices sévères, déclin cognitif, troubles du comportement, et la mort prématurée. À ce jour, aucune prévention ou traitement modificateur de la maladie, même symptomatique, n'existe pas.

La fonction normale du cerveau est maintenue par différents neurotransmetteurs, qui agissent par le biais de leurs récepteurs. Un exemple est le neurotransmetteur dopamine, qui est impliqué dans un large nombre de fonctions telles que la fonction motrice, le mécanisme de récompense, la cognition ainsi que l'émotion.

Les stabilisateurs dopaminergiques appartiennent à une nouvelle classe de composés du système neurocentral, qui peuvent a la fois améliorer ou inhiber l'activité psychomotrice dépendante du niveau initial de cette activité. Ces effets seraient médiés par une modulation des fonctions monoaminergiques et glutamatergique. Un de ces composés, pridopidine (ACR16), est actuellement en développement pour le traitement de la maladie de Huntington.

L'objectif de cette thèse était de mieux comprendre la physiopharmacologie des stabilisateurs dopaminergiques et à étudier leurs effets chez les sujets sains et les patients de la maladie de Huntington. Pour explorer les possibilités de cette thérapie dans la maladie de Huntington, trois études expérimentales ont été entreprises. Ces études ont donné un certain nombre de conclusions. Il a pu être démontré que la densité extrastriatal de récepteurs dopaminergiques D_2 est bien conservée chez les patients de la maladie de Huntington. Ce constat a des implications pour la thérapie avec pridopidine, puisque ce récepteur est considéré comme le récepteur cible primaire pour le composé. En outre, il a été montré que chez les patients atteints de la maladie de Huntington, le traitement pridopidine induits des changements général de l'activité métabolique cérébrale, et augmente l'activité métabolique cérébrale dans des régions cérébrales considérées comme importantes pour la médiation des mécanismes de compensation dans la maladie. Dans une autre étude élucider les mécanismes d'action des stabilisateurs dopaminergiques chez les sujets sains, il a pu être démontré qu'une seule dose du ce composé, résulter en des réductions modestes de la disponibilité des récepteurs dopaminergiques D_2 du striatum, et plus fortes fluctuations dans la disponibilité des récepteurs dopaminergiques D_1 corticale et striatale. Les résultats de cette étude suggèrent que le mécanisme des stabilisateurs dopaminergiques exerce leur glutamate propriétés de modulation via les effets indirects de la dopamine récepteurs D_1. Dans le cadre de cette thèse, un aperçu a été investigué des biomarqueurs d'imagerie disponibles pour étudier la progression de la maladie de Huntington, et propose des directions pour les méthodes à appliquer dans les études visant à modifier la progression de la maladie.

مـــروری کوتـــاه

عملکرد مغز انسان بر اساس فعل و انفعالات پیچیده بین میلیاردها نورونها استوار است. عملکرد مغـز بر اثر افزایش طبیعی طول عمر کاهش می یابد. اما علاوه بر این، عملکـرد مغـز بر اثر بیماری نوروپسیکیاتریک و بیماری های ناشی از مستحیل شدن مغز، نورودژنراتیو، دچار اختلال می شود.

بیماری هانتینگتون نوعی بیماری ارثی، اختلال اتوزومال غالب عصبی است، که با یک ردیف علائم پیچیده ای ناشی از کمبودهای شدید حرکتی، کاهش توان فکری، اختلالات روانی، و مرگ زودرس آشکار می شود. تا به امروز، هیچ درمان پیشگیری کننده، بهبود بیماری، و یا حتی درمانی برای علائم بیماری وجود ندارد.

عملکرد طبیعی مغز توسط انتقال دهنده های عصبی مختلف، که از طریق گیرنده های خود عمل می کنند، حفظ می شود. یکی از این انتقال دهنده ها دوپامین است، که در عملکرد مغز سالم نقش محوری ایفا می کند. سیستم دوپامین در طیف گسترده ای از عملکرد ها همچون؛ عملکرد حرکتی، پاداش و ارضا، شناخت و احساسات، نقش دارد. و بطور مهمی به مدولاسیون عملکردِ گلوتامات در مغز مرتبط است. در بررسی ها نشان داده شده است که در بیماری هانتینگتون سیستم دوپامینرژیک دچار اختلال می شود، و همچنین دیده شده است که در بیماران هانتینگتون، تعادل حساس متقابل بین دوپامین و گلوتامات نیز بهم خورده است.

تثبیت کننده های دوپامینرژیک متعلق به یک گروه جدید از ترکیبات برای سیستم عصبی مرکزی هستند که، بسته به سطح اولیه دوپامینرژیک، هم می تواند فعالیت های حرکتی ـ روانی (پسیکوموتور) را افزایش دهد و هم می تواند با آنها مقابله کند. باور بر این است که تأثیر این تثبیت کننده متقابل نسبی، مربوط به عملکرد مدولاسیون سیستم های منوآمینرژیک و گلوتاماترژیک می باشد. در حال حاضر تحقیق بر روی ترکیب پریدوپیدین "ACR16" ادامه دارد، تا با توسعه و تکمیل تحقیقات برای مداوای بیماری هانتینتگتون استفاده شود.

هدف از این پایان نامه درک بهتر فیزیوفارماکولوژی تثبیت کننده های دوپامینرژیک و تحقیق اثرات آنها بر افراد سالم و در بیماران هانتینگتن بوده است. برای کشف امکانات این نوع تثبیت کننده ها در بیمـاری هانتینگتون، سه تحقیق با استفاده از پرتونگاری مقطعی با تابش پوزیترون (پت) انجام شد. این تحقیقات، یافته های جدیدی را بدست داد. در تجربه نشان داده شد که تراکم در گیرنده های دوپامین D2 در خارج از استریاتوم در بیماران مبتلا به هانتینگتون به خوبی حفظ شده است. این یافته امر مهمی است در استفاده از پریدوپیدین، زیرا باور بر این است که گیرنده های D2 اولین هدف گیرنده برای این ترکیب می‌باشند. علاوه براین، نشان داده شد که استفاده از پریدوپیدین در بیماران مبتلا به بیماری هانتینگتون، فعالیت سوخت و ساز مغزی را تغییر می دهد. و نشان داده شد که فعالیت متابولیزم مغز توسط پریدوپیدین به ویژه در مناطقی از مغز، که در مکانیسم های جبران کننده مهم می باشند، افزایش می یابد.

در تحقیق دیگری برای روشن نمودن مکانیسم عمل تثبیت کننده های دوپامینرژیک در افراد سالم، نشان داده شد که یک دوز واحد از ترکیب، کاهش کمی در موجودیت گیرنده های دوپامین D2 در استریاتوم را ایجاد می کند، و همچنین نوسانات چشمگیری را در گیرنده های دوپامین D1 در کورتکس و در استریاتوم، بارز می‌کند. از نتایج این تحقیق اینطور استنباط می شود که، تثبیت کننده های دوپامینرژیک خواص مدولاسیون گلوتاماتِ خود را از طریق اثر غیر مستقیم گیرنده های دوپامین D1، اعمال می کنند.

علاوه بر این، در چارچوب این پایان نامه، مرور گسترده ای برتصویربرداری های موجودِ نشانگرهای زیستی برای تحقیق در پیشرفت بیماری هانتینگتون انجام گردیده است، و پیشنهاد راهبردی برای روش هایی که جهت تحقیق با اهداف بهبود و اصلاح بیماری انجام شود، ارائه داده شده است.

LIST OF PUBLICATIONS INCLUDED IN THIS THESIS

I. Esmaeilzadeh M, Farde L, Karlsson P, Varrone A, Halldin C, Waters S, Tedroff J.
Extrastriatal dopamine D_2 receptor binding in Huntington's disease.
Human Brain Mapping, 2010

II. Esmaeilzadeh M, Kullingsjö J, Ullman H, Varrone A, Tedroff J.
Regional cerebral glucose metabolism following pridopidine (ACR16) treatment in patients with Huntington's disease.
Clinical Neuropharmacology, 2011 (accepted for publication)

III. Esmaeilzadeh M, Farde L, Karlsson P, Halldin C, Sonesson C, Tedroff J.
A PET study investigating the effects of ACR325 on [^{11}C]raclopride and [^{11}C]SCH23390 binding in human brain.
Manuscript, 2011

IV. Esmaeilzadeh M, Ciarmiello A, Squitieri F.
Seeking brain biomarkers for preventive therapy in Huntington disease.
CNS Neuroscience & Therapeutics, 2010

LIST OF PUBLICATIONS NOT INCLUDED IN THESIS

I. Rominger A, Wagner E, Mille E, Boning G, Esmaeilzadeh M, Wangler B, Gildehaus F-J, Nowak S, Bruche A, Tatsch K, Bartenstein P, Cumming P. Endogenous competition against binding of [^{18}F]DMFP and [^{18}F]fallypride to dopamine D2/3 receptors in brain of living mouse.
Synapse, 2009

II. Giovacchini G, Squitieri F, Esmaeilzadeh M, Milano A, Luigi M, Ciarmiello A.
PET translates neurophysiology into images: A review to stimulate a network between neuroimaging and basic research.
Journal of Cellular Physiology, 2010

III. Squitieri F, Esmaeilzadeh M, Martino T, Ciarmiello A.
Brain glucose hypometabolism in a subject carrying an unstable allele of intermediate CAG33 repeat length in the Huntington disease gene.
Movement Disorders, 2011 (in press)

IV. Tedroff J, Esmaeilzadeh M, Waters S, on behalf of EHDN Registry Study Group.
Does neuroleptic treatment worsen the progression in HD?
Manuscript, 2011

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LIST OF ABBREVIATIONS

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Arc	Activity regulated cytoskeletal protein
BDNF	Brain-derived neurotrophic factor
B_{max}	Binding maximum
BP	Binding potential
CAG	Cytosine-adenine-guanine
Camp	Cyclic adenosine monophosphate
CNS	Central nervous system
COMT	Catecholamine O-methyltransferase
DA	Dopamine
DAT	Dopamine transporter
D_1	Dopamine 1 receptor
D_2	Dopamine 2 receptor
FDG	Fluoro-deoxy-glucose
FDG-6-P	FDG-6-PO_4 (fluoro-deoxy-glucose-6-phosphatase)
fMRI	Functional magnetic resonance imaging
FWHM	Full width at half maximum
GP_e	Globus pallidus externa
GP_i	Globus pallidus interna
HART	Huntington's disease ACR16 randomized trial
HD	Huntington's disease
HDRP	Huntington's disease related pattern
HRRT	High resolution research tomograph
K_d	Dissociation equilibrium constant
L-DOPA	L-dihydroxy-phenylalanine
LTD	Long-term depression
LTP	Long-term potentiation
MAO	Monoaminoxidase
MD	Mediodorsal
MermaiHD	Multinational European multicentre ACR16 study in HD
mMS	Modified motor score
MRI	Magnetic resonance imaging

NMDA	N-methyl-D-aspartate
MSN	Medium spiny neuron
PC	Principal component
PCA	Principal Component Analysis
PET	Positron emission tomography
PKA	Protein kinase A
PLS	Partial Least Squares
PSF	Point spread function
PVE	Partial volume effect
rCMRGlc	Regional cerebral metabolic rate of glucose
ROI	Regions of interest
SPM	Statistical Parametric Mapping
SRTM	Simplified reference tissue model
TH	Tyrosine hydroxylase
TMS	Total motor score
UHDRS	Unified Huntington's Disease Rating Scale
VTA	Ventral tegmental area

1 INTRODUCTION

1.1 HUNTINGTON'S DISEASE

1.1.1 Historical aspects

The first description of a patient with Huntington's disease (HD) was made by Waters, in 1842 (Roos 2010). At that time, HD was called the "magrums", a folk name for the disorder. In 1872, the physician George Huntington described a hereditary fatal disorder mainly characterized by uncontrollable movements (chorea) and mental impairment (Huntington 1872). A few years later, it was observed by Meynert that brains of patients with HD are affected by an extensive atrophy of the basal ganglia (Bates, et al. 2002). For a long time period, extensive research has been focusing on the neuropathology of this region. However, during the recent years more and more attention has been brought to the pathology in the rest of the brain, elucidating a better understanding of the heterogeneity of the disease. To date, there is no effective treatment for the disease; neither curative nor disease modifying or symptomatic, and patients affected with HD die within one or two decades after onset of manifest symptoms, which commonly occur in the ages of 35-45.

1.1.2 Genetic aspects

The mutant gene responsible for HD, IT15 ("interesting transcript 15") or HTT, is located on the short arm of chromosome 4 (4p16.3), which codes for the protein huntingtin. The disease is caused by an increased number of cytosine-adenine-guanine (CAG) repeats located near the 5'-end in exon 1 of the gene. Healthy individuals have typically less than 36 CAG repeats, whereas 36-39 repeats indicates an incomplete penetrance and that the individual is at risk of developing HD (McNeil, et al. 1997), while repeats of 40 or above results in HD with complete penetrance (Gusella, et al. 1993; Myers 2004).

The CAG repeat length is a main determinant for HD onset, accounting for nearly 70% of the variability in observed age at onset, and has impact also on disease progression (Ashizawa T 1994; Aziz, et al. 2009; Ravina, et al. 2008). The number of CAG repeats varies considerably among patients; a repeat length around 40 is associated with adult onset of disease whereas juvenile onset is characterized by expansions of more than 60 repeats (Brandt, et al. 1996; Trottier, et al. 1994).

The protein encoded by the HTT gene, huntingtin, is a multifunctional protein widely expressed throughout the body, in neuronal but also in non-neuronal cells (Hoogeveen, et al. 1993; Trottier, et al. 1995). Huntingtin is primarily localized in the cytoplasm of the cell, but is also present in the nucleus (Landles and Bates 2004). This protein is believed to be involved in several cellular processes such as vesicular transportation (Engelender, et al. 1997), transcriptional mechanisms (Marcora, et al. 2003; Zuccato, et

al. 2003), and in the production of brain-derived neurotrophic factor (BDNF); a factor promoting survival and growth of neurons (Zuccato, et al. 2001; Zuccato, et al. 2005; Zuccato, et al. 2003). Furthermore, it has been shown that normal huntingtin is crucial for embryonic development and has neuroprotective effects, resulting in homozygote mice models being lethal and heterozygote mice models (where for example one allele is deleted) resulting in various deficits such as testis atrophy, weight loss and difficulty of switching strategy tasks (Leavitt, et al. 2006; Nasir, et al. 1995; Pouladi, et al. 2010; Van Raamsdonk, et al. 2006; Van Raamsdonk, et al. 2007). It might thus be the case that it is the lack of normal huntingtin rather than the existence of mutant huntingtin that result in these dysfunctional mechanisms.

The classical hallmark of HD is degeneration of medium spiny neurons in the striatum (Folstein 1989), yet mutant huntingtin is expressed throughout the brain (Strong, et al. 1993). The mechanisms underlying the particular pattern of neurodegeneration in HD and the exact functions of the protein in human is thus not fully understood.
Mutant huntingtin has an expanded polyglutamine domain resulting in a misfolding of the protein, which leads to the formation of aggregates in the cells. Most of these aggregates are found as intranuclear inclusions (Lunkes, et al. 2002), in cell bodies, axons, and dendrites (Li, et al. 2003).

The cellular dysfunction and death caused by the mutant huntingtin could be induced through different mechanisms (Landles and Bates 2004). Such factor could be the saturation of the proteasome system by the misfolded protein, transcriptional dysfunction, mitochondrial impairment and oxidative stress (Browne and Beal 2004; Browne and Beal 2006; Lin and Beal 2006). HD cells are shown to have a reduced activity in different mitochondrial complexes (Arenas, et al. 1998; Gu, et al. 1996; Tabrizi, et al. 2000) thus resulting in a decreased ATP-production, an impaired metabolism, a decreased resting membrane potential and hence a reduced threshold for calcium induced depolarization, leading to an increase vulnerability for excitotoxicity. The theory of excitotoxicity leading to cell death in HD, is believed to be caused by an overstimulation of glutamatergic receptors such as N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), resulting in an increased influx of calcium in the cells, which amongst others leads to an activation of free radicals and enzymes such as proteases including caspases.

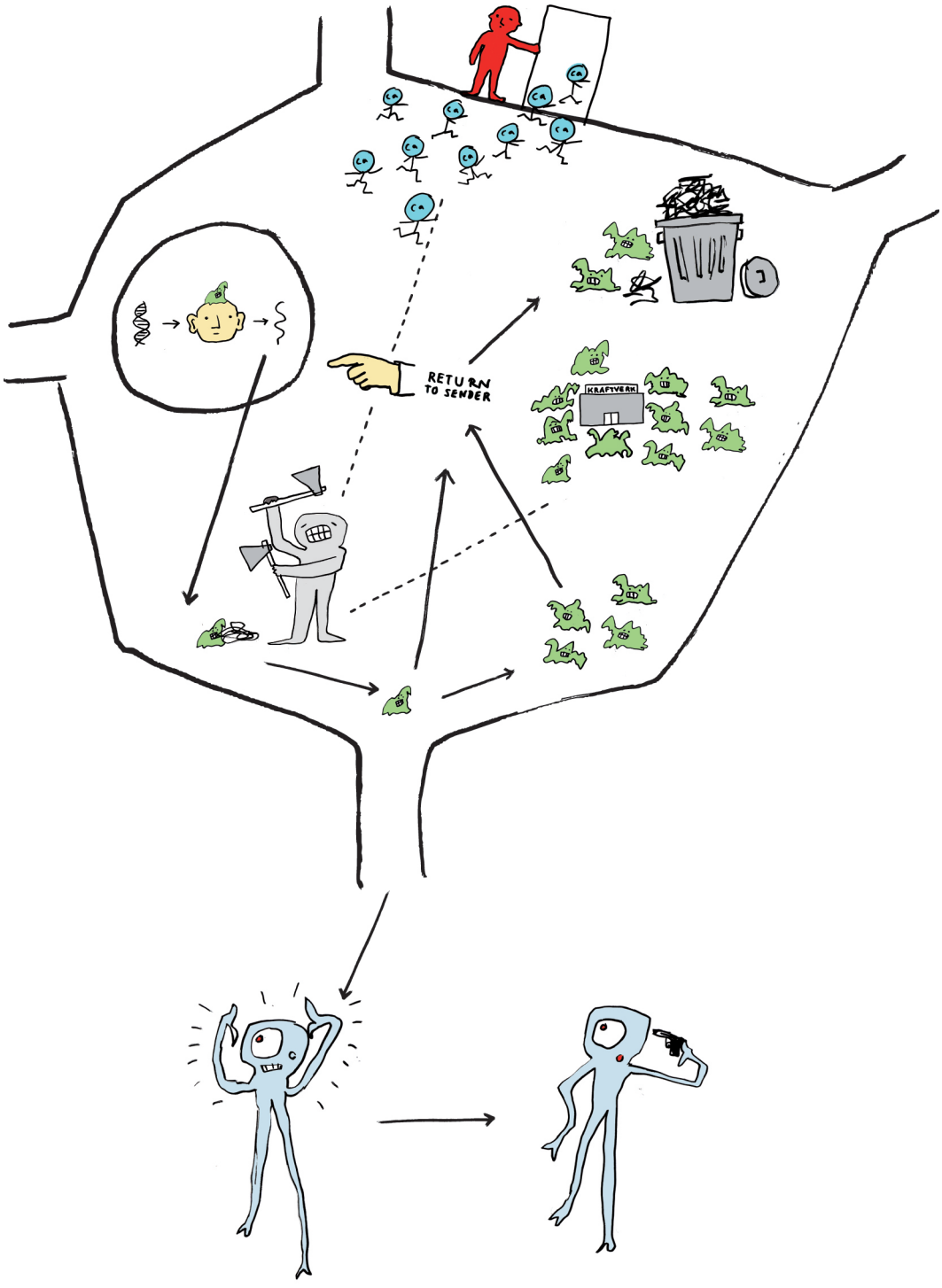

FIGURE 1

Schematic overview of some of the main pathophysiological mechanisms in HD. Dysfunctional processes induced by mutant htt result in aggregate formation, transcriptional inhibition, reduced proteasomal activity, increased Ca^{2+} influx by activation of extrasynaptic NMDA receptors as well as mitochondrial impairment resulting in increased caspase activity causing further aggregate formation. These complex pathophysiological mechanisms all result in oxidative stress, apoptosis and cell death.

1.1.3 Anatomical aspects

1.1.3.1 Basal ganglia

The basal ganglia are a group of nuclei in the brain situated at the base of the forebrain and connected with areas such as the cerebral cortex and thalamus. These structures are associated with a variety of functions, including motor control and learning, cognitive function, and emotions. Anatomically, the basal ganglia consist of the striatum (caudate nucleus, putamen and nucleus accumbens) and the globus pallidus (internal and external segments GP_i and GP_e). In addition, the substantia nigra and the subthalamic nucleus are often included in the basal ganglia, particularly due to their close anatomical and functional associations. It has previously been believed that the basal ganglia is exclusively involved in the planning and the generation of motor commands. It is now recognized that the basal ganglia also play important roles in cognitive and affective functions. Several nuclei of the basal ganglia are involved in circuits or loops relevant to neuropsychiatric and neurodegenerative disorders; the striatum is involved in all these loops.

1.1.3.2 Striatum

The striatum is the anatomically largest component of the basal ganglia and receives input from many brain areas but sends output only to other components of the basal ganglia. Being the major input structure of the basal ganglia, the striatum receives information from the cortex (most areas, in particular the motor and prefrontal cortices) and thalamus through excitatory glutamatergic neurons (Parent and Hazrati 1995a; Parent and Hazrati 1995b). The pallidum receives most of its input from the striatum, and sends inhibitory output to a number of motor-related areas such as the thalamus that project to the motor-related areas of the cortex. The limbic sector of the basal ganglia consists of nucleus accumbens, ventral pallidum, and ventral tegmental area (VTA). The VTA provides dopamine to nucleus accumbens and the ventral striatum whereas substantia nigra provides dopamine to the dorsal striatum. The dorsal striatum includes the caudate and the putamen, and is predominantly involved in motor control and habit learning whereas the ventral striatum, connecting to the nucleus accumbens, is primarily involved in emotional and behavioral aspects such as reward-motivated behaviors.

About 95% of striatal neurons consist of GABAergic medium spiny neurons (MSNs). The glutamatergic input from the cortex and thalamus is the essential drive behind excitatory synaptic transmission in the striatum. Apart from glutamatergic input, the striatum also receives dopaminergic input from the midbrain. Classically, it has been believed that the information that enters the striatum continues through two different pathways; either via the globus pallidus interna (GP_i), which also is called the direct pathway, or via the globus pallidus externa (GP_e), which also is called the indirect pathway (Albin, et al. 1989; Chesselet and Delfs 1996). In this model, the GABAergic neurons of the direct pathway express dopamine D_1 receptors, and the indirect pathway

express dopamine D_2 receptors. Disinhibition of the direct pathway facilitates movements while a disinhibition of the indirect pathway inhibits movements (Kandel, et al. 2000). The direct pathway inhibits the GP_i while disinhibiting the thalamus. The indirect pathway inhibits the GP_e resulting in a disinhibition of the subthalamic nucleus, leading to (through the glutamatergic neurons in subthalamic nucleus) an excitation of the GABAergic neurons in the GP_i thus causing an inhibition on the thalamus. This strict division of pathways has however been questioned, and has been a matter of controversies, where some evidence is suggesting that dopamine D_1 and D_2 class receptors are co-localized in nearly half of all MSNs (Surmeier, et al. 1996).

Striatal atrophy occurs early in HD, usually starting in the caudate nucleus, and progresses gradually (Vonsattel and DiFiglia 1998; Vonsattel, et al. 1985). MSNs are particularly vulnerable to this degeneration, while the aspiny interneurons are relatively unaffected (Ferrante, et al. 1987; Ferrante, et al. 1985). The MSNs projecting to the GP_i contain substance P whereas those projecting to the GP_e contain enkephalin and are the first to degenerate in HD (Reiner, et al. 2003; Sapp, et al. 1995). It is however not fully clarified why the striatum is particularly vulnerable to the degeneration in HD.

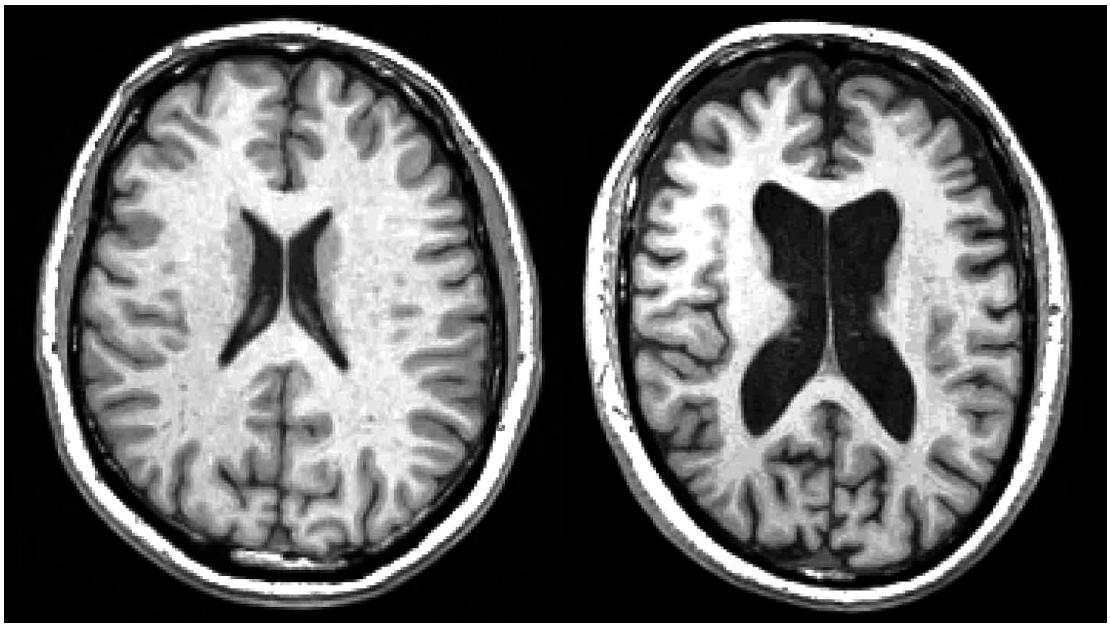

FIGURE 2
Brain magnetic resonance imaging of a healthy individual (left) and a patient with HD (right). Severe atrophy is apparent early in HD, in particular in the striatum.

1.1.3.3 Thalamus

The thalamus is a major relay station in the brain, since almost all information relays through thalamus en route to the cortex, and in turn, almost all areas of the cortex project to divisions of the thalamus (Taber, et al. 2004). Previous studies performing stereological quantifications have shown a neuronal loss of up to 55 percent in advanced cases of patients with HD (Heinsen, et al. 1996). Thalamic atrophy in patients with HD also correlates with cognitive performance (Kassubek, et al. 2005). In

addition, thalamus is part of the corticostriatal circuitry, connecting the basal ganglia and the neocortex, which might contribute to the motor dysfunctions seen in the disease (Cepeda, et al. 2007).

The mediodorsal (MD) thalamus is of special interest in HD. It is suggested that this structure is a key region for mediating compensatory mechanisms in premanifest HD (Feigin, et al. 2007). The MD thalamus has major cortical and subcortical interconnections. This structure is considered to be a key relay structure in the brain and is involved in a multitude of functions including motor, cognition, emotion, arousal and sleep patterns, behavioral functions such as inhibition of inappropriate behavior and executive functions (Armstrong 1990; Bentivoglio, et al. 1993; Mega and Cummings 1994; Taber, et al. 2004).

The MD thalamus has interactions with the prefrontal cortex, which within its anatomically and functionally segregated networks play important roles in cognitive functions (Shenton, et al. 1992). Other than having major reciprocal connections with the prefrontal cortices, MD thalamus has major reciprocal connections with the cortex in e.g. anterior cingulate as well as with supplementary motor and parietal cortices (Bachevalier, et al. 1997; Baleydier and Mauguiere 1980; Barbas, et al. 1991; Cavada, et al. 2000; Giguere and Goldman-Rakic 1988; Goldman-Rakic and Porrino 1985; Hatanaka, et al. 2003; Ilinsky, et al. 1985; Powell 1973; Russchen, et al. 1987; Selemon and Goldman-Rakic 1988; Siwek and Pandya 1991; Tanaka 1976; Vogt, et al. 1979). The amygdala, substantia nigra, and cerebellum also project to MD thalamus (Ilinsky, et al. 1985; Price 1986).

Several studies suggest an important role for the MD thalamus in HD. In a positron emission tomography (PET) study investigating premanifest HD gene carriers, activation responses during motor learning were abnormally increased in the left MD thalamus. Impaired learning performance in subjects with premanifest HD has been associated with increased activation responses in the precuneus. These data suggest that enhanced activation of thalamocortical pathways during motor learning can compensate for caudate degeneration in premanifest subjects (Feigin, et al. 2006; Feigin, et al. 2007).

1.1.3.4 Precuneus

The precuneus is a part of the superior parietal lobule, hidden in the medial longitudinal fissure between the two cerebral hemispheres. It is involved with episodic memory, visuospatial processing, reflections upon self, and aspects of consciousness; all functions being disturbed in HD. Functional imaging studies have linked the precuneus to the processes involved in self-consciousness such as reflective self-awareness, that involve rating the person's own personality traits compared to those judged of other people (Kjaer, et al. 2002; Lou, et al. 2004). Precuneus has been suggested to be the 'core node' of the default mode network that is activated during 'resting consciousness' in which people do not engage intentionally in sensory or motor activity (Fransson and Marrelec 2008; Wenderoth, et al. 2005). Precuneus is also involved in diverse cognitive processes such as attention, episodic memory retrieval, working memory and conscious perception (Lundstrom, et al. 2005).

The precuneus has been suggested to be involved in directing attention in space when observing movements as well as when imaging or preparing movements (Cavanna and Trimble 2006; Kawashima, et al. 1995). In addition, it is involved in motor coordination that requires shifting attention to different spatial locations (Wenderoth, et al. 2005). It is suggested that while the premotor area engages in the mental operation, the precuneus aids monitoring the success of that operation in terms of internally represented visual images (Oshio, et al. 2010). A functional magnetic resonance imaging (fMRI) study showed that precuneus together with the superior frontal gyrus and orbitofrontal cortex are the brain regions that get engaged when judging others' emotional states and the forgivability of their crimes (Farrow, et al. 2001). It has also been suggested that the precuneus together with the posterior cingulate, is pivotal for conscious information processing (Vogt and Laureys 2005).

The MD thalamus sends projections to the precuneus (Schmahmann and Pandya 1990). Thalamic projections to the precuneus are known to be important for both movement accuracy and learning. Data from several studies have shown that parietal association regions, including the precuneus, might be implicated in aspects of sequence learning, specifically regarding movement accuracy (van Mier, et al. 2004) and retrieval during spatial learning tasks (Parsons, et al. 2004). A PET study found a negative correlation between motor learning and metabolic activity in the precuneus in premanifest HD (Feigin, et al. 2006).

1.1.3.5 Cerebral cortex

Although MSN degeneration is the classical hallmark of neuropathology in HD (Hersch, et al. 2004), neuronal loss has also been identified in many other brain regions including the cerebral cortex (Braak and Braak 1992; Halliday, et al. 1998; Hedreen, et al. 1991; Heinsen, et al. 1994). Prior to degeneration, morphological changes such as dendritic remodeling and altered size and number of dendritic spines occur in cortical pyramidal cells (Sapp, et al. 1997). Projection neurons from cortical layers III, V and VI seem to be more prone for the neurodegeneration in HD (Gutekunst, et al. 1999; Hedreen, et al. 1991; Heinsen, et al. 1994; Jackson, et al. 1995; Sieradzan and Mann 2001). During the recent years, different magnetic resonance imaging (MRI) methods have demonstrated a specific regional cortical thinning pattern in patients with HD, as well as in premanifest individuals (Douaud, et al. 2006; Kassubek, et al. 2004; Rosas, et al. 2002; Rosas, et al. 2005). The selectivity, progression and heterogeneity of cortical atrophy in HD have been described, demonstrating the relationships between regional cortical thinning, progressive functional decline and prominent clinical features (Rosas, et al. 2008).

1.1.4 Clinical aspects and phenotype

The prevalence of HD is estimated to be around 70 per million in the Western world, and even more individuals are at risk for the disease. The gene responsible for the disease was identified as late as in 1993, making genetic testing possible and available. However, uptake of genetic testing has been low and seems to decrease (Bernhardt, et

al. 2009). HD is a stigmatizing disorder and as such there are indications that the prevalence of HD might be grossly underestimated (Rawlins 2010).

Despite being a strictly monogenetic disorder, the clinical phenotype of HD presents with considerable variability. The phenotype includes progressive motor impairments, cognitive deterioration, personality changes and susceptibility to severe mental disorder. As the disease progresses, gross motor functions, including gait and postural control, deteriorate. Such changes ultimately cause major impairment of function. Motor disturbances can be divided into positive (e.g. chorea and dystonia) and negative (e.g. bradykinesia) symptoms; most patients have a mixture of both. Although chorea remains the clinical hallmark of the disease, disruption of voluntary movement such as parkinsonism including bradykinesia and rigidity, clumsiness with impaired voluntary movement, and dystonia are also recognized motor features of HD (van Vugt, et al. 1996). Similarly, patients with HD often suffer from both positive and negative behavioral symptoms. Psychiatric manifestations are very common including, among other symptoms, irritability, depression, anxiety, apathy and obsessive-compulsive symptoms (Anderson and Marder 2001; Craufurd and Snowden 2002; Di Maio, et al. 1993; Harper 1992; van Duijn, et al. 2007). Another commonly clinically observed, but maybe less studied and subtler feature in these patients is sexual disinhibition and promiscuous behavior. The suicide risk is markedly increased in patients with HD as well as in the premanifest stages (Di Maio, et al. 1993). Cognitive difficulties in HD encompass multiple domains, including executive dysfunction, as well as disturbances in memory, visuospatial attention and praxis (Craufurd and Snowden 2002; Folstein 1989). Thus, planning, intellectual speed and flexibility deteriorate with disease progression, making it more difficult to retrieve previously learned information as well as making learning of new information less efficient. As the disease progresses, memory deficits tend to appear and eventually dementia is developed. There is no satisfactory explanation as to the considerable variability of the clinical symptoms seen in HD.

Albeit HD is primarily affecting brain functions, the disease affects many other parts of the body (van der Burg, et al. 2009). Patients with HD often suffer from muscle atrophy (Trejo, et al. 2004), osteoporosis (Bonelli, et al. 2002), weight loss (Nance and Sanders 1996), testis atrophy (Van Raamsdonk, et al. 2007) and cardiac failure (Lanska, et al. 1988; Sorensen and Fenger 1992). Weight loss is a widespread feature in HD. Interestingly, it does not correlate with chorea scores and occurs despite adequate nutrition or even higher caloric intake. Cardiac failure is one of the most common causes of death in patients with HD.

Traditionally, ‘onset of disease’ is considered as the occurrence of manifest motor symptoms of HD. Subtle clinical changes with soft motor and behavioral signs and symptoms evolve during years from premanifest stage towards manifest stages of the disease, thus determining the so called ‘zone-of-onset’ (Penney, et al. 1990). Furthermore, behavioral and cognitive symptoms are usually more subtle and difficult to characterize. Nevertheless, the Unified Huntington’s Disease Rating Scale (UHDRS) clinical assessment still represents the golden standard for assessing HD (Huntington Study Group 1996). Recently, a new technique has been developed for objective measurements of motor symptoms in patients with HD (Reilmann, et al. 2010a;

Reilmann, et al. 2010b; Reilmann, et al. 2001; Tabrizi, et al. 2009; Tabrizi, et al. 2011). However, the UHDRS has been developed to measure symptoms in patients with manifest HD, and is not suitable to assess subtle changes in the premanifest stage. The interpretation of the 'zone-of-onset' thus remains a very subjective evaluation by each physician with obvious limitations in the reliability of assessments. Theoretically, such limitations might be at least partially solved by including objective brain imaging biomarkers, directly recorded by modern imaging techniques. Although there is a progressive decline in UHDRS scores in manifest HD, the rate of UHDRS motor score progression in recently phenoconverted patients seem to be low (Mahant, et al. 2003). As an example, a longitudinal PET study investigating HD individuals close to phenoconversion over a period of 44 months, showed clear evidence of changes in cerebral metabolic patterns, while the UHDRS scores failed to show any significant changes in motor and cognitive scores (Feigin, et al. 2007). Similarly, MRI may detect degenerative processes years prior to onset of manifest disease (Antonini, et al. 1996; Aylward, et al. 1996; Aylward, et al. 2000; Paulsen, et al. 2004). *In vivo* neuroimaging studies have reported abnormalities such as reduced striatal volume (Aylward, et al. 1994; Aylward, et al. 1998), decreased striatal dopamine D_2 receptor density (Antonini, et al. 1996; Ichise, et al. 1993; Weeks, et al. 1996) and reduced striatal glucose consumption (Antonini, et al. 1996; Grafton, et al. 1992; Kuwert, et al. 1993; Mazziotta, et al. 1987) already in premanifest HD subjects. This raises possibilities for obtaining imaging biomarkers for monitoring disease progression and therapeutic effects already in premanifest HD subjects, which is further discussed in the appendix.

1.2 DOPAMINE SYSTEMS

The neurotransmitter dopamine (DA) was discovered in the 1950s and has since been in focus for research in neuroscience. DA plays a fundamental role in the human brain and is involved in different physiological functions, motor function, higher-order cognitive functions and reward mechanisms, as well as in neurological and psychiatric disorders (Creese, et al. 1977; Girault and Greengard 2004; Goldman-Rakic 1987; Koob and Bloom 1988; Kopin 1993; Le Moal and Simon 1991; Vallone, et al. 2000).

In the treatment of neurological and psychiatric disorders, modification of DA neurotransmission is an important and widely used pharmacological principle. Classical antipsychotic drugs act through blocking of DA receptors (by DA antagonists), reducing mainly positive symptoms in patients with schizophrenia. The DA precursor levodopa compensates for the shortage of DA in Parkinson's disease, alleviating the hypokinesia, rigidity and tremor characteristics for the disorder. For the treatment of attention deficit and hyperactivity disorder, methylphenidate, a drug that increases the intrasynaptic DA levels, improves hyperactivity and attentional deficits. In addition, DA is intricately involved in reward and hedonistic responses, demonstrated by the effects of psychostimulant drugs such as cocaine and amphetamine.

1.2.1 Synthesis and degradation of dopamine

Dopamine is synthesized in tyrosine hydroxylase (TH) containing neurons where it is stored in vesicles. The amino acid tyrosine passes the blood brain barrier, where it in catecholamine neurons is converted into L-3,4-dihydroxylphenylalanine (L-DOPA) by the enzyme TH. L-DOPA is then converted to DA by L-amino acid decarboxylase. The rate-limiting step in the synthesis of DA is the TH-activity. Dopamine is released into the synaptic cleft and extracellular space in response to action potentials. Once released, DA binds to receptors on the postsynaptic neuron as well as to autoreceptors on the presynaptic neuron, thereby evoking a cascade of intracellular biochemical events. Termination of the DA signaling is mainly dependent on the reuptake and degradation of DA. The membrane bound DA transporter (DAT), which allows rapid reuptake, removes extracellular DA. In addition, DA is removed by two degrading enzymes, monoaminoxidase (MAO) and catecholamine O-methyltransferase (COMT).

1.2.2 Dopaminergic pathways

The dopaminergic systems in the central nervous system (CNS) are divided into different pathways on the basis of the localization of dopaminergic neurons and their efferent projections (Di Chiara 2005; Missale, et al. 1998; Stahl 1996; Ungerstedt 1971; Vallone, et al. 2000). The mesostriatal system projects from the substantia nigra to the striatum, playing an important role for motor function. The mesolimbic system projects from the VTA to limbic structures such as the ventral striatum (i.e. nucleus accumbens), hippocampus and amygdala, while the mesocortical system projects from the VTA to cortical regions. These projections are important for emotions and motivation, thus being affected in e.g. schizophrenia. There is a fourth dopaminergic projection, the so-called tuberoinfundibular pathway, which originates in the arcuate nucleus of the hypothalamus and projects to the pituitary gland, where it regulates secretion of the hormone prolactin.

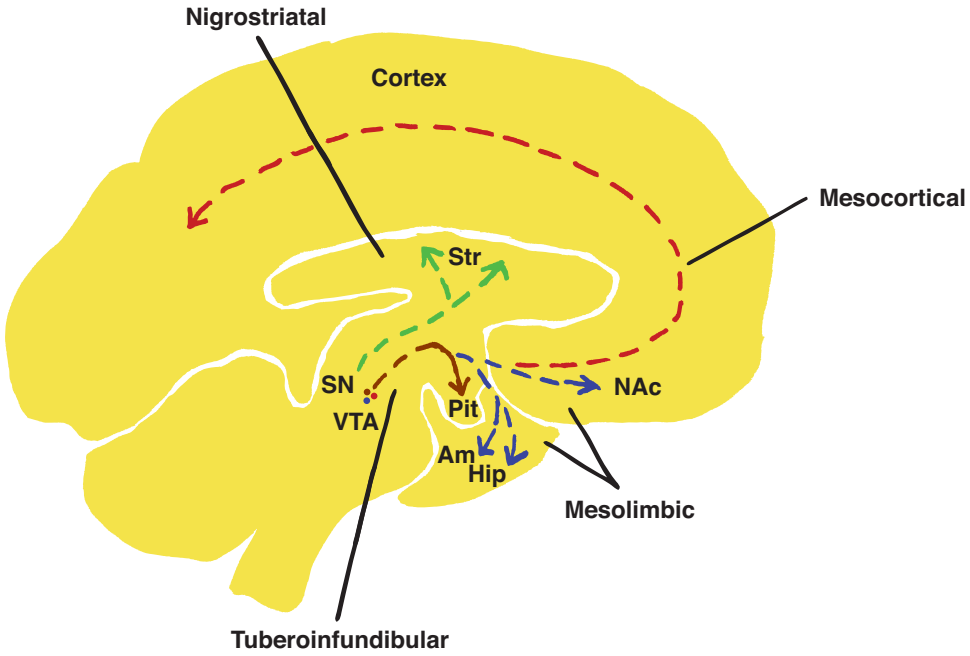

FIGURE 3
Schematic overview of dopaminergic pathways in the human brain. Originating from substantia nigra (SN) and ventral tegmental area (VTA), the projections go to the striatum (Str), limbic structures such as amygdala (Am), hippocampus (Hip), and nucleus accumbens (NAc), the cerebral cortex, and the hypothalamus and pituitary gland (Pit).

The nigrostriatal pathway constitutes about 80 % of all dopaminergic projection fibers. Having its cell bodies located in the substantia nigra pars compacta, this pathway projects to the MSNs in the dorsal striatum (caudate nucleus and putamen). Preclinical studies have estimated that one single presynaptic neuron results in an average of 370.000 connections in the striatum (Oorschot 1996; Wickens and Arbuthnott 2005). Hence, once the presynaptic nigrostriatal neuron has reached the striatum, there is a vast divergence of release sites. This pathway is classically believed to be in charge of regulation of motor functions and is important for the coordination and execution of movement. A clinical example of dysfunction in this pathway is Parkinson's disease, where symptoms are caused by degeneration of DA neurons in substantia nigra (Hornykiewicz 1966).

The mesolimbic pathway originates from the VTA, projecting to several limbic brain areas such as the ventral striatum (nucleus accumbens), amygdala and hippocampus, as well as to limbic cortical areas. This pathway is believed to be involved in behavioral aspects such as motivation and emotions.

The mesocortical pathway originates, as the mesolimbic pathway, from the VTA, but projects to cortical regions such as frontal and temporal cortices and the anterior cingulate. This pathway has been proposed to be involved primarily in learning and memory. The mesolimbic and mesocortical pathways are involved in reward and emotions, as well as in motivational aspects of motor activity (Alcaro, et al. 2007; Laviolette 2007; Wise and Bozarth 1987).

The tuberoinfundibular pathway has its projections from the periventricular and arcuate nucei of the hypothalamus in to the median eminence of the hypothalamus, where DA is released into the hypothalamic-hypophysial portal blood circulation and eventually reaches the pituitary, where it inhibits prolactin release.

1.2.3 Dopamine receptors

Dopamine mediates its actions through five distinct DA receptor subtypes, which are members of the seven-trans-membrane G-protein coupled receptors (Missale, et al. 1998). These receptor subtypes have, based on their biochemical and pharmacological properties as well as on sequence homology, been classified into D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4) receptors (Jaber, et al. 1996; Kebabian and Calne 1979; Missale, et al. 1998; Stoof and Kebabian 1984; Vallone, et al. 2000). Receptors of the D_1-like family stimulate adenylate cyclase, whereas the D_2-like family receptors inhibit this effector. The D_1-like receptors are coupled to a stimulatory G-protein, which causes an activation of adenylate cyclase, leading to an increase in the concentration of the intracellular second messenger cAMP (cyclic adenosine monophosphate). The D_2-like receptors are coupled to an inhibitory G-protein, which in contrast results in inhibiting adenylate cyclase, thus decreasing cAMP (Emilien, et al. 1999; Missale, et al. 1998). The major target of cAMP is PKA (protein kinase A). These intracellular events are starting points for several divergent electrophysiological and biochemical intracellular mechanisms. The D_1 and D_2 receptors have the most widespread and highest levels of expression of the DA receptors.

1.2.3.1 D_1-like receptors

Of all DA receptors, DA D_1 receptors, investigated in Study III, are the most widely distributed in the brain. The D_1 receptor is expressed with high concentrations in the caudate nucleus, putamen, nucleus accumbens and olfactory tubercle. This receptor is also expressed in amygdala, globus pallidus, substantia nigra, ventral tegmental area, hippocampus, hypothalamus and thalamus (Jackson and Westlind-Danielsson 1994; Missale, et al. 1998). In the cerebral cortex, the D_1 receptor is highly expressed in areas such as the prefrontal cortex, and has been implicated as a key player in several cognitive functions (Fremeau, et al. 1991; Hurd, et al. 2001).

The DA D_5 receptor, which is the other D_1-like receptor subtype, is expressed in lower levels throughout the brain, and is primarily present in the cortex including frontal areas, hippocampus, hypothalamus and certain areas of thalamus but is also found in the caudate nucleus, putamen, nucleus accumbens, substantia nigra and olfactory tubercle (Choi, et al. 1995; Khan, et al. 2000).

1.2.3.2 D_2-like receptors

The D_2 receptor, examined in Study I and III, is mainly located postsynaptically. About 5% is expressed presynaptically, acting as autoreceptors (Filloux, et al. 1987; Joyce and Marshall 1987). The highest densities of the D_2 receptors are found in MSNs in the

striatum, the nucleus accumbens, and olfactory tubercle (Weiner, et al. 1991). With the exception of substantia nigra, much lower densities are found in extrastriatal regions such as thalamus and throughout cortical regions (Kessler, et al. 1993). The distribution of DA D_2 receptors is thus rather similar to the D_1 receptors. However, in cortical areas, this receptor type is expressed to a lower extent than the D_1 receptor. Contrarily, in extrastriatal areas the D_2 receptor is present in higher levels in hypothalamus, thalamus, midbrain areas and in the pituitary gland (Hurd, et al. 2001; Jackson and Westlind-Danielsson 1994; Weiner, et al. 1991).

Albeit at lower concentrations, the DA D_3 receptor distribution is similar to the distribution of the D_2 receptor in several brain regions, and is primarily found in limbic areas such as nucleus accumbens, the islands of Calleja, and the dentate gyrus of hippocampus (Bouthenet, et al. 1991; Suzuki, et al. 1998), and may mediate abnormalities of memory, speech, and focused attention in schizophrenia (Sokoloff, et al. 1990; Suzuki, et al. 1998).

The DA D_4 receptor is highly expressed in the frontal cerebral cortex, hippocampus, hypothalamus, amygdala and olfactory tubercle (Defagot, et al. 1997; Jackson and Westlind-Danielsson 1994; Lahti, et al. 1995; Primus, et al. 1997). This receptor subtype has a more limited distribution with little or no expression in subcortical areas such as the caudate nucleus, putamen, and nucleus accumbens.

1.2.3.3 Function of dopamine D_1 and D_2 receptors

Enhanced dopaminergic transmission in the brain results in a behaviorally aroused state, and is referred to as psychomotor activation. In experimental animals, enhanced dopaminergic transmission such as by psychostimulants is observed as an increase in locomotor activity and repetitive stereotype behavior (Beninger 1983; Randrup and Munkvad 1974). A decreased DA signaling causes a hypoactive psychomotor state including motor disturbances such as parkinsonism or catalepsy (Johnels 1982). The DA D_2 receptor has been implicated as important for such symptoms. Dopamine D_2 receptor antagonists, e.g. neuroleptics, frequently cause extrapyramidal side effects whereas D_2 receptor agonists are often used to improve motor function in Parkinson's disease.

Contrarily to the D_2 receptor, the function of the DA D_1 receptor is less understood. Similar to the D_2 receptor, animal studies have shown that D_1 receptor agonists induce stereotypies (Deveney and Waddington 1997; Molloy and Waddington 1984). However, the overall effects on locomotion of D_1 receptor agonists are not clear, and both enhanced locomotion and inhibited locomotion has been reported (Desai, et al. 2005; Meyer and Shults 1993; Salmi and Ahlenius 1996). One explanation could be that the effects on locomotion by a D_1 receptor agonist are dependent on whether DA D_2 receptors are stimulated simultaneously. In that case, locomotion is enhanced in synergy, and it has been postulated that a concomitant stimulation of DA D_1 receptors is required to obtain maximum locomotor stimulation of a D_2 receptor agonist (Dreher and Jackson 1989; Gershanik, et al. 1983; Salmi 1998). Similarly to DA D_2 receptor blockade, antagonism of D_1 receptors result in hypoactivity and in higher doses catalepsy (Jackson and Westlind-Danielsson 1994; Morelli and Di Chiara 1985).

1.2.4 PET imaging of dopamine receptors

In vivo neuroreceptor PET imaging studies have contributed to a greater understanding of the DA system in health and disease. This method has also greatly contributed to drug development (Brooks 2005; Halldin, et al. 2001; Talbot and Laruelle 2002). A number of PET radioligands have been developed to measure DA D_1 and D_2 receptors (Farde, et al. 1987; Farde, et al. 1997; Halldin, et al. 1995; Halldin, et al. 1998; Halldin, et al. 2001; Karlsson, et al. 1993). PET imaging on D_2 receptors have contributed to the understanding of antipsychotic treatment in schizophrenia as well as for indirect studies of dopamine release (Farde, et al. 1988; Tedroff, et al. 1996). For imaging of D_2 receptor distribution, antagonist radioligands such as [^{11}C]raclopride has been widely used to measure striatal receptors; more recent development include antagonist radioligands with higher affinity, thus enabling measurements of extrastriatal receptor distribution (Farde, et al. 1986; Halldin, et al. 1995), as well as agonist radioligands (Seneca, et al. 2006). The D_1 receptors have been less studied. However, several D_1 antagonist radioligands such as [^{11}C]SCH23390 and [^{11}C]NNC112 have been developed and validated for human use (Hirvonen, et al. 2001; Slifstein, et al. 2007).

1.2.5 Dopamine and Huntington's disease

Neuropathological studies have revealed that striatal neurons expressing dopamine receptors are affected early in HD (Cross 1983; Reiner, et al. 1988; Reisine, et al. 1978; Spokes 1980), and alterations in dopamine signaling has been implicated to play a key role in the pathogenesis of HD (Johnson, et al. 2006). By inducing elevated Ca^{2+} signals in a synergistic effect with glutamate signaling pathways, dopamine may play an important role in striatal cell death in HD (Benchoua, et al. 2008; Tang, et al. 2007; van Oostrom, et al. 2009). Furthermore, it has been shown that low doses of DA can act in synergy with mutant huntingtin, resulting in activation of proapoptotic transcription factors. *In vitro*, DA has been shown to increase aggregate formation, which could be reversed by a selective D_2 antagonist (Charvin 2005). *In vivo*, a hyperdopaminergic mouse model of HD, which exhibited increased stereotypic activity followed by a locomotor hyperactivity, revealed that aggregates occurred to a bigger extent and much earlier in striatal and extrastriatal brain regions (Cyr, et al. 2006).

Dopamine released from midbrain DA neurons acts on postsynaptic DA receptors located on MSNs in the striatum to initiate a signaling cascade leading to altered transcription factor activity, gene expression and neuronal activity. The classical hallmark of HD is degeneration of MSNs in the striatum, and thus a marked loss of postsynaptic DA receptors has been demonstrated in HD (Cross 1983; Reiner, et al. 1988; Spokes 1980).

A postmortem autoradiography study showed DA D_1 and D_2 receptor loss early in the disease, where the D_1 receptor reduction was seen in the globus pallidus interna (GP_i) and substantia nigra pars reticulata and the decreased D_2 receptor density was most pronounced in the globus pallidus externa (GP_e) (Richfield, et al. 1991). In this study, striatal areas showed involvement of both D_1 and D_2 receptors but with greater D_1

receptor reductions. Another postmortem study investigating one subject with premanifest HD, reported a preferential loss of striatal neurons projecting to the GP_e (Albin, et al. 1992b). There are still controversies regarding whether there is a parallel loss of these receptor subtypes or whether one subtype is preferentially affected. In one PET study, D_1 and D_2 receptor binding in HD gene carriers were shown not to correlate, suggesting the occurrence of a variable dysfunction among individual HD gene carriers, a finding that may explain some of the heterogeneity in HD (Andrews, et al. 1999). However, other PET studies have shown a parallel loss of D_1 and D_2 receptors in patients with HD (Ginovart, et al. 1997; Turjanski, et al. 1995; Weeks, et al. 1996). A hypothesis has been suggested that the D_2 baring 'indirect pathway' is targeted preferentially as compared to the D_1 receptor rich 'direct' pathway from striatum to GP_i (Albin, et al. 1995; Hedreen and Folstein 1995). However, this theory has been widely questioned. One major concern is that it is not fully clarified whether DA receptor subtypes are strictly segregated with the striatal projection neurons on the direct and indirect pathways or if they are co-localized on individual striatal neurons (Albin, et al. 1992b; Bloch and Le Moine 1994; Gerfen 1992; Gerfen and Keefe 1994; Lester, et al. 1993; Reiner, et al. 1988; Surmeier DJ 1992; Surmeier, et al. 1993). Nevertheless, there is evidence suggesting that functional D_1 and D_2 class receptors are co-localized in nearly one-half of all MSNs (Surmeier, et al. 1996). Although it is not clear whether there occurs a parallel loss of these receptors in the disease and which receptor is primarily affected, it is however evident that both receptor subtypes are affected early in the disease, and can thus be interesting as biomarkers for HD progression.

In contrast to the relatively well-characterized integrity of postsynaptic dopamine receptors in HD, little has been investigated with regard to the presynaptic system. There are several studies suggesting a dysfunction of the presynaptic nigrostriatal dopamine system in HD. However, divergent results have been reported regarding neurochemical measurements in patients with HD. Dopamine and its two major metabolites, homovanillic and 3,4-dihydroxyphenylacetic acids, have been reported as reduced (Cunha, et al. 1981; Kish, et al. 1987), elevated (Spokes 1980), or unaltered (Bird and Iversen 1974) in the striatum or cerebrospinal fluid in these patients. Furthermore, while the dopamine neuron population in the substantia nigra appears preserved (Waters, et al. 1988), a loss of dopamine terminals has been reported (Ferrante, et al. 1987). This finding is supported by two PET studies demonstrating reductions in both DAT and vesicular transporter protein (Bohnen, et al. 2000; Ginovart, et al. 1997). However, the magnitude of such reductions in nerve terminal measurements in HD is not fully elucidated. It is possible that the results to some extent are affected by volume loss and decreased blood flow in the striatum. The integrity of the mesocortical and mesolimbic pathways has not been specifically investigated in HD.

1.2.6 Cognitive function, dopamine and HD

Several neuroimaging studies have shown a significant correlation between structural or functional striatal integrity and cognitive functions in symptomatic HD patients, such as executive function, memory and psychomotor speed (Bamford, et al. 1995; Berent,

et al. 1988). Another study has shown that assessments for executive functions such as the Wisconsin card sorting test in HD is associated with increased blood flow in the prefrontal cortex, concluding that a functionally intact frontal cortex needs to "work harder" to compensate for the striatal dysfunction (Goldberg, et al. 1990). However, yet other studies have shown that cortical dysfunction is better correlated to cognitive impairment than striatal atrophy (Harris, et al. 1996; Sax, et al. 1996). It is thus likely that both striatal and cortical dysfunction and degeneration contribute to the cognitive impairment in HD.

A critical level of DA and DA D_1 receptor stimulation is necessary for a proper performance in prefrontal cortex-related cognitive tasks like working memory and attentional functions (Granon, et al. 2000; Williams and Goldman-Rakic 1995). Studies have demonstrated a relationship between DA D_2 receptor density in the striatum and cognitive performance (Volkow, et al. 1998), in particular in processes involving switching behavior, working memory and planning (Arnsten, et al. 1995; Mehta, et al. 1999); cognitive processes which are particularly affected in HD. Furthermore, striatal D_2 receptor reduction has been associated with impairments in executive functions such as planning, memory, sequence process and response inhibition in premanifest HD individuals (Lawrence, et al. 1998). In addition, there are increasing data indicating that D_2 receptors in extrastriatal regions, such as amygdala, hippocampus, anterior cingulate, ventrolateral frontal cortex, and thalamus are involved in cognitive processes (Aalto, et al. 2005; Christian, et al. 2006).

1.2.7 Synaptic plasticity

1.2.7.1 Glutamate receptors

The amino acid L-glutamate is the major excitatory transmitter in the brain. This neurotransmitter is involved in many different brain functions, such as neuronal cell survival and death, proliferation and development of neuronal and glial cells, and plastic changes in efficacy of synaptic transmission (Nakanishi 1992). However, glutamate neurotoxicity can result in neurodegeneration and neuronal cell death in disorders such as Alzheimer's and Huntington's disease. There are two different glutamate receptor families: ionotropic receptors which are ion channels and metabotropic receptors which are G-protein coupled receptors linked to second messenger pathways (Conn and Pin 1997; Schoepp, et al. 1999). Ionotropic glutamate receptors are glutamate-gated ion channels that when activated increase cellular excitability. The NMDA receptor is one subgroup of ligand-gated channel receptors, which is highly permeable to Ca^{2+}, Na^{+}, and K^{+}, and the resultant increase of intracellular Ca^{2+} is thought to be responsible for evoking both neuronal plasticity and neurotoxicity (Nakanishi 1994).

1.2.7.2 Dopamine and glutamate interaction

Long-term potentiation (LTP) and long-term depression (LTD) are well-characterized mechanisms underlying learning and memory (Malenka, et al. 2004; Martin, et al.

2000). Dopamine is involved in synaptic plasticity by modulating LTP and LTD (Malenka, et al. 2004; Martin, et al. 2000; Otani, et al. 2003; Picconi, et al. 2003). Furthermore, by the same mechanisms, dopaminergic neurotransmission in primary motor cortex plays a crucial role for motor skill learning and the related synaptic plasticity (Molina-Luna, et al. 2009).

The interaction between the dopamine receptors is not fully understood. There is evidence that D_1 and D_2 receptors act in functional synergy (La Hoste, et al. 1993). However, it is also demonstrated that the activation of each subtype may in some conditions result in antagonistic effects (Nestler 1994). Interestingly, the D_1/D_2 receptor synergy dissolves in perturbed experimental conditions such as in dopamine depletion or receptor blockade (Gerfen, et al. 1990; La Hoste, et al. 1996). Thus, the effects of dopamine are very heterogeneous and there seem to be a number of variables and conditions that contribute to its actions. Dopamine might thus suit better defined as a neuromodulator, since it *per se* is neither inhibitory nor excitatory, but rather has the ability to alter the action of other neurotransmitters (Cepeda, et al. 1998).

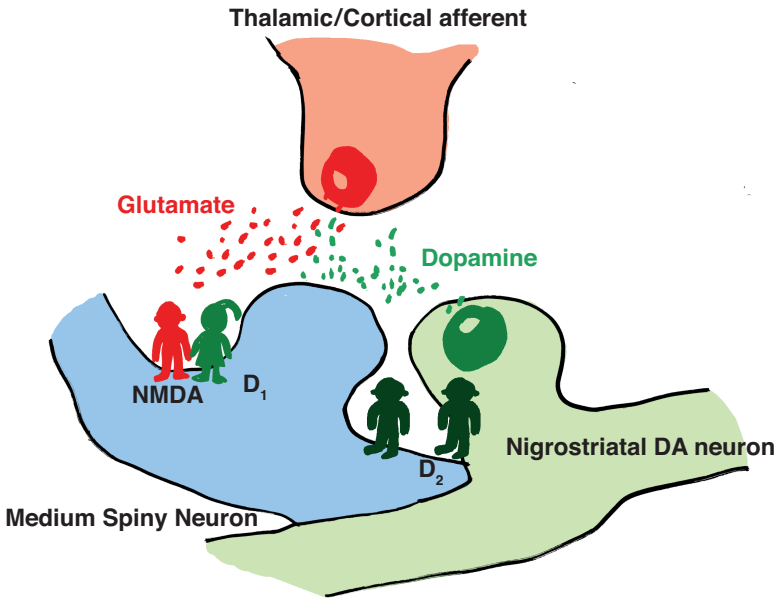

FIGURE 4
Localization of dopamine and glutamate receptors in the striatum. The postsynaptic MSN receives presynaptic input from nigrostriatal dopamine neurons as well as from corticostriatal and thalamostriatal neurons.

There is evidence that glutamate receptors such as the NMDA receptor and the AMPA receptor are co-localized on the majority of MSNs in the striatum (Albin, et al. 1992a; Ariano, et al. 1997; Standaert, et al. 1994; Tallaksen-Greene, et al. 1992). In the cortex, *in vivo* animal studies investigating the prefrontal cortex have shown that dopamine stimulates PKA through D_1 receptors to facilitate LTP (Gurden, et al. 2000). On the other hand, LTP in the prefrontal cortex requires functional NMDA receptors (Hirsch and Crepel 1991; Jay, et al. 1995) indicating that D_1 and NMDA receptors may

cooperate in LTP-inducing mechanisms (Otani, et al. 2003). Data from electrophysiological studies have revealed that the enhancement of NMDA receptor responses is mediated by the activation of D_1 receptors and blocked by D_1 antagonists, whereas this did not apply to D_2 receptor activation or D_2 antagonists, which decreased or did not affect NMDA activation (Cepeda, et al. 1993; Cepeda and Levine 1998). Thus, the direction of receptor subtype activation can determine the modulatory effects of dopamine (Cepeda, et al. 1998), filtering afferent striatal input (Cepeda, et al. 1993; Cepeda, et al. 1992). Dopamine and D_1 receptor mediated enhancement of NMDA responses have been described in different parts of the brain, including the cerebral cortex and subcortical regions such as the striatum (Cepeda, et al. 1993; Cepeda and Levine 1998; Cepeda, et al. 1992; Chen, et al. 2004; Chergui and G. Lacey 1999; Wang and O'Donnell 2001).

FIGURE 5
Dopamine D_1 receptors interact physically with the NMDA receptor. This interaction is important for the induction of LTP and synaptic plasticity.

Synaptic responses studied in cortical pyramidal neurons show that enhancement of NMDA receptor mediated responses follows an inverted U-shaped dose-response curve (Seamans and Yang 2004). This is in agreement with the idea that optimal D_1 receptor activity is required for cognitive performance such as in working memory (Lidow, et al. 1998). Thus, neither too little nor too much of D_1 receptor activation is favorable for optimal cortical function. Similarly, the prevailing excitotoxic hypothesis of HD is

based on the assumption that hyperglutamatergia at the corticostriatal terminals associated with altered sensitivity of NMDA receptors may trigger apoptosis and cell death in vulnerable neurons (DiFiglia 1990). Experimental results suggest that activation of extrasynaptic NMDA receptors may cause cell death and apoptosis, whereas synaptic activation may trigger anti-apoptotic effects in hippocampal neurons (Hardingham 2002).

The activation of D_1-like receptors is also required for the induction of LTP in the striatum. Antagonism of D_1 receptors block NMDA-dependent LTP, whereas this effect is reversed by the activation of D_1 receptors (Calabresi, et al. 2000; Kerr and Wickens 2001). Similarly, D_1 antagonists have deleterious effects on working memory (Sawaguchi and Goldman-Rakic 1994). Similar to other neuropsychiatric diseases such as schizophrenia, patients with HD often suffer from both positive and negative symptoms, i.e. lack of voluntary movements and chorea, as well as productive neuropsychiatric symptoms alongside with apathy. Thus, there is a need for a treatment that can both enhance and counteract different activities in different brain regions depending on their initial levels. An appropriate treatment should be able to reverse both positive symptoms such as chorea, psychosis, irritability and aggression, as well as negative symptoms such as impairment of voluntary movements and apathy, and without impairing cognitive functions. As such, there is a need for a treatment that would increase both D_1 and NMDA receptor function (Cepeda and Levine 2006), without overstimulation of the dopaminergic or glutamatergic system, maintaining a functional balance between the D_1 and D_2 receptors (Scott and Aperia 2009).

1.3 IMAGING

1.3.1 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an imaging modality often used in brain imaging. The human body is to a vast degree composed of water molecules consisting of hydrogen nuclei or protons, which is used by MRI. Placing an individual inside the magnetic field of the MRI scanner, the magnetic moments of some of these protons change, resulting in an alignment with the direction of the field. A radio frequency transmitter in the MRI is briefly turned on, producing an electromagnetic field. The resonance frequency is made by the photons of this field that have just the right energy to flip the spin of the aligned protons in the body. More aligned spins are affected, as the intensity and duration of application of the field increase. When the field is turned off, the protons decay to the original spin-down state and the difference in energy between the two states is released as a photon. What the scanner detects is the electromagnetic signal created by these photons. The frequency the protons resonate at depends on the strength of the magnetic field. The protons in different tissues return to their equilibrium state at different rates, thus constructing an image.

1.3.2 Positron emission tomography

Positron emission tomography (PET) is an *in vivo* imaging technique, which uses radioactive isotopes that decay by positron emission, to map molecular interactions of biological processes producing a three-dimensional image of functional processes in the body. PET has been widely used to study brain function, pathophysiology and therapeutic interventions. The PET technique is based on the utilization of radiotracers labeled with positron-emitting radionuclides (e.g. ^{18}F or ^{11}C), allowing for the study of different biological variables such as anatomical distribution, metabolism of the tracer, and drug-related receptor occupancy. The radionuclides are incorporated either into compounds normally used by the body such as glucose and water, or into molecules that bind to receptors or other sites of drug action. Such labeled compounds are known as radiotracers.

Isotope	Half-life (min)	Tracer compound	Physiological process	Typical application
^{11}C	20.3	Raclopride	D_2 receptor antagonist	Movement disorders
^{11}C	20.3	SCH23390	D_1 receptor antagonist	Cognition
^{13}N	9.97	Ammonia	Blood perfusion	Myocardial perfusion
^{15}O	2.03	Water	Blood perfusion	Brain activation studies
^{18}F	109.8	FDG	Glucose metabolism	Oncology, neurology

TABLE 1
Examples of commonly used isotopes in PET imaging.

The tracer molecule is injected intravenously and distributed throughout the body through the blood stream, binding to the target molecule in the brain after passing the blood brain barrier. As the radioactive molecule decays, the emitted positron (β+) particle annihilates with one electron (β−). The distance that the positron travels before annihilation consists of about 1 mm, depending on the tissue and the β+ energy of the isotope. The annihilation results in two photons (γ particles) with an energy of 511keV respectively. The photons travel at approximately 180°±1° and the coincidences are then detected by the PET system.

The scanners contain several rings of positron-sensitive scintillation detectors, with up to 25.000 individual scintillators. The rings of scintillation detectors register thousands of coincidence events emitted from the subject per second (Cherry 2001; Phelps and Mazziotta 1985). The technique depends on simultaneous or coincident detection of the pair of photons; photons which do not arrive in pairs (i.e. within a timing window of few nanoseconds) are ignored. The data gathered from the coincidence events are used

to determine the source of positron annihilation at a given time. These are then converted into a tomographic image via reconstruction algorithms.

The divergence degree of the photons depends on the momentum of the annihilating positron and electron at the time they meet. This, together with the β+ range, is the factor that set the lower limit to the spatial resolution of PET systems (Eriksson, et al. 1990). Accuracy in PET image data is mainly determined by the sensitivity and spatial resolution of the PET system. The spatial resolution is defined as the degree to which the representation of an object is blurred in the image, commonly expressed in terms of its full width at half maximum (FWHM). The point spread function (PSF) describes the response of an imaging system to a perfect point source where the imaging system introduces a non-perfect and blurred version of this original point or object. FWHM is defined in the Gaussian representation of the perfect point source, as the distance where the intensity in the image is half of the maximal value. By consequence of the PSF, quantitative PET measurements of objects smaller than two to three times the FWHM will result in an underestimation of the signal. Also, activity from surrounding tissue will influence the signal measured in a volume element (spill-over effect). These phenomena are summarized as partial volume effects (PVE) and have to be taken into consideration when measuring radioactivity in small regions (Hoffman, et al. 1979; Kessler, et al. 1984).

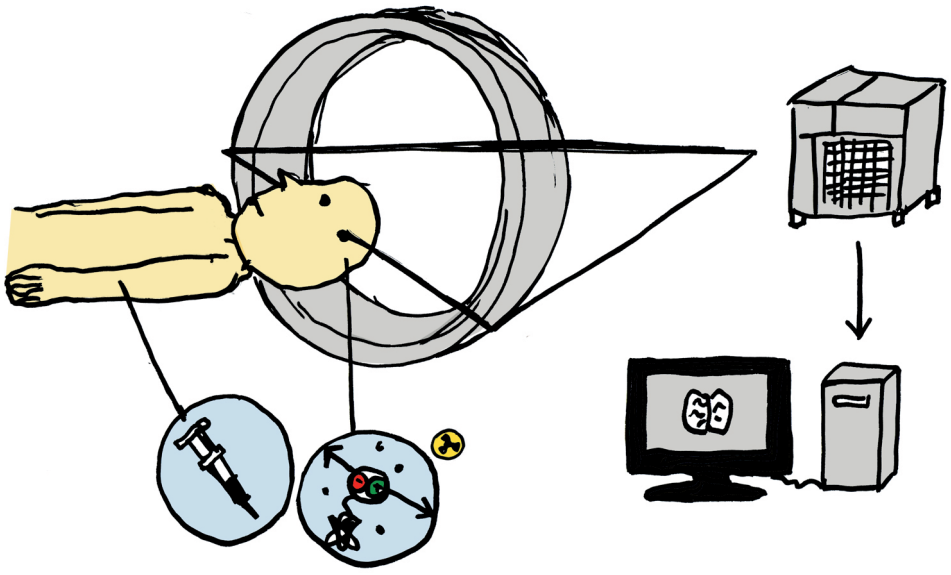

FIGURE 6
Schematic overview of PET data acquisition and image reconstruction.

1.3.3 PET imaging in HD

1.3.3.1 Dopamine receptor imaging in HD

PET imaging has been used to measure and elucidate various functional changes in HD such as aspects of dopaminergic transmission and cerebral metabolic changes (Antonini, et al. 1996; Ciarmiello, et al. 2006). The integrity of striatal dopamine D_2 receptors has been extensively studied in patients with HD. PET studies using the D_2 antagonist [^{11}C]raclopride shows a progressive loss of D_2 receptors in the striatum in patients with HD as well as in premanifest subjects (Andrews, et al. 1999; Antonini, et al. 1996; Brandt, et al. 1990; Farde, et al. 1987; Feigin, et al. 2007; Ginovart, et al. 1997; Lawrence, et al. 1998; Leenders, et al. 1986; Turjanski, et al. 1995; van Oostrom, et al. 2009; Weeks, et al. 1996). Decreasing striatal D_2 receptor expression might be one of the earliest physiological manifestations in HD, potentially related to progressive cell death and neuronal dysfunction due to altered neuronal metabolism and intradendritic huntingtin aggregates as well as transcriptional dysregulation induced by the CAG repeat expansion (Augood, et al. 1997; Beal 2000; Cha, et al. 1999; Gutekunst, et al. 1999; Panov, et al. 2002).

There is a normal age-related loss of D_2 receptors, both in the striatum (Ichise, et al. 1998) and in extrastriatal regions (Kaasinen, et al. 2000). However, the striatal [^{11}C]raclopride binding decline is only 0.6% per year in normal subjects (Antonini, et al. 1993). This natural decline accounts only for about 10% of the decline seen in premanifest mutation carriers (Antonini, et al. 1996). Clinically manifest HD patients have an annual loss of striatal dopamine D_2 receptor availability of in the magnitude of 5-10% (Andrews, et al. 1999; Antonini, et al. 1996; Feigin, et al. 2007). Extrapolation of available data indicates that a loss of D_2 could occur already 25 years before manifest disease (Feigin, et al. 2007).

There seems to be a certain threshold level for receptor density or neuronal density under which clinical manifestations are observed. In fact, an individual might have an intact neurological examination despite a 50% receptor loss of normal mean value, illustrating that the affected subject may remain clinically unaffected even at severe degrees of dopamine receptor binding loss (Antonini, et al. 1996). This further strengthens the notion of the presence of effective compensatory mechanisms in the premanifest phase of HD.

While a multitude of studies describing the integrity of D_2 receptors in the striatum have been reported, the distribution and integrity of such receptors extrinsic to the striatum in HD patients is less well known. Dopamine D_2 receptor density ranges between 0,2 – 40 nM in different human brain regions, with an intrastriatal/extrastriatal ratio of approximately 1:100 (Kessler, et al. 1993). Albeit at low density, dopamine D_2 receptors are thus also present in the cerebral cortex and subcortical regions. An early study performed on postmortem tissue from three HD patients treated with antipsychotic medication showed a marked reduction in [^{3}H]-spiroperidol binding in the striatum and frontal cortex (Reisine, et al. 1977). Another study including six patients with HD showed a longitudinal decline in [^{11}C]raclopride binding in several extrastriatal regions, but were however not able to quantify this stated loss (Pavese, et

al. 2003). A recent study from the same laboratory found clusters of cortical [^{11}C]raclopride binding potential reductions in 62% of patients with HD (Pavese 2010). However, due to its low affinity for D_2 receptors, the appropriateness of using [^{11}C]raclopride for measuring dopamine D_2 receptor binding in extrastriatal regions is questionable. To quantify such low density receptor populations the high affinity radioligand [^{11}C]FLB457 has been developed (Delforge, et al. 2001; Farde, et al. 1997; Halldin, et al. 1995; Olsson and Farde 2001; Olsson, et al. 1999; Suhara, et al. 1999). Because of its slow kinetics, this high affinity radiotracer has been considered less suitable for high-density regions such as the striatum, since a receptor density above 7 nM causes the time of equilibrium to fall beyond the time of data acquisition (Olsson and Farde 2001).

As for the extrastriatal D_2 receptor integrity, surprisingly few PET studies have been performed to investigate the integrity of the D_1 receptor in HD. Postmortem studies have indicated an early and marked loss of cerebral D_1 receptors in patients with HD (Cross 1983; Filloux, et al. 1990; Joyce, et al. 1988; Reisine, et al. 1977; Richfield, et al. 1991). A PET imaging study showed a reduced D_1 receptor number by 75 percent (compared to a striatal volume reduction of 50 percent) in patients with mild to moderate stage disease compared to controls (Sedvall, et al. 1994). Another PET study showed a reduction of D_1 receptor densities in the striatum and in the cerebral cortex (Ginovart, et al. 1997). As the D_1 receptor is closely related to synaptic plasticity and cognitive functions, further investigations on this topic are clearly needed in HD.

1.3.3.2 PET and cerebral glucose metabolism in HD

Measurements of cerebral blood flow and glucose metabolism are valuable in assessing neuronal function and are often associated with clinical changes in neurodegenerative disorders. Study of brain metabolism can thus capture aspects of functional abnormalities other than those reflected by impaired neuroreceptor integrity. An early and well-established finding is the hypometabolism in the striatum in manifest as well as in premanifest HD (Antonini, et al. 1996; Berent, et al. 1988; Hayden, et al. 1986; Kuwert, et al. 1990; Kuwert, et al. 1993; Mazziotta, et al. 1987; van Oostrom, et al. 2009; Young, et al. 1986). Longitudinal studies also demonstrate about three percent annual reduction in striatal glucose metabolism in premanifest subjects compared to normal ageing (Antonini, et al. 1996; Grafton, et al. 1992). Striatal metabolic decline can evolve in absence of atrophy, indicating that metabolic and structural cerebral changes may develop independently (Grafton, et al. 1992; Mazziotta, et al. 1987). In addition to such findings in the striatum, thalamic and cortical abnormalities in metabolism and perfusion have also been demonstrated both in patients and premanifest subjects (Grafton, et al. 1992; Martin, et al. 1992; Sax, et al. 1996).

An interesting HD specific spatial covariance pattern of metabolism has been described discriminating premanifest HD gene carriers from healthy subjects (Feigin, et al. 2001; Ma and Eidelberg 2007; Trost, et al. 2002). This HD related pattern (HDRP) is characterized by relative bilateral increases in glucose metabolism in the thalamus, cerebellum, visual and primary motor cortices and relative decreases in striatum and anterior cingulate. The HDRP expression increases significantly in premanifest subjects, but starts to decline as approaching phenoconversion; however, still being

elevated compared to controls. It has been argued that this non-linear trajectory of HDRP might be a compensatory process active prior to phenoconversion. Further analysis of key nodes of HDRP reveals that the striatal metabolism declines progressively and remains low at all times as compared to controls, even after atrophy correction. Contrarily, the elevated thalamic metabolism at baseline is normalized falling to subnormal levels at phenoconversion. This increase was particularly seen in the left MD thalamus. In line with these results, a study in premanifest individuals could demonstrate an increase in this structure during performance of a motor learning task (Feigin, et al. 2006). Taken together, it is likely that the increase in thalamic activity may compensate for loss of corticostriatal activity in the early premanifest period. As neurodegeneration progresses, this compensatory mechanism diminishes and symptoms begin to appear. Loss of thalamic compensatory mechanism might thus be what finally leads to phenoconversion.

1.4 TREATMENT OF HD

1.4.1 Current pharmacological management

During the last decade, results from several clinical trials aiming to find a treatment for HD have been reported. However, no such treatments have been shown to provide clinically significant benefit, or to slow down disease progression and disability in patients with HD. Recent reviews, analyzing available therapeutic interventions for the symptomatic treatment of HD, failed to result in any treatment recommendations of clinical relevance (Bonelli and Hofmann 2004; Bonelli and Wenning 2006; Mestre, et al. 2009). Nevertheless, in current clinical practice, numerous medications approved for other indications are used to treat patients with HD.

1.4.1.1 Treatment of motor symptoms in HD

Antidopaminergic therapy is frequently used in patients with HD to treat chorea and behavioral disturbances (van Duijn, et al. 2010). Although chorea could be regarded as a hallmark symptom in HD, it is probably the least disabling symptom of the disease. Nevertheless, patients with HD are frequently treated with typical and atypical neuroleptics, and dopamine-depleting agents to reduce chorea (Tyler, et al. 1996). There is insufficient evidence for the efficacy of neuroleptics in HD and such treatments are frequently associated with adverse reactions. As an example, moderate doses of haloperidol (<10 mg/day) was associated with a slight reduction of chorea, but at an expense of worsening gait and swallowing, and the acceleration of cognitive and functional decline (Barr, et al. 1988; Louis, et al. 1999; Moskowitz and Marder 2001; Schott, et al. 1989). Tetrabenazine is a monoamine-depleting agent causing dopamine and serotonin depletion by blocking vesicular transporters, and is currently the only drug approved for the treatment of chorea in HD. Tetrabenazine has been used for decades in Europe where its efficacy in HD was established in a number of limited clinical trials (Asher and Aminoff 1981; Swash, et al. 1972). A more recent pivotal double blind placebo controlled trial underlying the approval of tetrabenazine in North

America showed that the compound was efficacious in reducing chorea in patients with HD (TETRA-HD and The Huntington Study Group 2006). However, tetrabenazine also proved to worsen a number of exploratory outcome measures, such as the functional assessment, the Hamilton depression scale, the Epworth sleepiness scale, and the Stroop word reading test, once more confirming previous experience that the drug has disabling side effects in patients with HD.

A number of drugs with glutamate antagonist properties have also been studied. Clinical trial results for the NMDA antagonist amantadine have been contradictory. The effects of the drug has either been reported to reduce the median maximal chorea and median rest chorea (Verhagen Metman, et al. 2002) or to be inefficacious in reducing chorea (O'Suilleabhain and Dewey 2003). In one of the largest clinical trials ever conducted in HD, riluzole treatment was not efficacious for HD (Landwehrmeyer, et al. 2007). Moreover, in a double blind clinical trial in more than 300 HD patients over more than two years, the glutamate antagonist remacemide was shown to be ineffective for the treatment of HD (Huntington Study Group 2001).

In addition to antidopaminergic and antiglutamatergic drugs, other compounds have been investigated for the treatment of HD. All attempts to decrease chorea by influencing the GABAergic neurotransmission have failed (Foster, et al. 1983; Goetz, et al. 1990; Manyam, et al. 1987; Perry, et al. 1980; Perry, et al. 1982; Schoulson, et al. 1978; Scigliano, et al. 1984; Symington, et al. 1978). Likewise, trials with other compounds such as cannabidiol, donepezil, fluoxetine, minocycline, piracetam, and trans-dyhidrolisuride have been investigated, and all showing negative results for efficacy outcome measures (Como, et al. 1997; Consroe, et al. 1991; Cubo, et al. 2006; Mateo and Gimenez-Roldan 1996; MINO and The Huntington Study Group 2004; Stocchi, et al. 1989). Negative results have also been obtained from clinical trials with ethyl-eicosapentaenoic acid, L-acetyl carnitine and creatine (Goetz, et al. 1990; Hersch, et al. 2006; The Huntington Study group 2007).

A recent Cochrane review on the symptomatic treatment of HD concludes that no intervention has proven to provide efficient symptomatic improvement in HD (Mestre, et al. 2009). Although tetrabenazine is regarded as the anti-choreic medication with best available clinical evidence, only one trial has been of sufficient quality to be included in this systematic review. In addition, tetrabenazine was shown to worsen other clinical aspects of the patient important for their functional capacities and quality of life. No statement could thus be made regarding the effectiveness of available medication in other areas of symptomatic control of motor functions due to the lack of evidence extractable from clinical trials.

1.4.1.2 Treatment of psychiatric symptoms in HD

Non-motor symptoms in HD have not been adequately addressed in interventional studies. In fact, none of the selected trials in the recently published Cochrane review was primarily conducted to study therapeutic effects on the control of psychiatric symptoms or cognitive decline; symptoms which have a significant effect on the quality of life of HD patients and their families (Mestre, et al. 2009).

To date, there have been no controlled trials in HD addressing depression or anxiety as primary objectives, and as such no evidence based treatment recommendations can be given. For other psychiatric symptoms, results have also been inconsistent. Intervention trials to treat psychotic symptoms in HD have yielded negative results (Folstein, et al. 1983; Jensen, et al. 1993; Mendez 1994; Oliver 1970; Watt and Seller 1993).

Common behavioral symptoms in HD include irritability, aggression and impulsivity. Although neuroleptics such as haloperidol and olanzapine have been indicated to be useful in patients with irritability and aggressive outburst (Leonard, et al. 1975; Paleacu, et al. 2002; Squitieri, et al. 2001), none of these trials provide sufficient evidence for such treatment claims. Hypersexuality is an often-neglected symptom in patients with HD. There are however a few case reports on patients with HD treated with for example leuprolide, a gonadotropin-releasing hormone agonist, and medroxyprogesterone acetate to reduce exhibitionism and hypersexuality (Blass, et al. 2001; Rich and Ovsiew 1994). Apathy as well as obsessive-compulsive behavioral disorder are very common features in patients with HD. Although the prevalence of such symptoms have been reported as high as 50-60% of patients, no pharmacotherapy has yet been studied for the treatment of these symptoms in HD (Anderson, et al. 2001; Pflanz, et al. 1991).

1.4.1.3 Treatment of dementia in HD

Dementia is a cardinal clinical feature in HD. Although it usually develops in the late stage of the disease, slight neuropsychological deficits are commonly found already in the premanifest stage (Tabrizi, et al. 2011). Patients with HD develop a type of dementia, which is mainly characterized by a dysexecutive syndrome including slowness of thoughts, impaired flexibility to gain newly acquired knowledge, impaired abstraction ability, apathy and altered personality (Zakzanis 1998). There have been few clinical trials addressing dementia in HD. None of these trials have provided evidence for efficacy. One compound showed to improve the mini-mental state examination, but failed to show any effect on dysexecutive syndrome in HD (Kieburtz, et al. 2010).

1.4.2 Towards a novel treatment of HD

It is well established that pharmacological treatments that modify dopaminergic function have impact on the clinical expression of HD. Levodopa treatment provokes chorea in HD; in fact, before genetic testing was available, levodopa challenge tests were used for diagnostic purposes in premanifest HD (Klawans, et al. 1980). Moreover, parkinsonian symptoms such as bradykinesia and hypokinesia in HD seem to be linked to dopaminergic impairment; such symptoms deteriorate by the use of neuroleptic medication (van Vugt, et al. 1997). Thus, it seems that symptoms of HD are modified by dopaminergic modulation. The challenge is to find an optimum, balancing the delicate state between hypo and hyper function.

Dopaminergic stabilizers belong to a novel class of compounds called dopidines. One such compound, pridopidine (ACR16), is in development for the treatment of HD. The hallmark characteristics of compounds belonging to this class are their stabilizing properties on psychomotor functions *in vivo*. Dopaminergic stabilizers such as pridopidine exert their primary effects by binding to dopamine D_2 receptors. Despite being D_2 receptor antagonists, there are several important differences in the pharmacology of these compounds compared to the traditional D_2 receptor antagonists (i.e. the neuroleptics). Dopaminergic stabilizers antagonize the actions of dopamine but, unlike lipophilic antagonists such as neuroleptics, lack the ability to stabilize the inactive state of the D_2 receptor and also show fast dissociation kinetics like the more hydrophilic agonists do. Unlike the agonists, pridopidine has no detectable intrinsic activity, and unlike the antagonists, the compound displays much lower affinity for D_2 receptors, binding preferentially to the activated high affinity state of the D_2 receptor (dopamine-bound D_2 receptor) (Seeman, et al. 2009). *In vitro*, similar to agonists, pridopidine dissociates rapidly from D_2 receptors. The D_2 receptor antagonism of pridopidine is surmountable by dopamine and has a rapid recovery of D_2 receptor mediated responses after washout (Dyhring, et al. 2010; Natesan, et al. 2006). Also, unlike other dopamine antagonists, pridopidine does not induce extrapyramidal side effects, hypokinesia or catalepsy (Pettersson, et al. 2010). *In vivo*, the stabilizing properties of pridopidine are demonstrated by the compound's ability to attenuate amphetamine-induced hyperactivity (to a normal level) and to stimulate psychomotor activity in states of hypoactivity (Ponten, et al. 2010). There are also several additional pharmacological features, making the effects and mechanism of action intriguing. While pridopidine exerts clear effects on rat brain monoaminergic systems as manifested by e.g. dose dependent increases in extracellular levels of dopamine and noradrenaline, as well as increased tissue levels of dopamine metabolites in the frontal cortex, basal ganglia and limbic areas, the compound also induces a dose-dependent increase in mRNA levels of activity regulated cytoskeletal (Arc) protein in the brain. Arc is an early immediate gene regulated in response to synaptic NMDA receptor activation (Martin 2001) and is associated with LTP and cognitive functions. The glutamate modulating properties of pridopidine is also demonstrated by the ability to restore psychomotor activity in hypoglutamatergic conditions, such as after MK-801 administration. Thus, the pharmacological activity of pridopidine extends beyond the dopaminergic system.

It could be argued that the psychomotor stabilizing properties of the dopaminergic stabilizers may partly be explained by their preference for the active state of the DA D_2 receptor (Seeman, et al. 2009). Since presynaptic DA receptors (autoreceptors) have a shorter isoform than the postsynaptic DA receptors and DA has a higher affinity to the short isoform, it is likely that DA autoreceptors are preferentially targeted by pridopidine. Thus, at times when DA transmission is low pridopidine binds to active state presynaptic receptors, reducing presynaptic inhibition and thus removing the negative feedback on DA release, thereby increasing dopaminergic tone. In states when DA transmission is excessive, pridopidine would bind predominantly to the activated postsynaptic receptors, thus antagonizing the effect of DA neurotransmission (NeuroSearch 2009; Pontén, et al. 2009).

Pridopidine has undergone several clinical trials in HD. An initial 4-week phase II study conducted in Scandinavia demonstrated that pridopidine 45 mg was safe and well tolerated in patients with HD (Lundin, et al. 2010). In this fairly short duration trial, assessments for cognitive, motor and psychiatric symptoms indicated that pridopidine improved voluntary motor functions while chorea was not affected by treatment. Based on data from this trial a more extensive trial program was initiated. For these trials a modified motor score (mMS) was used as the primary endpoint. The mMS is a subscale of the broader UHDRS total motor score consisting of items relating to voluntary motor function. The MermaiHD study (Multinational EuRopean Multicentre ACR16 study In Huntington's Disease) was a multicentre, multinational, randomized, double blind, parallel group, efficacy study comparing pridopidine 45 mg once daily or twice daily versus placebo, in a total of 437 patients studied for 6 months. In this study the primary endpoint was voluntary motor function, assessed by the mMS. Secondary and other endpoints included effects on global improvement, cognitive functions, behavior and symptoms of depression and anxiety as well as the safety and tolerability of the drug treatment over this extended period of time. In the MermaiHD study, pridopidine 45 mg twice daily improved voluntary and involuntary motor function, although the primary study endpoint, the mMS, did not meet the pre-specified level of $p<0.025$. For the primary endpoint, the mMS, the p-value was 0.042. Although the mMS effect did not meet the criteria for statistical significance, the effects of pridopidine on the broader motor measure, the total motor score (TMS), was highly significant with a p-value of 0.004 (Squitieri, et al. 2010). The TMS sub-items, dystonia and eye movements were significantly improved compared to placebo, while the scores for chorea were unchanged. Patients who received pridopidine in the highest dose group showed little progression of motor symptoms over these 6 months, while within the placebo group there was a strong correlation between the CAG repeat length and the rate of motor symptom progression, indicating a potential disease modifying effect of pridopidine. Concomitant treatment with neuroleptics, constituting approximately 40% of patients included in the study, did not change positive treatment effects of pridopidine or the side effects.

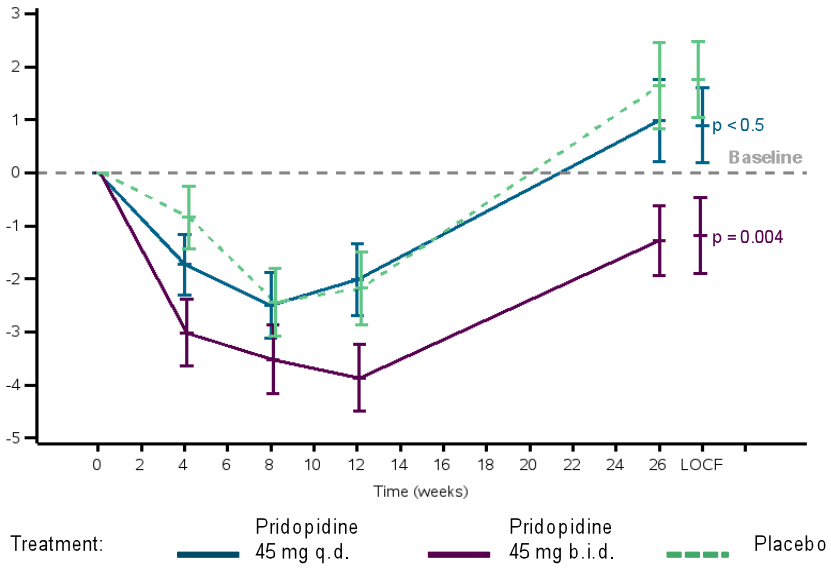

FIGURE 7
TMS assessments in the MermaiHD study. A significant improvement in TMS (about 3 points) compared to placebo was seen after treatment with pridopidine 45 mg twice daily at 6 months.

A similar study, the HART-Study (Huntington's disease ACR16 Randomized Trial), was a randomized, double-blinded, placebo-controlled, phase IIb study, where 28 clinical centers across the USA and Canada included 227 patients. Patients received pridopidine 10 mg, 22.5 mg or 45 mg twice daily or placebo, for 12 weeks. This study demonstrated a statistically significant dose-response relationship both for the primary endpoint mMS and for the broader secondary endpoint TMS. The magnitude of improvement for both mMS and TMS for the highest dose was similar to that seen in the MermaiHD study (NeuroSearch 2010).

It can thus be concluded that pridopidine is the first compound to have a significant effect on voluntary motor symptoms and dystonia in patients with HD. Further studies are needed in order to investigate whether the compound also has disease modifying properties in HD.

2 AIMS

The general objective of the present thesis was to investigate aspects of HD with relevance for developing a therapy. This was achieved by a number of experimental studies examining cerebral dopaminergic and metabolic functions in patients with HD and healthy individuals, and by reviewing and summarizing putative imaging biomarkers for studying the progression of HD. In particular, we aimed to investigate:

I *The extrastriatal dopamine D_2 receptor integrity in patients with HD.*

II *The regional cerebral glucose metabolism following pridopidine (ACR16) treatment in patients with HD.*

III *The effects of ordopidine (ACR325) on [^{11}C]raclopride and [^{11}C]SCH23390 binding in human brain.*

In addition to these experimental studies, an overview of putative imaging biomarkers in HD was performed, providing guidance for the use of such biomarkers in therapeutic interventions aiming for disease modification.

3 MATERIALS AND METHODS:

3.1 STUDY CONDUCT AND APPROVALS

All experimental studies of this thesis were performed in accordance with the Declaration of Helsinki and with the approval of the Ethics and Radiation Safety Committees of the Karolinska University Hospital in Stockholm. In addition, the studies were in consistency with Good Clinical Practice, and Study II and Study III were conducted after obtained approved permission from the Swedish Medical Products Agency. Written informed consent was obtained from all subjects previous to the conduction of the investigations. PET studies were conducted according to written standard operational procedures at the Karolinska PET Centre.

3.2 CLINICAL ASSESSMENTS

3.2.1 Unified Huntington's Disease Rating Scale (UHDRS)

All patients included in the studies of this thesis were assessed with the UHDRS including motor, cognitive, behavioral and functional components. The motor assessments included oculomotor score (ocular pursuit, saccade initiation and velocity), the modified motor score (dysarthria and tongue protrusion, finger taps, pronate/supinate hands, Luria, rigidity, bradykinesia, dystonia), chorea, gait and retropulsion test. The cognitive assessment included the verbal fluency test, the symbol digit modalities test, and the Stroop interference test. The behavior assessment included scores for depressed mood, guilt, anxiety, suicidal thoughts, aggression, irritability, obsessional thinking, compulsive behavior and delusions, hallucinations and apathy. The functional assessment included scores for total functional capacity and independence (Huntington Study Group 1996). UHDRS training and rater certification was obtained before performing clinical assessments.

3.2.2 MRI experimental procedure

Subjects in the experimental studies of this thesis underwent MRI using a 1.5 Tesla Signa MRI system (General Electric, Milwaukee, WI, USA). Two examinations were carried out in one session, with duration of about 15 minutes, consisting of a T2-weighted scan for clinical evaluation of pathology, and a T1-weighted scan for co-registration with PET and delineation of anatomical brain regions or regions of interest (ROI).

The T2-weighted sequence was a fast spin echo with the following parameters: repetition time 6000 ms, echo time 90 ms, 47 slices, slice thickness/gap 3 mm/0.125 mm, matrix 256×256, field of view 260×195, and imaging time 2 minutes. The T1-weighted sequence was a three-dimensional spoiled gradient recalled protocol with the

following settings: repetition time 21 ms, echo time 6 ms, flip angle 35°, 156 slices, thickness/gap 1 mm/0 mm, matrix 256×256, field of view 260×195, and imaging time 10 minutes 49 seconds.

3.2.3 PET experimental procedure

PET examinations of Study I were performed using a high resolution research tomograph (HRRT, Siemens Molecular Imaging). This PET system has: an axial field of view of 25.2 cm, corresponding to 207 planes in the reconstructed images, a slice thickness of 1.218 mm and thus a pixel size of 1.218×1.218×1.218 mm^3. The resolution has been improved by implementation of point spread function modeling. Using resolution modeling (OP-3D-OSEM-PSF), the in-plane resolution is 1.5 mm FWHM in the centre of the field of view and 2.4 mm at 10 cm off-centre directions (Varrone 2009).

Participants in Study I underwent one PET investigation with the radioligand [^{11}C]FLB457. The radioligand was prepared from [^{11}C]methyl triflate as previously described and according to standardized procedure at the PET Centre at the Karolinska University Hospital (Langer, et al. 1999). On average, 406 MBq, prepared in a 10 mL saline solution, was injected as a bolus for three seconds via a venous cannula positioned in the left arm, followed by a flush of 10 mL of saline solution. The specific radioactivity of the injected radioligand was on average 12414 Ci/mmol, corresponding to a mean injected mass of 0.49 μg (range: 0.16–1.28 μg). There were no differences in the injected mass between healthy individuals and patients with HD. Images were reconstructed for 19 time frames, equating to the total measurement duration of 87 minutes following injection of the radiotracer.

In Study II and III, PET investigations were performed with an ECAT Exact HR 47 system (CTI/ Siemens, Knoxville, TN, USA) run in three-dimensional mode with dual-energy windows scatter correction (Wienhard, et al. 1994). The transaxial resolution of the reconstructed images is 3.8 mm FWHM at the centre of the field of view, 4.5 mm FWHM tangentially, and 7.4 mm radially at 20 cm from the centre. The axial resolution is 4 mm FWHM at the centre and 6.8 mm at 20 cm from the centre. After correction for attenuation, random and scattered events, images were reconstructed using a Hann filter (2 mm FWHM). The reconstructed volume was displayed as 47 horizontal sections with a centre-to-centre distance of 3.125 mm and a pixel size of 2×2×2 mm^3.

Subjects in Study II underwent FDG PET scanning procedures at baseline and following two weeks of pridopidine treatment according to the standard operational procedures for [^{18}F]FDG PET scans at the PET Center at the Karolinska University Hospital. The scans were performed with the subject's eyes open in a dimly lit room and with minimal auditory stimulation. About 200 MBq [^{18}F]FDG was injected as a bolus during three seconds through a venous cannula inserted in an antecubital vein, and subsequently flushed with 10 ml saline solution. PET emission scans constituting 2×10 minute time frames were started at about 35 minutes following the administration of radioactivity.

In Study III, the radiotracers were produced according to standard operational procedures at the PET Centre at the Karolinska University Hospital (SOP number, [^{11}C]raclopride: QA PET-7015-2, [^{11}C]SCH23390: 2003-06-10). The radioligands were given intravenously as a rapid bolus and the cannula was flushed with 10 ml saline. Radioactivity in brain was measured during 51 minutes following radiotracer injection. For each PET investigation about 300 MBq of radioactivity was injected. Ordopidine (ACR325) was measured in plasma using validated liquid chromatographic methods at a GLP certified laboratory (Quintiles AB, Uppsala, Sweden).

3.2.3.1 Image processing

After acquisition and reconstruction, the T1 MRI and PET images were transferred to Statistical Parametric Mapping 5 (SPM5) software for spatial normalization and co-registration (Wellcome Trust Centre for Neuroimaging). For each subject, the MRI images were spatially normalized to position the anterior-posterior commissural line in the horizontal plane, and the inter-hemispheric plane orthogonal to the anterior-posterior commissural plane. The reoriented T1 images were then resliced to 1 mm voxels in a matrix of 220×220×170.

3.2.3.2 Regions of interest

The delineation of all regions of interest (ROI) was made manually on the spatially normalized MRI images in three orthogonal projections using the Human Brain Atlas software (Roland and Zilles 1994). All ROIs were delineated for each hemisphere and for the entire anatomical definition. For the striatum (caudate nucleus and putamen), hippocampus, and temporal, parietal and occipital cortices, the ROIs were delineated on sagittal projections, while for the frontal regions (dorsolateral and dorsomedial prefrontal cortices, orbitofrontal cortex) and amygdala, the ROIs were delineated on coronal sections. For the anterior cingulate, insula and subregions of thalamus, the ROIs were delineated on horizontal projections. The thalamic subregions (centromedial, centrolateral, anteromedial, anterolateral, posterior) were delineated using a procedure described previously (Gilbert, et al. 2001). Finally, the cerebellum was delineated below the appearance of the petrosal bone in the horizontal projections. For cortical regions the initial delineation was schematic, also including surrounding cerebrospinal fluid and white matter. To define grey matter boundaries accurately, the MRI images were co-registered with the PET images and segmented into grey and white matter and cerebrospinal fluid. The initial crude cortical ROIs were then segmented using the grey matter mask in order to include with precision only pixels belonging to grey matter. All ROIs were superimposed on the PET images using predefined co-registration parameters. Radioactivity concentrations (nCi/mL) in each ROI were calculated for each sequential frame, corrected for radioactivity decay, and plotted versus time.

3.2.3.3 Partial volume effect correction

In Study I, a partial volume effect (PVE) correction method was used (Meltzer, et al. 1990). In this method, the segmented grey matter and white matter masks are summed to obtain a brain tissue mask. The tissue mask is then convolved with the resolution of

the PET system, resulting in a correction map for the PET images. The original PET image is divided by the correction map, resulting in a PVE corrected PET image in which the count density represents activity per volume of brain tissue. The MRI segmentation procedure was performed with SPM5 and the PVE correction algorithm was implemented in Matlab 7.5.

3.3 QUANTITATIVE ANALYSES

3.3.1 Binding potential

Binding potential (BP) is referring to the density of "available" receptors. BP is thus a combined measure that depends on receptor density and affinity. Throughout the thesis, BP refers to BP_{ND}, which represents the ratio at equilibrium of specifically bound radioligand to that of non-displaceable radioligand in tissue (Innis, et al. 2007).

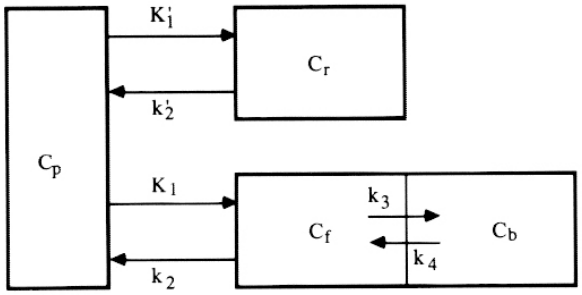

FIGURE 8
Three-compartment model. C refers to radioligand concentration in: C_P = plasma; C_f = free; C_b=specifically bound. The arrows indicate the rate constants between the different compartments.

To quantify radioligand binding in the investigations of this thesis, the BP was calculated for each ROI. At tracer doses, BP is proportional to the ratio B_{max}/K_D, where B_{max} is the total concentration of specific receptor binding sites and K_D is the dissociation constant of the radioligand at equilibrium (Mintun, et al. 1984). The BP was calculated using the simplified reference tissue model (SRTM) (Lammertsma and Hume 1996). Cerebellum was used as reference tissue, serving as an indirect approximation of free and non-specifically bound radioligand concentration, due to its minute density of dopamine receptors (Hall, et al. 1996). All BPs were calculated using Matlab 7.4, where SRTM was implemented in a program designed by the author (M.E.), which has previously been validated (Rominger, et al. 2009).

3.3.1.1 Simplified reference tissue model (SRTM)

Different reference region models have been described and further developed for the quantification of the BP (Blomqvist, et al. 1989; Cunningham, et al. 1991; Gunn, et al. 1997; Lammertsma and Hume 1996). These models rely on the existence of a tissue region with a negligible concentration of specific (saturable) binding sites. The simplified reference tissue model (SRTM) is a method, which allows calculations of

both binding potential and the delivery of the ligand relative to the reference region. However, this formulation involves several major assumptions; A reference region exists and can be defined; Labeled metabolites of the parent tracer do not cross the blood brain barrier; The degree of nonspecific binding and the ratio of the rate constants describing the exchange of tracer between plasma and the free/nonspecific compartment are the same in both tissue and reference regions; The exchange between free and specifically bound compartments is sufficiently fast for their composite behavior to be approximated by a single compartment.

The principle advantages of SRTM are robustness and computational speed, which is due to the small number of parameters in the model; the original model containing four parameters was modified to contain only three parameters (Lammertsma and Hume 1996). Nevertheless, during the iterative processes fitting the SRTM model to the experimental data, insecurity remains regarding local and global minima. It is therefore important to control the obtained results and to optimize the parameters of the model manually, which was perfomed in the studies of this thesis. In addition, the advantages of the SRTM are that there is no need for arterial cannulation and sampling or measurements of labeled metabolites.

The time course of radioligand uptake in tissue of interest is expressed in terms of its uptake in the reference tissue, where it is assumed that the level of nonspecific binding is the same in both tissues. The compartment model illustrates the exchange of radioligand between plasma and reference tissue (1), and between plasma and free (2) and bound (3) compartment of the region of interest.

(1) $dC_r(t)/dt = K'_1 C_p(t) - k'_2 C_r(t)$

(2) $dC_f(t)/dt = K_1 C_p(t) - k_2 C_f(t) - k_3 C_f(t) - k_4 C_b(t)$

(3) $dC_b(t)/dt = k_3 C_f(t) - k_4 C_b(t)$

Assuming that:

$C_t = C_f + C_b$
$R_1 = K_1 / K'_1$

Yielding:

(4) $K'_1 / k'_2 = K_1 / k_2$
$\rightarrow k'_2 = k_2 / R_1$

By replacing k_4 by k_3 / BP:

$(BP = k_3 / k_4)$

Yielding an operational equation through a standard nonlinear regression analysis, fitting the concentrations, C_t and C_r as a function of time:

$$CP(t) = R_1C_r(t) + [k_2 – R_1k_2/(1 + BP)]C_r(t) * \exp [-k_2t/(1 + BP)]$$

The expression thus includes the BP and is solved in a convolution manner and fitted to the data in a least squares sense. The SRTM was applied in Study I and III of this thesis. In addition, the graphical method Logan was used for validation of the BPs obtained with SRTM in the studies of this thesis, confirming these results (Logan, et al. 1996).

3.3.2 Quantification of the regional cerebral glucose metabolism

The metabolic uptake of glucose by the brain is a two-stage process. The first step involves a carrier-mediated transport across the blood brain barrier. Glucose is then transported into the brain by a saturable facilitated mechanism (Culter and Sipe 1971; Fishman 1973). Fluoro-deoxy-glucose (FDG) is a glucose analog that competes with glucose for facilitated transport sites with hexokinase for phosphorylation to FDG-6-PO_4 (FDG-6-P). The underlying rationale for using this glucose analog is that while it is transported across the blood brain barrier and phosphorylated at rates proportional to those of normal glucose, it is not metabolized further, and since the resulting intracellular FDG-6-P is not transported through the cell membrane at any substantial rate, nor is the activity of the hydrolyzing enzyme (glucose-6-phosphatase) high enough to convert significant amounts of FDG-6-P back to FDG, the glucose analog is effectively trapped within the tissue (Hers 1957; Hers and De Duve 1950; Prasannan and Subrahmanyan 1968; Raggi, et al. 1960; Yudilevich and DeRose 1971; Phelps, et al. 1979; Sokoloff, et al. 1977).

The regional cerebral metabolic rate of glucose (rCMRGlc) calculations in Study II are based on an adaptation and simplifications of a method originally developed for the *in vitro* measurement of glucose metabolism using tracer amounts of carbon 14-labeled deoxyglucose (Sokoloff, et al. 1977), which includes three rate constants, k_1, k_2, k_3. This compartment model was later modified to provide regional measurements of glucose metabolism *in vivo* using [^{18}F]FDG and PET (Phelps, et al. 1979). In this model, the initial method is modified to include the hydrolysis reaction mediated by a fourth rate constant (k_4). However, these rate constants are not universal constants, but constants for a particular steady-state condition of rCMRGlc, measured in normal brain tissue. A model including rate constants would hence increase the sources of error in the calculation of rCMRGlc in pathological brain tissue, such as in HD.

Initially, the distribution of FDG is highly dependent on cerebral blood flow for the unidirectional transport of FDG into cerebral tissue. However, because of the trapping of FDG-6-P, steady state appears after 40 to 50 minutes, and these factors are usually then no longer significant. Thus, at this point the uptake of radioactivity reflects rCMRGlc since the tissue concentration is dominated by the intracellular FDG-6-P. Hence, the initial model excluding the hydrolyzation process can be used, assuming that at times after 45 minutes, the measured tissue isotope concentration arises solely from FDG-6-P. However, the need to obtain an accurate measure of the k values, regionally and for each individual study, imposes great practical and technical demands. Hence, an alternative approach has been sought, replacing the problem of

"rate constant" measurement with the visualization in terms of a tissue "uptake" measurement (Rhodes, et al. 1983).

In Study II, the simplistic model was used, where all the k values are excluded. The rate of cerebral glucose metabolism (CMRGlc) was calculated using the measured tissue concentration of tracer (Ci*(T)) at a time T, multiplied by the plasma glucose concentration (Cp), divided by lumped constant (LC) (Huang, et al. 1980) and the integral of the input function (Cp*(t)) from time 0 to T (Rhodes, et al. 1983).

$$CMRGlc = Ci^*(T)Cp \Big/ \left[LC \int_0^T Cp^*(t)dt \right]$$

The Cp*(t) values were obtained from a population based input function (Takikawa, et al. 1993), using a single venous blood sample obtained at 45 minutes post injection. To obtain an equidistant time scale, the input function was interpolated, maintaining values with an interval of 15 seconds from time 0 to T. All calculations were performed using custom-made Matlab programs written by the author M.E., which have been validated in a recent HD study (Squitieri, et al. 2011).

Implicitly, this method assumes that a) the tissue concentration of FDG activity is composed solely of FDG-6-P, b) that the proportion of FDG-6-P hydrolyzed back to FDG during the course of the study is small, and c) that the plasma concentration of FDG [Cp*(t)] equilibrates instantaneously with the extravascular tissue precursor pool. The initial model was developed including the rate constants to “fine tune” this simplistic equation, because of the presence of nonphosphorylated tissue FDG, and the fact that it is the extravascular concentration of FDG and not the plasma concentration that determines the availability of the substrate for phosphorylation (Sokoloff, et al. 1977). This model (including the rate constants) has been well established for use in normal physiological states (Huang, et al. 1981; Huang, et al. 1980; Kuhl, et al. 1982; Mazziotta, et al. 1987; Phelps, et al. 1979; Phelps, et al. 1982).

Provided a), b), and c), the calculation of CMRGlc becomes less dependent on the use of accurate k values when steady state is reached, which is the reason why CMRGlc is measured after 45 minutes post injection. In addition, regarding that the k values are based on studies from normal subjects, including these values would not be reasonable. The lumped constant (LC), however, remains as an uncertain parameter in the calculation of CMRGlc, since the LC value (0.42) used in these equations is quoted for normal brains, and since LC changes for different cerebral tissues in various physiological and pathological states. However, owing to that our study investigated the same individuals before and after treatment, thus being their own references, these

parameters become less important. Hence, any error of this kind will be a systematic error, which will be self-corrected, calculating the change in CMRGlc in the investigated patients.

3.4 STATISTICAL ANALYSIS

3.4.1 Univariate statistical analysis

In Study I, the mean differences between patients with HD and controls were assessed by Student's *t*-test. No correction was made for multiple comparisons. Correlations analyses in all experimental studies of the thesis were carried out using Pearson's correlation coefficient (*r*).

3.4.2 Multivariate statistical analysis

The multivariate statistical methods Principal Component Analysis (PCA) (Eriksson, et al. 2006a; Pearson 1901) and Partial Least Squares (PLS) (Clark and Cramer III 1993; Eriksson, et al. 2006b) where used in Study I and II of this thesis. In Study I, PCA and PLS models were generated describing covariance patterns of receptor binding data in patients and controls. In Study II, rCMRGlc data in patients before and after treatment and their relationship to clinical assessments were described by means of PCA.

PCA is most commonly interpreted with mainly two closely related plots, the score-plot and the loading-plot. The score plot shows the projection of subjects onto the principal components. Subjects located close to each other are similar with respect to the measured data, while subjects located on the opposite side of *origo* have opposite characteristics and if they are located in a perpendicular direction to each other (*origo* is the reference) have independent characteristics. Thus, a score plot is used to find clusters or patterns in the distribution of the subjects in the model. Loadings are derived as the eigen-vectors of the correlation matrix sorted by the eigen-values. Loadings reveal the inherent correlation structure present in the data. Variables located close to each other have a positive correlation and variables located on the opposite direction of *origo* (approximately fitting a straight line) have a negative correlation. If lines from two different variables that cross each other in *origo* have an approximate perpendicular angle they are uncorrelated and linearly independent. The scores and loading plots are tightly connected and can be approximately interpreted by overlaying the graphs.

PCA is a method that preserves as much (linear) information as possible in the data while projecting the observations onto a lower dimensionality (usually 2-3 principal components), reducing noise and making it possible to both investigate clusters among the studied subjects as well as variable patterns and correlations. The first principal component (PC) will always contain the largest amount of variation (i.e. information) among the PCs and all subsequently derived PCs will describe less of the total variation

in data. All derived PCs are orthogonal to each other (i.e. only containing variance not taken into account of by previously derived PCs), which also implies that they are linearly independent. PCA is also sensitive for strong outliers, which should be removed in the analysis process. However, a removed subject can always be predicted into the final model, thus being visualized while not having an influence on the model.

Partial Least Squares analysis (PLS) is a multivariate method similar to PCA. However, in a PLS two sets of data (dependent and independent variables) are related. Instead of maximizing all the variation in the first PCs, a PLS maximizes the variation that relates Y (dependent) with X (independent) variables. Thus the PCs will not maximize the variation in X but will maximize the correlation to Y. Often the Y variable is set to discriminate between groups of subjects.

The statistical significance of PCA models was assessed using the cross-validation procedure (Jackson 1991; Wold 1978). That is, subjects were divided in seven approximately equally sized groups (i.e. all subjects belongs to exactly one cross-validation group) and calculations were performed by leave one group out. Outliers can be detected by using a 95% confidence region according to Hotelling's T2 (Hotelling 1931) and thus be removed from the model. However, this was not the case for any of the investigated studies. All multivariate statistical analyses were carried out using the software SIMCA-P+, version 12 (Umetrics AB, Umeå, Sweden).

3.4.3 Statistical Parametric Mapping (SPM)

Statistical Parametric Mapping (SPM) is a useful tool in the standardization of measurement and data analysis in functional neuroimaging. Generally, its concept is similar to the ROI technique with the difference that the regions of interest are voxels in a standardized stereotaxic room. This software not only spatially normalizes PET images to the standardized stereotaxic atlas (Talairach and Tournoux 1988), but can in addition perform statistical analyses on study groups on a voxel-by-voxel basis (Friston, et al. 1991; Friston, et al. 1995), which allows for reliable and objective image handling that could improve inter-study variability due to the analytical process itself. The use of SPM for automated voxel-based quantification usually includes the comparison of individual PET data with a group of normal controls and utilizes a standard morphological template (‘‘standard brain’’) for the visualization of results. However, alterations of brain structure such as focal atrophy in the course of neurodegenerative diseases such as HD, can lead to misinterpretation of functional effects caused by their lesions. Thus, the ‘‘standard brain’’ template is of limited applicability in many cases of pathological change. The individual morphological information gained by MRI images is of some helps to reach a better understanding of the correlation between function and individual morphology (Otte and Halsband 2006).

Statistical Parametric Mapping thus enables all the parametric images to be transformed into the standard stereotaxic space of Talairach and Tournoux (Talairach and Tournoux 1988) and, consequently, allows comparisons to be made across scan datasets in analogous voxel regions of the brain volume and, combining datasets from different subjects, also allows between-group and within-group analyses. This method was used

in Study II investigating the effects of pridopidine in patients with HD. To localize changes in rCMRGlc at a voxel level, spatial processing and statistical analysis of the PET data was conducted using SPM (SPM8, Institute of Neurology, University College, London) implemented in Matlab (Mathworks Inc, USA). Images were transformed from MNI anatomical space into standard anatomical space (Talairach and Tournoux 1988), using a previously described method (Lancaster, et al. 2007), allowing the comparison to be made across scan datasets in analogous voxel regions of the brain volume, as well as combining datasets from different subjects, and thus between-group and within-group analyses. The spatially normalized images were smoothened using an 8 mm FWHM isotropic Gaussian kernel to increase the signal to noise ratio. To reduce intersubject variability, rCMRGlc values were ratio-normalized to white matter. Normalization was thus done by dividing each voxel with white matter signal.

In Study II, a between-group comparison was made between baseline and post treatment investigations. The resulting images were analyzed using paired t-test. Two different masks were used to evaluate cortical and subcortical structures. The mask for the delineation of cortical structures was based on a cutoff value applied to the mean image of all scans. Due to low metabolism in subcortical structures, a mask was created through images from Study I using the radioligand [^{11}C]FLB457 on six of the patients included in Study II. Using this dopamine D_2 receptor specific high affinity ligand, a mask delineating thalamus and striatum was created. Applying these masks, the images were analyzed using a paired *t*-test. Uncorrected significance threshold was set at $p<0.001$ for voxel analysis. For the analysis of the cerebral cortex, a threshold of 300 continuous voxels was set. For subcortical structure clusters, the threshold was set to 50 continuous voxels. Clusters with a p-value corrected for multiple comparisons of $p\leq0.05$ on both peak voxel level and cluster level were considered significant.

4 RESULTS AND DISCUSSION

4.1 STUDY I – EXTRASTRIATAL DOPAMINE D_2 RECEPTORS ARE WELL PRESERVED IN HD

HD is primarily affecting the MSNs in the striatum. The integrity of striatal dopamine D_2 receptors has been extensively studied in HD. However, little is known about the integrity of these receptors outside the striatum. To investigate extrastriatal D_2 receptor densities, patients with HD and age-matched healthy individuals underwent PET imaging by a high resolution PET camera system, HRRT, using the high affinity D_2 receptor radiotracer [^{11}C]FLB457. This study shows that D_2 receptor densities extrinsic to the striatum are well preserved in patients with early to mid-stage HD. Given the importance of dopamine and D_2 receptor function for normal motor and behavioral activity, and given that the dopaminergic stabilizers bind to the D_2 receptor to exert their function, the finding of relative preservation of extrastriatal D_2 receptor densities may have implications for potential therapeutic interventions in HD.

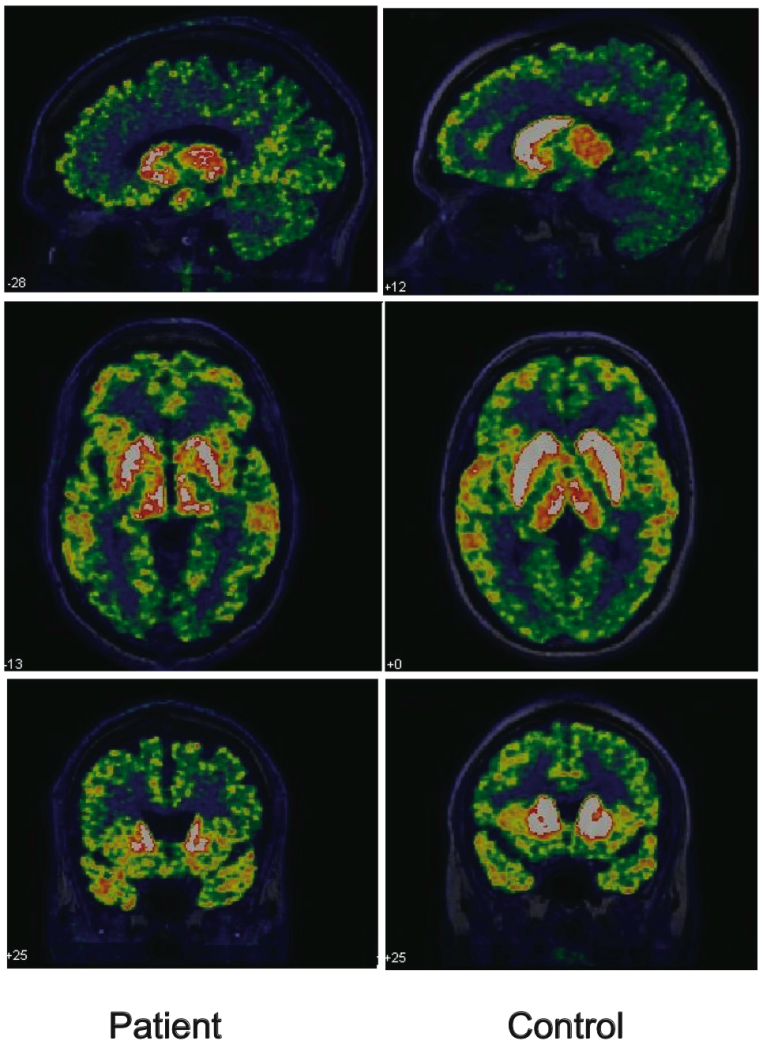

FIGURE 9
Parametric PET images showing [^{11}C]FLB457 binding in a patient with HD and a healthy control.

4.2 STUDY II – PRIDOPIDINE ALTERS CEREBRAL METABOLIC ACTIVITY IN HD

The dopaminergic stabilizer, pridopidine (ACR16), is currently under development for the treatment of HD. Pridopidine belongs to a novel class of compounds modulating psychomotor activity by affecting dopaminergic and glutamatergic activity. Although the compound has undergone several clinical trials, the mechanisms underlying its actions in HD remain elusive. While it is known from preclinical experiments that the compound state dependently affects psychomotor function, the global effects on cerebral function caused by the compound in patients with HD has not been previously investigated. In this study, it was found that pridopidine treatment resulted in increased cerebral metabolic activity in regions previously described as important for the compensatory mechanism in HD. In addition, pridopidine treatment markedly strengthened the correlation between motor and cognitive symptoms and the cerebral metabolic activity.

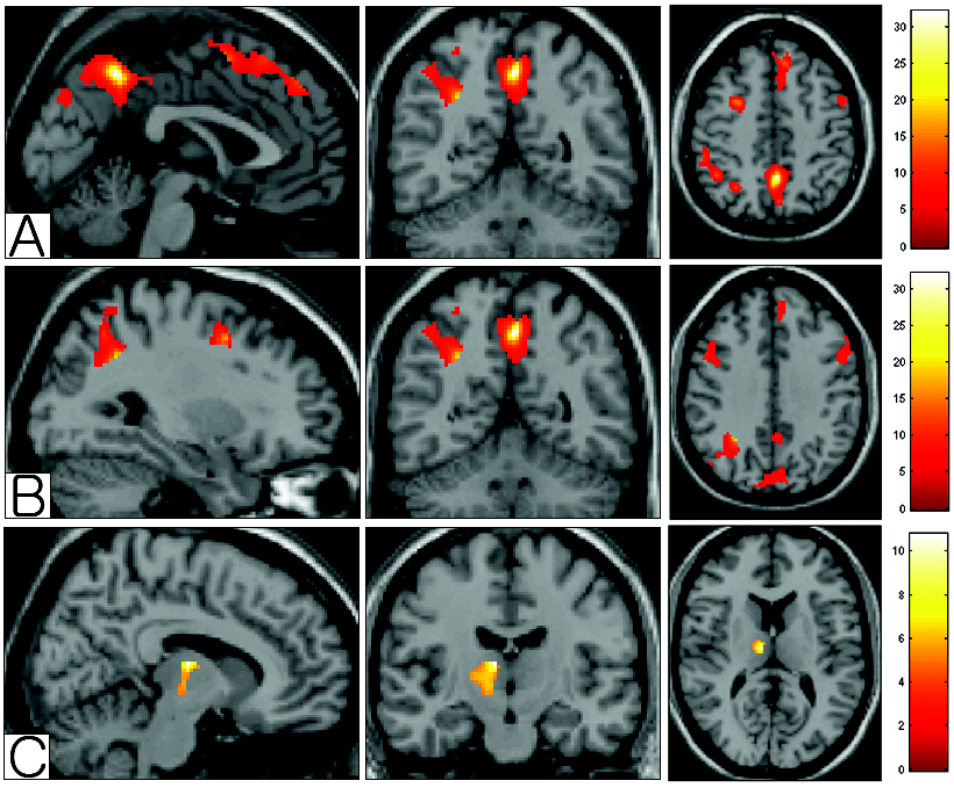

FIGURE 10
Statistical Parametric Mapping showing metabolic changes in the brain in response to pridopidine treatment in patients with HD. A) Changes in precuneus and left middle frontal gyrus. B) Changes in left superior temporal gyrus. C) Changes in left mediodorsal nucleus of thalamus. Left mediodorsal nucleus of thalamus and precuneus are previously described as regions important for mediating compensatory mechanisms in HD

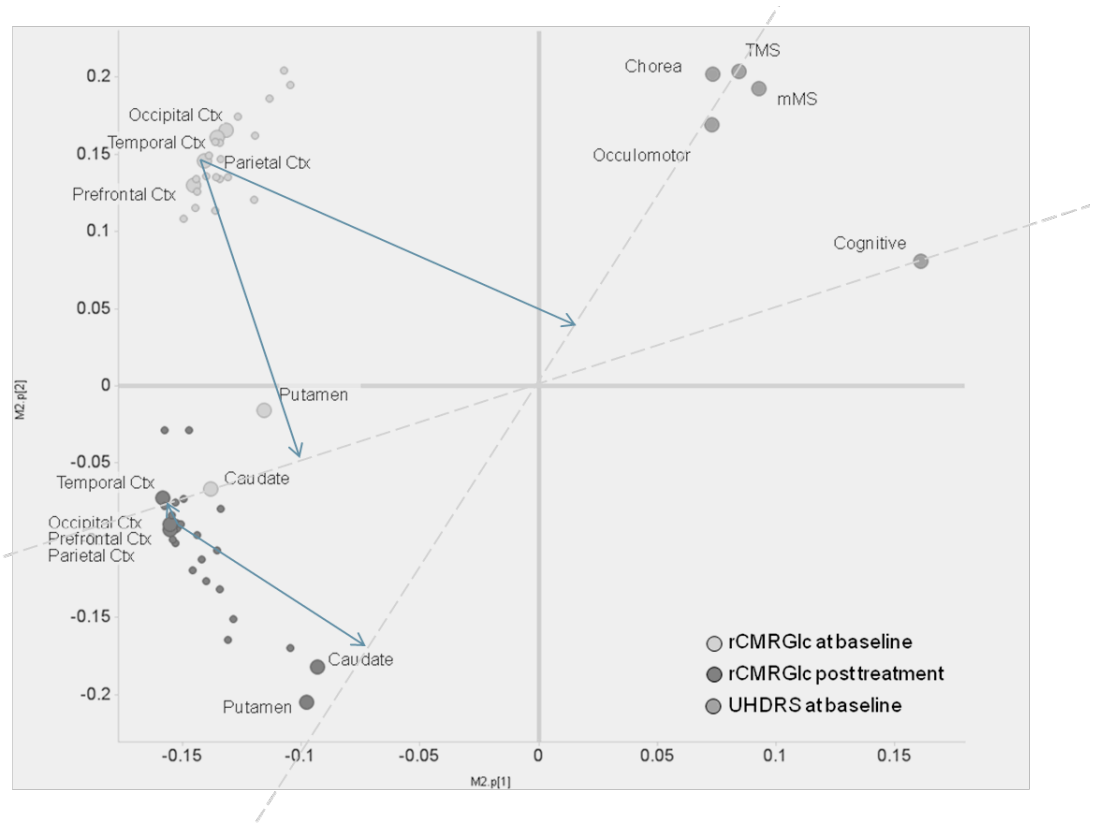

FIGURE 11
Significant two-component model obtained using Principal Component Analysis demonstrating that the correlations between clinical motor and cognitive scores are strengthened after two weeks of pridopidine treatment in patients with HD.

4.3 STUDY III – DOPAMINERGIC STABILIZERS, A BALANCING INTERACTION BETWEEN NEUROTRANSMITTER SYSTEMS?

Ordopidine (ACR325) belongs to a novel class of modulators of dopaminergic functions with similar pharmacology as pridopidine. The primary mechanism of action of ordopidine is its binding to the dopamine D_2 receptor. Although ordopidine does not interact with any other neuroreceptors, preclinical studies demonstrate that the compound induces synaptic glutamatergic activation in the cortex and the basal ganglia. To further study the effects of ordopidine on dopamine D_1 and D_2 receptor availability *in vivo*, healthy subjects were investigated with PET using [^{11}C]raclopride (n=6) and [^{11}C]SCH23390 (n=18) at baseline and following single oral doses of ordopidine. A single dose of 75 mg ordopidine produced a mild reduction in striatal D_2 receptor availability; a finding in accordance with the preclinical pharmacology of the compound. However, ordopidine administration also induced marked and rapid changes in striatal and cortical dopamine D_1 receptor availability, increases or decreases in [^{11}C]SCH23390 binding potential that were well beyond the normal test-retest variability of this radiotracer. The marked changes in dopamine D_1 receptor availability could be a result of an indirect effect on this receptor post treatment. Given the well-described interactions of dopamine D_1 receptor with NMDA function, this finding may provide an explanation for the glutamate enhancing properties of the dopaminergic stabilizers.

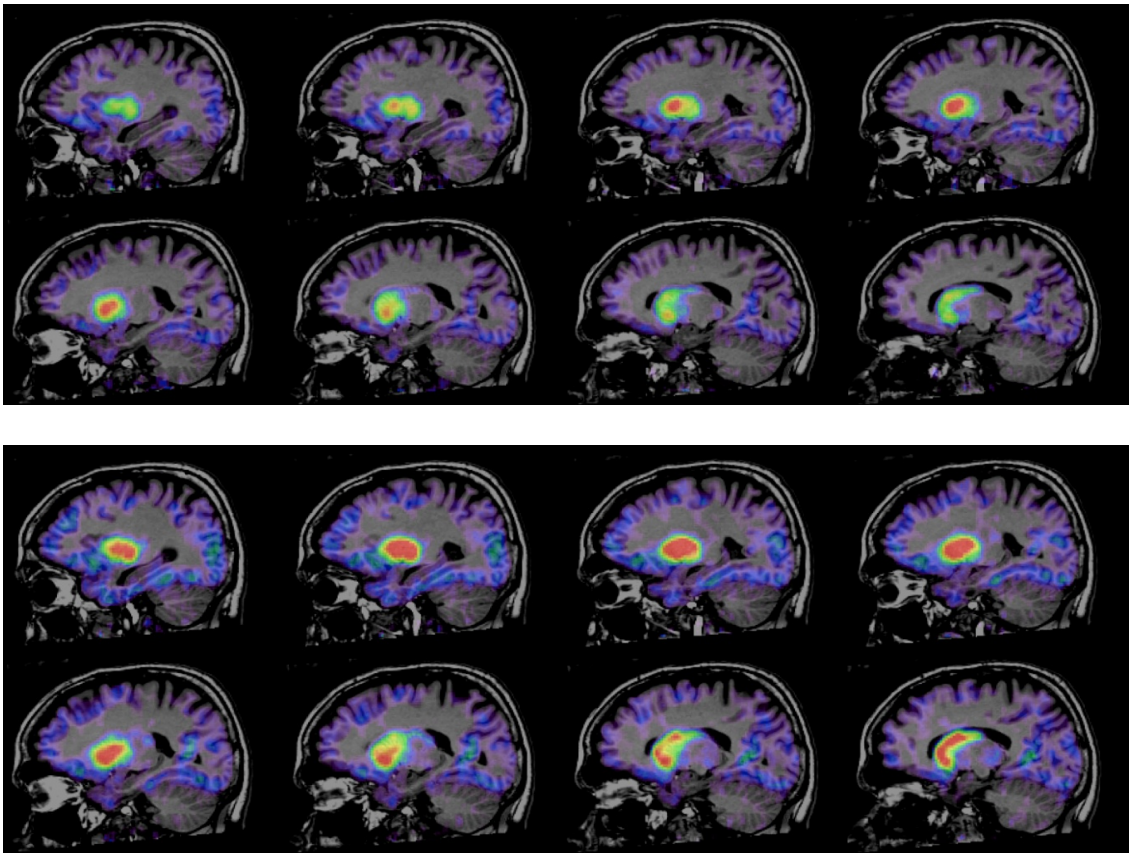

FIGURE 12
Parametric PET images superimposed on MRI scans showing D_1 receptor binding in a subject at baseline (upper) and two hours after (lower) a single dose of 25 mg ordopidine.

4.4 APPENDIX – TOWARDS A NOVEL TREATMENT FOR HD; IMAGING BIOMARKERS SUITABLE FOR POTENTIAL DISEASE MODIFYING THERAPIES IN HD

HD is unique among neurodegenerative disorders, since it can be genetically confirmed before the symptoms become clinically apparent. As such, it opens possibilities to study disease processes before clinical symptoms become manifest and also to tailor a therapy aimed at preventing or delaying phenoconversion. Data from previous studies suggest that the cerebral abnormalities and pathophysiological changes in HD start years before clinical symptoms become obvious. Hence, there is a need to identify biomarkers that can accurately monitor aspects of the progression of relevant pathology in various stages of HD, as well as to study the pharmacodynamic responses to therapeutic intervention.

By systematically reviewing previous imaging publications in HD, it was concluded that a number of screening tools might be more useful for following the progression of the disease during different stages.

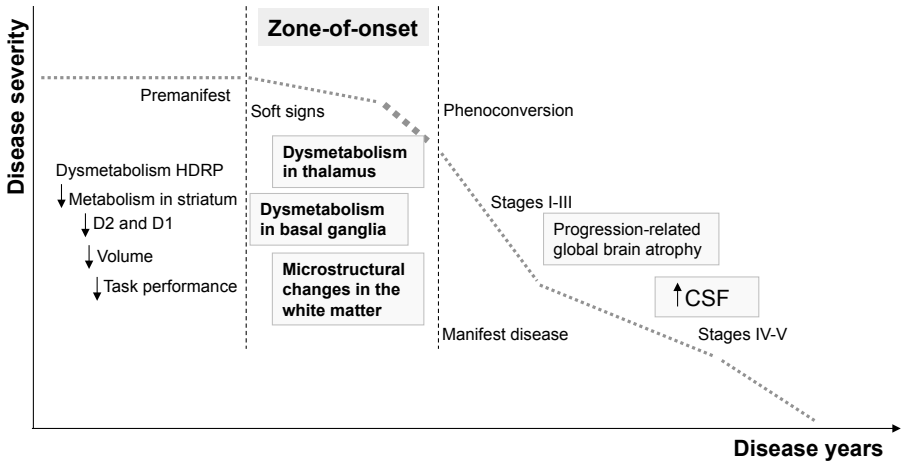

FIGURE 13
Schematic overview of putative imaging biomarkers during different stages of HD.

In the review it is concluded that during the early premanifest stage of HD the HDRP network expression, glucose metabolism in the striatum, and striatal D_2 receptor binding seem to be relatively sensitive tools. Conversely, closer to phenoconversion thalamic and/or caudate glucose metabolism are more suitable, whereas whole striatal measures and HDRP seem to be less sensitive to disease progression in this stage. The observation that striatal dopamine D_2 receptor integrity decreases steadily throughout the premanifest period makes it suitable as a biomarker during this phase. Although MRI techniques have provided several ways of following the progression of the disease, such techniques need to be combined with PET early on in the premanifest stage.

There is a need for highly sensitive multimodal imaging techniques, which provide objective and standardized tools for the pathophysiological process, with sensitive readout in response to therapeutic interventions. To achieve these aims, there is a need for step up efforts and research in premanifest HD gene carriers in early ages. Collaborative projects involving research groups using various imaging modalities including PET are required in order to tailor a multimodal imaging biomarker suitable for potential disease modifying therapy for individuals with HD.

5 METHODOLOGICAL CONSIDERATIONS

A general consideration of the studies investigating the binding potentials is that BP represents the product of receptor density and apparent affinity (Mintun, et al. 1984) and it is thus not possible to differentiate between these two parameters. Another consideration with regard to the investigations of the D_2 receptor BP (Study I and III) is the interference of endogenous DA and thus the accuracy of these measurements. Although receptor density has shown to account for most of the interindividual variability in BP for both radioligands (Farde, et al. 1995; Olsson, et al. 2004), [^{11}C]raclopride and [^{11}C]FLB457 are both radioligands sensitive to endogenous DA (Aalto, et al. 2005; Hagelberg, et al. 2004; Laruelle 2000; Montgomery, et al. 2007). Hence, it cannot be excluded that the present findings can be attributed also to differences in endogenous DA levels. Contrarily, the DA D_1 receptor does not seem to be much affected by endogenous DA levels (Abi-Dargham, et al. 1999; Chou, et al. 1999).

The findings of Study I, where no statistical significant differences were found in extrastriatal dopamine D_2 receptor integrity in patients with HD compared to controls, might be affected by the limited amount of subjects investigated, thus being an issue of statistical power. While BPs were numerically slightly lower in patients with HD, the differences did not reach statistical significance. Considering the standard deviation of the measurement and the magnitude of the possible difference in patients with HD versus controls, a sample size of about 30 subjects would have been needed to reach statistical significance. In addition, in this study, we decided to include also striatal regions in the analysis. Due to high receptor density in these regions in healthy individuals, no pseudo-equilibrium is reached during acquisition time. Due to the lower receptor densities in the striatum in patients with HD, it can be assumed that the SRTM model is more correct in estimating BPs relative to healthy controls during the same acquisition time. Although there have been methodological concerns in using [^{11}C]FLB457 to measure striatal D_2 density in healthy subjects, the appropriateness of the measurements in patients with HD was demonstrated by the correlation to clinical measures such as chorea in the patients and were also shown to be in reasonable agreement with previous studies on striatal D_2 densities using [^{11}C]raclopride.

It might be of concern that patients with HD have widespread atrophy, making the clustering in the SPM (Study II) less reliable. To reduce this interference, we chose not to use the MRI template of the software, but rather a template made out of the individual MRIs of the investigated patients. More importantly, using the same subjects before and after treatment and being merely interested in the relative changes between these two conditions, the methodological consideration related to atrophy correction is managed. The same argument could be used for the normalization process, using the white matter values to reduce intersubject variability in this study. The strength of this study has thus been that the patients are their own controls, making considerations of this kind negligible.

6 CONCLUSIVE REMARKS AND FUTURE PERSPECTIVES

Huntington's disease is a devastating genetic disorder, causing considerable suffering to patients and their relatives. Until today, no effective therapeutic possibilities have been available. Nevertheless, patients with HD are frequently treated with medications approved for other indications, some which may even exacerbate pathology and worsen disease progression. Thus, there is a critical need for better evidence-based treatment for HD.

Dopaminergic stabilizers like pridopidine have a potential to open the way for a novel treatment of this devastating disorder. In this thesis three major findings supporting the role of such compounds are presented; Firstly, the target to which the compound binds to exert its pharmacological effects are well preserved in extrastriatal regions in patients with HD; Secondly, the cerebral metabolic activity is modified post treatment, in particular in regions important for the compensatory mechanisms occurring before phenoconversion in the premanifest stage of the disease; Thirdly, the particular interaction of such compounds with their primary target, the dopamine D_2 receptor, allows for a more flexible balancing between the D_1 and D_2 receptor activity, thus without resulting in the detrimental side effects seen with other D_2 antagonizing compounds. The dopaminergic stabilizers seem to induce an indirect effect on the D_1 receptor in humans *in vivo*, which is in line with observations from preclinical pharmacological studies. Considering the interactions between NMDA and D_1 receptors, it is possible that this indirect interaction with the D_1 receptor might explain the glutamate strengthening properties of such compounds as well as their propensity to restore psychomotor activity in the hypoglutamatergic state. Hence, an essential mechanism of the dopaminergic stabilizers might possibly be a restoration of the balancing act between the dopaminergic and glutamatergic systems. Interestingly, the indirect effects on D_1 receptors seem not unidirectional, but might rather be condition dependent. A similar phenomenon is found in studies investigating the correlation between D_1 receptor availability and cognitive performance, where improvements in performance are associated with bidirectional changes in receptor availability. These effects might indicate that optimal brain functioning requires a flexible system allowing for brain plasticity (possibly through an interaction between D_1 and NMDA receptors), rather than being optimized by a unidirectional effect on the dopaminergic system.

Imaging techniques such as PET have the potential to identify biomarkers and targets for potential therapies for diseases such as HD. In addition, as demonstrated in Study II of this thesis, using multivariate statistical analysis, PET imaging can provide a means of evaluating new compounds in a very cost-effective way to distinguish the clinical relevance of the compound before entering resource consuming clinical trials. Dopamine receptors as well as brain metabolic activity have shown to be disturbed in HD years prior to disease manifestation. Using PET imaging, these biomarkers can be monitored for disease progression, being a guide for when to introduce potential future disease modifying interventions, hopefully making it possible to prevent or delay

phenoconversion. Although HD is a relatively rare disease, it may serve as a model for other neurodegenerative diseases, making it interesting to further investigate the effects of dopaminergic stabilizers not only in the premanifest stage of the disease but also in other neuropsychiatric and neurodegenerative diseases.

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