Neurotoxicity Research, 2006, VOL. 10(3,4). pp. 167-179

F.P. Graham Publishing Co.

Dopaminergic Dysbalance in Distinct Basal Ganglia Neurocircuits: Implications for the Pathophysiology of Parkinson´s Disease, Schizophrenia and Attention Deficit Hyperactivity Disorder

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(Submitted 10 January 2005; Revised 3 August 2006; In final form 3 August 2006)

The basal ganglia form a forebrain system that collects signals from a large part of the neocortex, redistributes these cortical inputs both with respect to one another and with respect to inputs from the limbic system, and then focuses the inputs of this redistributed, integrated signals into particular regions of the frontal lobes and brainstem involved in aspects of motor planning and motor memory. Movement disorders associated with basal ganglia dysfunction comprise a spectrum of abnormalities that range from the hypokinetic disorder (from which Parkinson´s disease, PD, is the best-known-example) at one extreme to the hyperkinetic disorder (exemplified by Huntington´s disease and hemiballism) at the other. In addition to disorders of movement, major mental disorders including schizophrenic-like states and attention deficit hyperactivity disorder (ADHD) have been linked to abnormalities in the basal ganglia and their allied nuclei.

In this paper we discuss recent evidence indicating that a dopamine-induced dysbalance of basal ganglia neurocircuitries may be an important pathophysiological component in PD, schizophrenia and ADHD. According to our model, the deprivation of dopaminergic nigrostriatal input, as in PD, reduces the positive feedback via the direct system, and increases the negative feedback via the indirect system. The critical consequences are an overactivity of the basal ganglia output sites with the resulting inhibition of thalamo-cortical drive. In schizophrenia the serious cognitive deficits might be partly a result of a hyperactivity of the inhibitory dopamine D_2 transmission system. Through this dysinhibition, the thalamus exhibits hyperactivity that overstimulates the cortex resulting in dysfunctions of perception, attention, stimulus distinction, information processing and affective regulation (inducing hallucinations and delusions) and motor disabilities. Recent studies have strongly suggested that a disturbance of the dopaminergic system is also involved in the pathophysiology of ADHD. The most convincing evidence comes from the demonstration of the efficacy of psychostimulants such as the dopamine transporter (DAT) blocker methylphen-idate in the symptomatic treatment of ADHD. Genetic studies have shown an association between ADHD and genes involved in dopaminergic neurotransmission (for example the dopamine receptor genes *DRD4* and *DRD5*, and the DAT gene *DAT1*). DAT knockout mice

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ISSN 1029 8428 print/ ISSN 1476-3524 online.

display a phenotype with increased locomotor activity, which is normalized by psychostimulant treatment. Finally, imaging studies demonstrated an increased density of DAT in the striatum of ADHD patients. Which system is disturbed and whether this system is hyper- or hypoactive is not unambiguously known yet.

Keywords: Dyskinesia; Extrapyramidal motor symptoms; Motor loop; Parkinsonism psychosis; Sleep disturbances; Limbic loop

INTRODUCTION

Based on the clinical experience, certain psychiatric disorders require opposite pharmacological mechanisms for therapeutic effectiveness. For example, the motor symptoms of Parkinson´s disease (PD, synonyms: idiopathic Parkinson syndrome, *paralysis agitans*), resulting from nigro-striatal dopaminergic neurodegeneration, can be alleviated by dopamimetic drugs. On the other hand, in schizophrenia dopamine overactivity in the mesolimbic system can be treated with dopamine receptor antagonists (neuroleptics, synonym antipsychotics). The latter, however, thus might induce dyskinesias as an unwanted side effect; whereas dopamine receptor agonists in PD could provoke psychotic symptoms. Recent investigations also revealed an involvement of dysfunctional dopamine neurotransmission in the pathogenesis of attention deficit hyperactivity disorder (ADHD), presenting with excessive motor activity that responds to psychostimulants, obviously by inhibiting the presynaptic dopamine transporter (DAT). Overdose of psychostimulants, however, is known to potentially induce psychosis, whereas ADHD psychosis surprisingly profits from psychostimulant treatment. After all, the relationship of dopaminergic dysbalances and pathophysiology underlying the symptomatology of ADHD, PD and schizophrenia are not yet understood. This paper aims to outline the knowledge on dopaminergic neurotransmission and brain circuitry pathways of these disorders. Empirical data (Medline research) focused on the neurobiological background of motor and psychiatric (especially psychotic) symptoms will be presented in order to enhance our understanding and ability to diagnose and treat these disorders.

PD

PD, first described as a clinical entity by James Parkinson, is the second most common neurodegenerative disease after Alzheimer´s disease, affecting approximately 2% of the human population aged 65 and above (De Rijk *et al.*, 1997). On the basis of aetiological factors the frequently encountered idiopathic form is distinguished from the various less frequently occurring symptomatic forms, and from those disease presentations that are accompanied by multi-system degeneration. The cardinal clinical features of PD are resting tremor, rigidity, and bradykinesia or motor slowing. However, signs of postural instability, autonomic dysfunctions, psychiatric symptoms such as depression and dementia are also present in a large percentage of patients. Moreover, 8-40% of patients with PD experience psychotic symptoms, probably related to chronic anti-PD medication. Core symptoms are brief visual hallucinations (30%), usually occurring at the end of day, correlating with potentially epiphenomenal vivid dreams, nightmares and sleep disturbances, while reality testing mostly remains intact. Older age, longer duration of disease, severity of PD, comorbid depression, sleep disturbances and cognitive impairment (especially dementia) are proposed as risk factors for the development of psychotic symptoms in PD (Aarsland *et al.*, 2001; Ismail and Richard 2004; Marsh *et al.*, 2004). Therefore, an association between cognition (mainly regulated by acetylcholine and glutamate), emotional processing (serotonin), psychosis and neuromotor abilities (dopamine) has to be considered.

Pathologically, PD is characterized by a preferential loss of neuromelanin-containing dopamine neurons in the pars compacta of the substantia nigra (SNc), with intracellular proteinaceous inclusions named Lewy bodies and a reduction in striatal dopamine (for review see Jellinger 1989; Sian *et al.*, 1999). This ongoing loss of nigral dopaminergic neurons mainly leads to clinical diagnosis due to occurrence of motor symptoms such as rigidity, tremor and bradykinesia, which results from a reduction of about 70% of striatal dopamine (Bernheimer *et al.*, 1973; Riederer and Wuketich, 1976). This is the rationale for the dopamine-substitution therapies, including treatment with L-DOPA (L-3,4-dihydroxyphenylalanine, levodopa) and peripheral aromatic amino acid decarboxylase- and catecholamine-*O*-methyltransferase (COMT)

inhibitors, dopamine receptor agonists, selective monoamine oxidase (MAO) type B inhibitors and drugs which indirectly improve dopaminergic functions (for example, glutamate antagonists).

Schizophrenia

Schizophrenia comprises both positive symptoms like hallucinations and delusions and negative symptoms like loss of interests and activation, depressive mood and social withdrawal. Patients initially often reveal non-specific neuropsychological symptoms, *e.g.*, indistinct cognitive impairments concerning attention, memory, concentration, task performance, reactivity, stimulus perception or differentiation and behavioural abnormalities like hyperactivity, irritability and impulsiveness. Investigations of prodromal signs in children and adolescents at high risk for schizophrenia primarily revealed negative symptoms like social withdrawal (62%), deterioration in school functions (38%), depression or anxiety (32% each), suggesting cognitive deficits, affective complaints, social isolation and school failure as a psychopathological substrate for schizophrenia (Lencz *et al.*, 2004). These characteristics resemble ADHD or developmental disorders.

Movement disorders might be an inherent feature of first-episode neuroleptic-naïve schizophrenia (Srinivasan *et al.*, 2001; Honer *et al.*, 2005) which is discussed as a specific endophenotype (Gottesman and Gould 2003). The prevalence of dyskinesia and parkinsonism in schizophrenia prior to treatment has been found to range between 13 and 28% and often remains stable despite of psychopathological response to antipsychotics (Cortese *et al.*, 2005). McCreadie *et al.* (2003) also found higher rates of dyskinesia in siblings of schizophrenic patients. These findings emphasize that some motor abnormalities in schizophrenia might reflect trait characteristics.

Schizophrenia is associated with dysfunctions of dopaminergic neurons especially of the ventral tegmental area (VTA) of the midbrain projecting to the prefrontal cortex and limbic system (Farmer and McGuffin, 1988), necessitating the use of dopamine D_2-receptor antagonists. Antipsychotic drug-induced dopamine D_2-receptor blockade in nigro-striatal pathways, however, is known to be associated with secondary extrapyramidal motor symptoms like dystonia, dyskinesia, parkinsonism, akathisia and tardive dyskinesia. The prevalence of extrapyramidal symptoms induced by typical antipsychotics is about 32% each concerning akathisia and tardive dyskinesia and about 23% concerning parkinsonism (Janno *et al.*, 2004).

ADHD

ADHD presents with hyperactivity, impulsiveness and various cognitive impairments like deficits of attention, working memory, reaction time, responsiveness, perception and self-management. Moreover, ADHD patients often show neurological soft signs, mostly concerning motor functions. ADHD psychosis with hallucinations and delusions might be a clinical manifestation of psychostimulant overdose, increasing dopamine availability in the synaptic cleft. However, common neurobiological pathways support the idea of a potential comorbid association of ADHD and schizophrenia. Interestingly, case reports on ADHD and comorbid neuroleptic-refractory adult-onset psychosis presenting with delusions and hallucinations observed improvement of schizophrenic symptoms when adding psychostimulants to ongoing antipsychotic treatment and even after withdrawal of the antipsychotics (Pine *et al.*, 1994). It has been suggested that ADHD psychosis favourably responding to psychostimulants constitutes a distinct entity with key symptoms like brief hallucinations, delusions with evident compensatory functions concerning low self-esteem, poor impulse control, aggression and impaired judgement whereas interest in social life maintains and disorganization of thoughts is rare (Opler *et al.*, 2001). Psychotic symptoms usually disappear quickly after administration of psychostimulants, however, long-term prognosis of recurring psychotic episodes and social adjustment is poor (ibid.). Schizophrenia successive to childhood ADHD seems to be associated with more severe developmental deficits in infancy, failure to respond to antipsychotics, more insidious course of disease, and reveals poorer outcome than schizophrenia only (Elman *et al.*, 1998).

Neurochemical and Functional Organisation of the Basal Ganglia Circuits

The basal ganglia, as the name implies, include deep-lying structures of the cerebral hemisphere: the striatum comprising the caudate nucleus, the putamen and the nucleus acccumbens, the pallidum comprising the medial (GPm) and the lateral

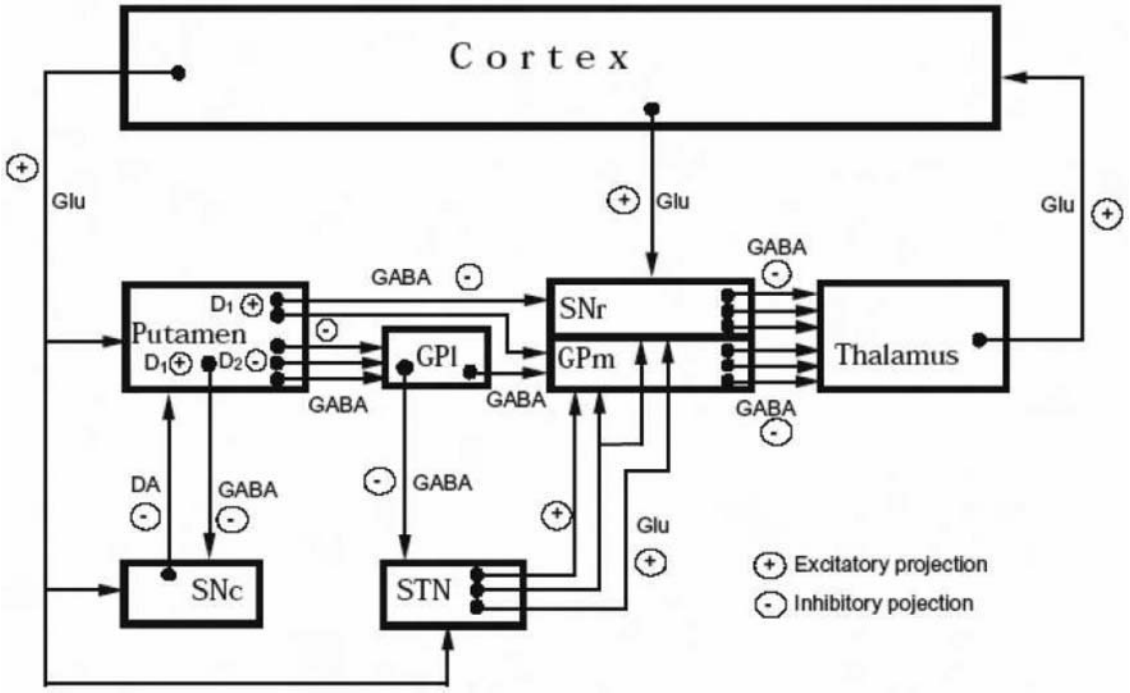

FIGURE 1 A schematic representation of the standard basal ganglia motor circuit (Taken from Sian *et al.*, 1999; with permission of Springer, Vienna New York). D_1, subtype of dopamine receptor; D_2, subtype of dopamine receptor; DA, dopamine; GABA, γ-aminobutyric acid; Glu, glutamate; GPl, lateral globus pallidus; GPm, medial globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.

segment of the globus pallidus (GPl), and also the amygdala (Graybiel, 1990). Functionally, the striatopallidal complex acts in conjunction with its allied nuclei, the subthalamic nucleus (reciprocally connected with the pallidum), and the substantia nigra, with its dopamine-containing SNc and its pars reticulata (SNr) interconnected with the striatum. The basal ganglia form a forebrain system that collects signals from a large part of the neocortex, redistributes these cortical inputs both with respect to one another and with respect to inputs from the limbic system, and then focuses the inputs of this redistributed, integrated signals into particular regions of the frontal lobes and brainstem involved in aspects of motor planning and motor memory.

Certain features shared by all of the basal ganglia thalamo-cortical circuits are indicated schematically in figure 1. In each case, specific cortical areas send excitatory, glutamatergic projections to selected portions of the striatum, which is generally thought to represent the "input" stage of the basal ganglia. In primates, the inputs to the basal ganglia portion of the motor circuit are focused principally on the putamen (Fig. 1), whereas the caudate nucleus and the nucleus accumbens are the principal input sites of the limbic circuit. According to the origin and distribution of cortico-striatal inputs the striatum is subdivided into three anatomo-functional areas. They are referred to respectively as 1) the sensorimotor area processing sensorial and motor information; 2) the associative area processing cognitive information; and 3) the limbic area processing emotional and motivational information (Alexander *et al.*, 1986). Tangible evidence suggests the existence of five segregated basal ganglia thalamo-cortical circuits by which it controls the functioning of the frontal regions of the cerebral cortex (Alexander and Crutcher, 1990). These five circuits include the "motor circuit" which is primarily directed to the precentral motor fields, the two prefrontal circuits projecting to the dorsolateral prefrontal and lateral orbitofrontal cortex, the oculomotor circuit leading to the frontal and supplementary eye fields, and finally the limbic circuit connected to the cingulated and medial orbitofrontal cortex. Each of these five circuits is constructed in a parallel manner, in addition all are functionally and structurally separated from each other (Alexander *et al.*, 1986).

By virtue of their high rates of spontaneous discharge, the basal ganglia "output" nuclei GPm and SNr exert a tonic, γ-aminobutyric (GABA)-mediated, inhibitory effect on their target nuclei in the thalamus (FIG. 1). Within each circuit, this inhibitory outflow appears to be differentially modulated by two opposing but parallel pathways that pass from the striatum to the basal ganglia output nuclei. The direct pathway originates from the striatum and contains the inhibitory efferents of GABA co-localised with substance P. Thus, the output pathway exerts an inhibitory GABA-induced affect on the thalamus. The indirect output pathway includes striatal projections (GABA co-localised with enkephalin) that pass through the GPl, then trough the nucleus subthalamicus (STN, GABA only) and finally leading to the output nuclei via an excitatory glutamatergic tract. Stimulation of both the direct and the indirect pathway releases the restraint on STN. However, the indirect one results in amplification of the excitatory influx to the output nuclei. Therefore, although both the direct and the indirect pathway are oriented in a parallel manner, nevertheless, they operate differentially and elicit different affects on the output nuclei in the basal ganglia. Indeed, the direct pathway contributes to the positive feedback to pre-central motor areas and the indirect pathway provides the negative feedback.

The basal ganglia serve a crucial role in both, abolishing unwanted activity and the automatic processing of desired movements (Marsden, 1990). It implements such a role, primarily through the operation of the "motor circuit" (Fig. 1). Increasing evidence suggests that the GPm and STN execute a crucial role in the performance of motor orientated movements. Activation of the GPm neurons may be related to the inhibition of excess unwanted movements. The "motor circuit" may effectively serve a binary function on cortically initiated motor movements, by virtue of its ability to modulate and enhance through the direct pathway and inhibit the conflicting patterns via the indirect pathway. In addition to disorders of movement, certain forms of drug addiction and major mental disorders including schizophrenic-like states, ADHD and obsessive compulsive disorders have been linked in abnormalities in the basal ganglia and their allied nuclei (Carlsson, 2000; 2006).

Abnormalities of Neuronal Circuits in PD: Motor Symptoms

Movement disorders associated with basal ganglia dysfunction comprise a spectrum of abnormalities that range from the hypokinetic disorder (from which PD is the best-known-example) at one extreme to the hyperkinetic disorder (exemplified by Huntington´s disease and hemiballism) at the other. Both extremes of this movement disorder spectrum can be accounted for by postulating specific disturbances with the basal ganglia thalamo-cortical motor circuit (DeLong *et al.*, 1990; Foley and Riederer, 2000).

According to the standard model of human basal ganglia organization, that was postulated on the basis of animal experiments and clinical experience in the normal brain, there exists a balance between direct inhibitory input and indirect excitatory input to GPm, which in turn controls thalamo-cortical activation (Fig. 1). The deprivation of dopaminergic nigro-striatal input, as in PD, reduces the positive feedback via the direct system, and increases the negative feedback via the indirect system. The critical consequences are an overactivity of the STN, GPm and SNr, with the resulting inhibition of thalamo-cortical drive. The standard model posits that the hyperactivity of the STN following reduced dopaminergic nigrostratal input is responsible for the bradykinesia of PD, and the hyperactivity of the SNr for the akinesia and rigidity. L-DOPA-induced dyskinesias are attributed to an over-correction of this situation - that is, the direct pathway then gets overactivated and the indirect pathway under-activated from the striatum (Foley and Riederer, 2000). Hypoactivity of the GPl in PD, in turn, is believed to underlie the increased activity of the STN. Bilateral deep-brain stimulation of the GPm and the STN (The deep-brain stimulation for Parkinson´s disease study group, 2001) but also thalatomy and posteroventral pallidotomy alleviate motor functions of patients with PD (Narabayashi *et al.*, 1984; Laitinen, 1995). However, electrical stimulation of the STN whether reversible or destructive, induces dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys and in PD patients, suggesting that these side effects are associated with decreased STN output (Bergman *et al.*, 1990; Limousin *et al.*, 1995).

There is an interesting case report of a PD patient following deep brain stimulation showing that dis-

abling dyskinesias were ameliorated, but new-onset manic and psychotic symptoms induced (Herzog *et al.*, 2003). The dorsolateral part of the STN comprises sensorimotor functions but beside immediate motor effects deep brain stimulation obviously also seems to have an additional, more progressively appearing influence on affective and motivational functions, either by direct interference with the limbic territory or secondary via the orbitofrontal basal ganglia circuit (ibid.). The latter pathway would elucidate that affective and psychotic symptoms are not instantly reversible but need some time for remission, whereas motor functions directly depend on on/off-stimulation.

Abnormalities of Neuronal Circuits in PD: Psychotic and Cognitive Symptoms

In PD, atrophy of the nucleus basalis Meynert and cortical cholinergic deficiency and/or chronic dopamine replacement therapy provoke psychosis. Dopaminergic agents initially improve these deficits in PD, however, in the chronic course, the positive effects wear off, probably as a result of a relative hyperdopaminergic state concerning the mesolimbic and mesocortical areas as in schizophrenia (Kulisevsky 2000), finally resulting in altered perceptions. However, it is also possible that neurobiological features of PD can increase the propensity for hallucinations. Indeed, there are studies reporting hallucinations in drug-naive PD or patients treated with anticholinergic drugs (Holroyd *et al.*, 2001). Moreover, the dosage levels of dopaminergic agents are not correlated with the risk of hallucinations (Sanchez-Ramos *et al.*, 1996). Even the use of L-DOPA infusions did not increase hallucinations and therefore failed to constitute a simple relationship with dopaminergic functions (Holroyd *et al.*, 2001).

It has been hypothesized that PD hallucinations might derive from impairments of rapid eye movement (REM) sleep controlling factors (Perry *et al.*, 1999) since hallucinating PD patients report significantly more often a history of preceding increased dream activity (48%), sleep disruptions (62%) and general sleep disturbances (excessive daytime sleepiness, parasomnias, nocturnal myoclonus) than PD patients without hallucinations (Arnulf *et al.*, 2000; Ismail and Richard 2004). The core item of the continuum of hallucinations in PD, however, is altered dream phenomena but not fragmentation of sleep (Pappert *et al.*, 1999). Polysomnographic studies in hallucinatory PD observed lower sleep efficiency, reduced total REM sleep time and REM percentage, a higher propensity to muscle atonia and decreased daytime sleep latencies compared to non-hallucinatory PD (Arnulf *et al.*, 2002). A correlation between reduced night sleep duration and decreased daytime sleep latency was ruled out suggesting that sleepiness might be disease-related (ibid.). Some authors compared PD psychosis with narcolepsy-like REM sleep disorder with the hallucinations coinciding with daytime REM episodes or hypnagogic states (Schafer and Greulich, 2000). Hypnagogic phenomena and cataplexy also resemble narcoleptic symptoms. It has been hypothesized that delusions might be the consequence of daytime emerging dreams, altering the patient´s perceptive functions of reality (Arnulf *et al.*, 2000).

Especially in the pontine area (*e.g.*, pedunculopontine nucleus), including ponto-geniculo-occipital circuits, cholinergic neurons control REM sleep characterized by vivid dreams. The degeneration of cholinergic neurons in PD could therefore be related with the development of hallucinations. This would be in keeping with reports of the antipsychotic efficacy of acetylcholinesterase inhibitors in some cases of PD hallucinations and with the ability of anticholinergic drugs to facilitate psychoses (Kulisevsky, 2000).

In single photon emission computed tomography (SPECT) studies, REM sleep disorder patients in general presented with a reduced striatal DAT density compared with healthy controls (Eisensehr *et al.*, 2000). In particular, destruction of VTA neurons induced excessive sleepiness and REM sleep (Decker *et al.*, 2002). Takakusaki *et al.* (2004) suggested a model of REM disturbances in PD and proposed that reductions of dopaminergic projections from the SNc to the basal ganglia might interfere with GABAergic output from the SNr to REM- and atonia-regulating areas of the pedunculopontine tegmental nucleus, resulting in REM disturbances and changes of muscular atonia. Treatment with L-DOPA and dopamine receptor agonists also is correlated with REM changes: low doses are supposed to stimulate presynaptic D_2 autoreceptors in the VTA, inhibiting dopaminergic activity and therefore increasing somnolence and REM sleep, whereas high doses might stimulate postsynaptic D_1 receptors resulting in wakefulness

and decreased REM sleep (Pauletto *et al.*, 2004).

Visual processing and categorization (*e.g.*, colour discrimination and contrast sensitivity, visual cognition, visuo-spatial functions) have been reported to be abnormal in PD with hallucinations (Barnes *et al.*, 2003). In functional magnetic resonance imaging studies, these patients not only activated posterior parietal and occipital lobe areas following visual stimulation like PD patients without hallucinations, but also activated frontal lobes which therefore seem to be involved with the pathogenesis of hallucinatory behaviour (Wint *et al.*, 2004).

In PD, deficits of cognitive skills essential for executive functions (planning, anticipation, initiation, monitoring) correlate with reduced dopaminergic functions in the dorsolateral prefrontal cortex because of the loss of mesocortical projections from the VTA (Cools *et al.*, 2002). Cognitive impairment (verbal fluency, working memory, attention) in PD has been correlated with reduced [^{18}F]fluorodopa uptake in the caudate nucleus and frontal cortex, indicating an involvement of dopaminergic dysfunctions in these areas (Thanvi *et al.*, 2003). Magnetic resonance imaging studies have shown in naïve monkeys marked changes of the regional cerebral blood volume in striatal, limbic and midbrain regions following administration of the dopamine releaser and dopamine re-uptake blocker amphetamine (Jenkins *et al.*, 2004), reflecting the direct release of dopamine in these areas with a high density of dopamine receptors.

However, dopaminergic therapy (*e.g.*, L-DOPA, selegiline) have not shown significant improvement of cognition in PD related dementia. Therefore, it is suggested that other transmitter systems like the cholinergic are of greater importance as is shown by the beneficial effects of cholinesterase inhibitors.

Abnormalities of Neuronal Circuits in Schizophrenia

With regard to schizophrenia, specific disturbances within the basal ganglia thalamo-cortical loops are discussed (Carlsson, 2006). Carlsson (1977) was the first to hypothesize that the serious cognitive deficits in schizophrenia are partly a result of a hyperactivity of the inhibitory dopamine D_2 transmission system. Alternative hypotheses are overactivation of the serotonergic 5-HT_2 transmission system, hypoactivity of the excitatory glutamatergic *N*-methyl-D-aspartate (NMDA) system and hyperactivity of the inhibitory GABA transmission system (for review see Carlsson, 2006).

One of the central issues of the concept of the hyperactive dopamine D_2 transmission system was the role of the dopamine D_2 receptors that are found in the striatum that the antipsychotic drugs are acting upon. The experimental evidence demonstrated that the projection of dopaminergic neurons from the SNc and the area VTA to the striatum complex (SNc neurons innervate the putamen and caudate nucleus, whereas VTA neurons project to the nucleus accumbens) plays a central role in schizophrenia. The striatal complex usually has inhibiting effects on the thalamus via GABAergic neurons. The thalamus thus can act as a filter of sensory information. Dopamine D_2 receptors in striatal neurons inhibit the inhibitory output projecting to the thalamus. Hyperactivity of the dopamine system thus inhibits the inhibitory influence on the thalamus. Through this dysinhibition, the thalamus exhibits hyperactivity that overstimulates the cortex, resulting in dysfunctions of perception, attention, stimulus distinction, information processing and affective regulation (inducing hallucinations and delusions), but beside these psychotic symptoms also motor disabilities. Reduction of glutamate neurotransmission by NMDA-receptor antagonists such as phencyclidine (Keshavan, 1999) also enhances psychotic symptoms by secondary activation of D_2-receptors (Riederer *et al.*, 1992; Laruelle *et al.*, 2005), whereas agonists of glutamate reduce psychotic symptoms, suggesting a balance between dopamine and glutamate system.

The important cue for motor versus psychotic symptoms is obviously the balance between inhibition and stimulation in the striatal cortex (Carlsson and Carlsson, 1990; Carlsson, 2006). Animal experiments have shown that reserpine-induced depletion of the nigro-striatal dopamine system results in an immobility in the animals similar to motor impairment in PD. After application of phencyclidine, the animals move again. A balance between glutamate and dopamine activity is thus important for undisturbed information processing - hypoglutamatergic and also hyperdopaminergic activity result in reduced activation of the striatum and may induce psychotic symptoms.

Boks *et al.* (2004) investigated neurological soft signs in 191 first episode schizophrenic patients, comparing them with mood disorders and healthy

controls. Coordination deficits - probably reflecting fronto-cerebellar malfunctions - increased reflexes, dyskinesia and surprisingly also catatonia were not significantly increased compared to mood disorders. Movement disorders like eye movement disorders (saccade blink suppression etc.), decreased gait movements and parkinsonian symptoms were specific for schizophrenia and therefore suggest that the frontal cortex and - again - basal ganglia are specifically involved in dyskinetic symptoms of schizophrenic patients (ibid.).

Effects of Antipsychotic Treatment

Conventional antipsychotic drugs are known to exert dopamine D_2-receptor antagonism which in the mesolimbic dopaminergic system is supposed to be responsible for the antipsychotic properties but in the dopaminergic nigro-striatal system might induce secondary extrapyramidal symptoms like dystonia, tremor, ataxia, abnormal gait, involuntary muscle movements, akathisia and muscle rigidity. There are two main hypotheses for the pathogenesis of tardive dyskinesia: One is the dopamine supersensitivity hypothesis, suggesting that the dopamine receptor antagonism of neuroleptic medication could induce a supersensitivity of these receptors resulting in a secondary hyperdopaminergic state in motor regulation areas (Klawans and Rubovits 1972). Another explanation of tardive dyskinesia might be the neuronal degeneration hypothesis, based on free radical mechanisms following dopamine and antipsychotic drug metabolism (Cadet and Lohr, 1989). It has been shown that the prevalence of extrapyramidal symptoms in schizophrenic patients treated with antipsychotics is increased in young-onset patients and in case of a positive family history of primary movement disorders, suggesting that primary and secondary movement disorders share common genetic factors but also probably common impairments of dopaminergic pathways (Lencer *et al.*, 2004). A candidate gene for tardive dyskinesia is the serine to glycine polymorphism (Ser9Gly) of the dopamine D_3 receptor. Homozygotes for the dopamine D_3 receptor glycine allele revealed more often tardive dyskinesia following neuroleptic treatment (Steen *et al.*, 1997). This is in line with the finding that the dopamine D_3 receptor serine alleles have lower frequencies in African-American patients than in European-American patients; the latter suffer less frequently from tardive dyskinesia (Wonody *et al.*, 2004).

Atypical neuroleptics, on the other hand, are associated with fewer drug-induced movement disorders. They inhibit both dopamine D_2-receptors and - in even greater extent - serotonergic 5-HT_{2A}-receptors. The occupancy of D_2-receptors is lower than 80% and probably of shorter duration than with conventional agents, and the induction of nigro-striatal dopamine supersensitivity therefore might be omitted (Casey, 2004). Another hypothesis speculates that the prefrontal cortical, mesolimbic, nigro-striatal and tuberoinfundibular 5-HT_{2A} antagonism of atypical antipsychotics might increase the release of dopamine reversing the D_2 blockade by medication (ibid.). This model is based on the assumption that serotonin interacts with the dopamine system by decreasing dopamine release from dopaminergic axon terminals.

These findings in schizophrenic patients underline specific involvement of direct and indirect pathway mechanisms and dopamine/glutamate balance aspects in disease or medication related schizophrenic versus motor symptoms. This biochemical context strengthens the importance of developing antipsychotics with brain area related differentiated receptor affinities in order to further support drug effectiveness and safety. The glutamate pathway has to be considered a promising therapeutic approach.

Comorbid Associations of Schizophrenia and ADHD?

Clinically, premorbid negative, cognitive or motor symptoms of schizophrenia are quite similar with ADHD. Recently, various investigational findings outline neurobiological commonalities of schizophrenia and ADHD:

Cognitive impairments seem to be genetically linked to schizophrenia since non-psychotic parents of childhood-onset schizophrenic patients performed worse in neurocognitive tasks than parents of ADHD children (Asarnow *et al.*, 2002) and relatives of schizophrenic patients revealed a higher percentage of ADHD symptoms (31%; especially higher scores on magical ideation, perceptual aberration and more neurological impairments) than relatives of healthy controls (Keshavan *et al.*, 2003).

Neuroimaging studies showed that childhood-onset schizophrenia presents with significant total brain volume reduction (for review see Mehler

and Warnke, 2002), especially concerning primary parietal gray matter loss, followed by frontal and temporal gray matter volume decreases, suggesting a continuum of back-to-front tissue loss in late development (Thompson *et al.*, 2001). We previously reported that very young-onset patients (≤12 years) already at the beginning of schizophrenia reveal significantly increased brain ventricle volumes compared to healthy controls, whereas children and adolescents older than 12 years developed secondary ventricular enlargement during the course of the disease (Badura *et al.*, 2001). These findings support the neurodevelopmental hypothesis of very early-onset schizophrenia, constituting its own pathogenetic entity. Correlations between negative symptoms of schizophrenia and hypofrontality or frontal lobe atrophy, respectively, have been reported, and also in ADHD with its resembling symptoms of cognitive impairments frontal lobe dysfunctions seem to be involved in the pathophysiology of the disease (Faraone and Biederman, 1998).

Recent studies have strongly suggested that ADHD represents a deficiency in parts of the basal ganglia linked to associative prefrontal cortex and to secondary motor cortical areas involved in attention processes and motor planning. For example, rodent studies demonstrated that the core processes which are deficient in ADHD are mediated by the right prefrontal cortex and that the mesocortical dopamine system plays a central role in the modulation of these functions (Sullivan and Brake, 2003). These studies also demonstrated that the prefrontal cortex is highly vulnerable to a wide variety of early developmental insults, which parallel the known risk factors for ADHD (Biederman and Faraone, 2005); Nicotine exposure during pregnancy, for example, is correlated with hyperactivity of the offspring, because nicotinic receptors coupled with dopamine neurotransmission cause enhanced dopamine release; further and finally, prenatal hypoxia, clinically presenting with later-onset hyperactivity, especially harms the striatum which is rich of dopaminergic synapses. With anatomic brain magnetic resonance imaging in post stroke children lesions within the dopamine-rich ventral putamen, which is part of the ventral or limbic striatum, correlated with an increased risk of ADHD traits (Max *et al.*, 2002). This has also been reported for thalamic lesions (Gerring *et al.*, 2000). ADHD therefore might be a disinhibition syndrome associated with dysfunctions in the cortical-striato-thalamocortical loop. Pharmacological studies in non-human primates using axonal tracer injections have shown that the pallidal sites related to dyskinesia, attention deficit with or without hyperactivity, and stereotyped behaviour, were respectively in motor, associative and limbic territories (Francois *et al.*, 2004). Using functional magnetic resonance imaging, unmedicated ADHD adolescents differed from healthy comparison subjects in the activation of the left ventral aspects of the basal ganglia during the performance of a divided attention task (Shafritz *et al.*, 2004). When the ADHD adolescents were given a challenge dose of methylphenidate before scanning, they recruited this region of the basal ganglia to a similar degree as the normal subjects. These findings of reduced striatal activation for adolescents with ADHD are consistent with previous neuroimaging studies showing that ADHD subjects exhibit less activity in basal ganglia structures both at rest and during the performance of cognitive tasks (Lou *et al.*, 1989; Vaidya *et al.*, 1998; Rubia *et al.*, 1999). Moreover, the finding that methylphenidate normalized striatal activation is consistent with previous reports that methylphenidate preferentially modulates striatal activity in ADHD patients (Lou *et al.*, 1989; Vaidja *et al.*, 1998) and increases extracellular dopamine in the striatum in healthy adults (Volkow *et al.*, 2001).

There is further evidence that a disturbance of the dopaminergic system is involved in the pathophysiology of ADHD. For example, genetic studies using the candidate gene approach have revealed the most robust and replicated findings for polymorphisms in genes for the dopamine receptors (*DRD4*, *DRD5*) and *DAT1* that is blocked by methylphenidate (for review see Heiser *et al.*, 2004). Genetically engineered "knockout" mice lack a functional DAT and demonstrate striking spontaneous behavioural hyperactivity compared to wild-type mice that can be inhibited by psychostimulants such as amphetamine and methylphenidate (Gainetdinow and Caron, 2001). Finally, SPECT studies have shown an increased striatal DAT density in drug naïve patients with ADHD (Krause *et al.*, 2001; Larisch *et al.*, 2006). All these first and uncomplete evidences suggest major involvement of both the motor loop and the limbic circuit in the pathobiochemistry of ADHD and its treatment strategies.

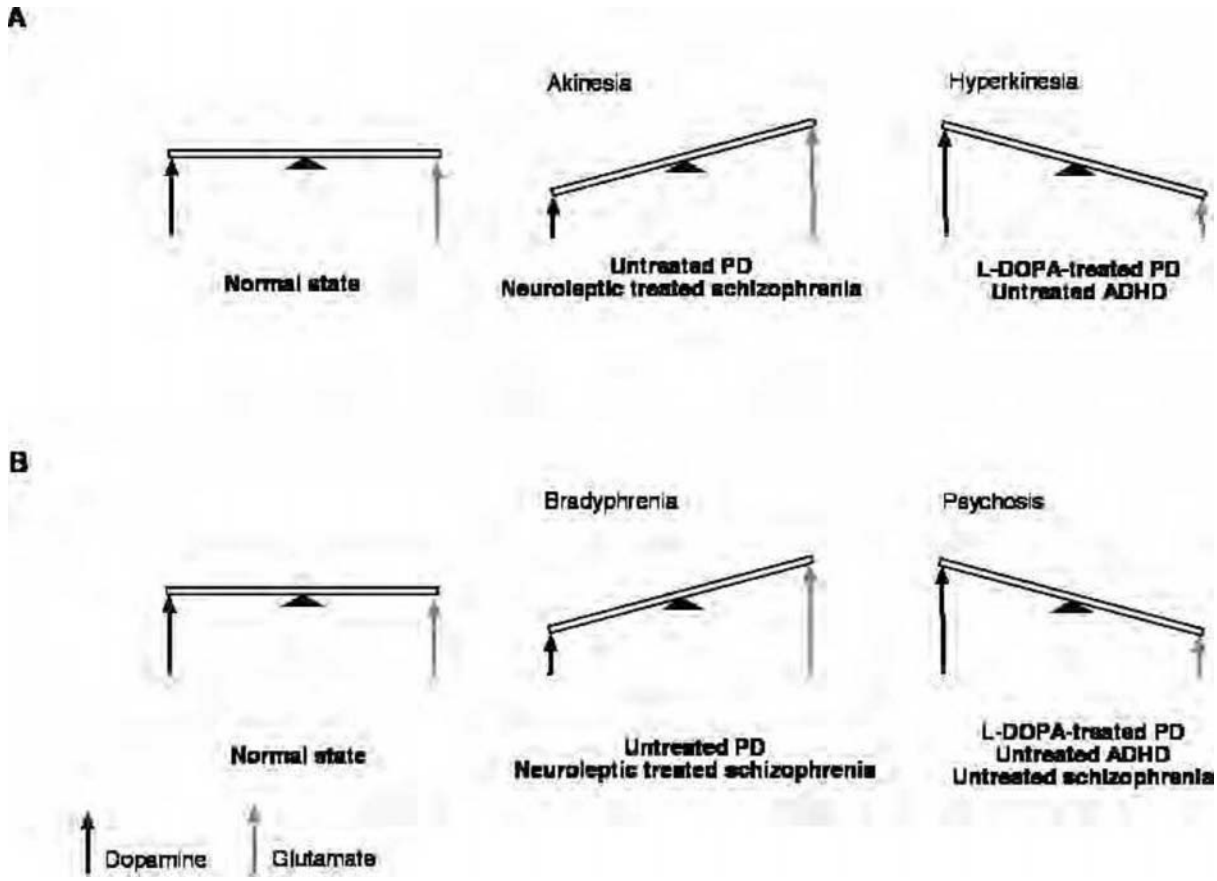

FIGURE 2 Simplified model showing the imbalance of the glutamatergic and dopaminergic system in the motor (**A**) and lmbic loop (**B**) underlying the symptomatolgy in Parkinson´s disease (PD), schizophrenia and attention deficit hyperactivity disorder (ADHD).

After all, it is of high clinical relevance to understand the neuropathological function of dopamine in ADHD as psychostimulants as an effective medication on hyperkinesia, on the other hand, might induce dopamine system derived drug dependency and psychotic side effects in the case of abuse. The recent findings on methylphenidate´s modulating mechanisms at the DAT and genetic research results on ADHD candidate genes of the dopamine system are promising insights and warrant further investigations in order to optimize and specify psychopharmacological treatment.

Psychotic and motor symptoms in PD, schizophrenia and ADHD are related to dopaminergic dysregulation in distinct neuronal basal ganglia circuitries.

In conclusion, the interaction of neurotransmitter circuits is of eminent importance to the understanding of the pathophysiology and treatment strategies of classical neurodegenerative disorders such as PD and Chorea Huntington as well as of classical neurodevelopmental disorders such as schizophrenia and ADHD. Figure 2 schematically depicts possible relationship of the dopaminergic and glutamatergic system underlying the pathopyhsiology of PD, schizophrenia and ADHD.

In PD it is the dysfunction of the balance between the direct and indirect pathways of the motor loop that predominates symptomatology: Dopamine loss and glutamate increase, respectively, cause motor symptoms. With dopaminergic treatment and under certain conditions facilitation of psychotic symptoms may appear, while motor symptoms improve.

This contrasts subtypes of schizophrenia: Neurodevelopmental disturbances lead to a dopaminergic preponderance in the limbic circuits with the appearance of psychosis. The motor loop, how-

ever, is affected mainly in catatonic states and/or after treatment with antidopaminergic drugs, thus eventually inducing parkinsonoid symptoms.

The motor circuits in ADHD resemble more the situation of hyperactivity/increased motoricity and such may mirror the situation of hyperkinesias. In addition, the limbic loop also appears to be overactive. Loss of dopamine receptor function due to mutations of receptor genes might be responsible for the need of enhanced dopamine concentration in the synaptic cleft leading to improvement both of feedback regulation and of postsynaptic dopamine action. Treatment with psychostimulants, although paradoxical at first glance, leads to a normalization in both circuits with clinical reduction of hyperkinesia in ADHD on the one hand and therapeutic effectiveness even in ADHD psychosis on the other hand.

References

Aarsland D, C Ballard, PJ Larsen and E McKeith (2001) A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson´s disease with and without dementia. *Int. J. Geriatr. Psychiatry* **16**, 528-536.

Alexander GE and MD Crutcher (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci.* **13**, 266-271.

Alexander GE, MR DeLong and PL Strick (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann. Rev. Neurobiol.* **9**, 357-381.

Arnulf I, AM Bonnet, P Damier, BP Bejjani, D Seilhean, JP Derenne and Y Agid (2000) Hallucinations, REM sleep and Parkinson´s disease. *Neurology* **55**, 281-288.

Arnulf I, E Konofal, M Merino-Andreu, JL Houeto, V Mesnage, ML Welter, L Lacomblez, JL Golmard, JP Derenne and Y Agid (2002) Parkinson´s disease and sleepiness. An integral part of PD. *Neurology* **58**, 1019-1024.

Asarnow RF, KH Nuechterlein, KL Subotnik, DL Fogelson, RD Torquato, DL Payne, J Asamen, J Mintz and D Guthrie (2002) Neurocognitive impairments in nonpsychotic parents of children with schizophrenia and attention-deficit/hyperactivity disorder: the University of California, Los Angeles, Family Study. *Arch. Gen. Psychiatry* **59**, 1053-1060.

Badura F, GE Trott, C Mehler, P Scheuerpflug, E Hofmann, M Warmuth-Metz, M Nadjmi, L Solymosi and A Warnke (2001) A study of cranial computer tomograms in very early and early onset schizophrenia. *J. Neural Transm.* **108**, 1335-1344.

Barnes J, L Boubert, J Harris, A Lee and AS David (2003) Reality monitoring and visual hallucinations in Parkinson´s disease. *Neurpsychologia* **41**, 565-574.

Bergman H, T Wichman and MR DeLong (1990) Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* **249**, 1436-1438.

Bernheimer H, W Birkmayer, O Hornykiewicz, K Jellinger and F Seitelberger (1973) Brain dopamine and the syndromes of Parkinson and Huntington: clinical, morphological and neurochemical correlations. *J. Neurol. Sci.* **20**, 415-445.

Biederman J and SV Faraone (2005) Attention-deficit hyperactivity disorder. *Lancet* **366**, 237-248.

Boks MPM, PF Liddle, JGM Burgerrhof, R Knegtering and RJ van den Bosch (2004) Neurological soft signs discriminating mood disorders from first episode schizophrenia. *Acta Psychiatr. Scand.* **110**, 29-35.

Cadet JL and JB Lohr (1989) Possible involvement of free radicals in neuroleptic-induced movement disorders. Evidence from treatment of tardive dyskinesia with vitamin E. *Ann. NY Acad. Sci.* **570**, 176-185.

Carlsson A (1977) Does dopamine plays a role in schizophrenia? *Psychol. Med.* **7**, 583-597.

Carlsson ML (2000) On the role of cortical glutamate in obsessive-compulsive disorder and attention-deficit hyperactivity disorder, two phenomenologically antithetical conditions. *Acta Psychiatr. Scand*. **102**, 401-413.

Carlsson A (2006) The neurochemical circuitry of schizophrenia. *Pharmacopsychiatry* **39** [Suppl. 1], S10-S14.

Carlsson M and A Carlsson (1990) Interactions between glutamatergic and monoaminergic systems within the basal ganglia - implications for schizophrenia and Parkinson´s disease. *Trends Neurosci.* **13**, 272-276.

Casey DE (2004) Pathophysiology of antipsychotic drug-induced movement disorders. *J. Clin. Psychiatry* [Suppl. 9] **65**, 25-28.

Cools R, E Stefanova, RA Barker, TW Robbins and AM Owen (2002) Dopaminergic modulation of high-level cognition in Parkinson´s disease: the role of the prefrontal cortex revealed by PET. *Brain* **125**, 584-594.

Cortese L, MP Caligiuri, AK Malla, R Manchanda, J Takhar and R Haricharan (2005) Relationship of neuromotor disturbances to psychosis symptoms in first-episode neuroleptic-naïve schizophrenia patients. *Schizophr. Res.* **75**, 65-75.

DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* **13**, 281-285.

De Rijk MC, C Tzourio, MMB Breteler, JF Dartigues, L Amaducci, S Lopez-Pousa, JM Manubens-Bertran, A Alperovitch and WA Rocca (1997) Prevalence of parkinsonism and Parkinson's disease in Europe. The EUROPARKINSON collaborative study. *J. Neurol. Neurosurg. Psychiatry* **63**, 10-15.

Decker MJ, G Keating, GE Hue, AA Freeman and DB Rye (2002) Mesolimbic dopamine´s modulation of REM sleep. *J. Sleep Res.* [Suppl. 1)] **11**, 51-52.

Eisensehr I, R Linke, S Noachtar, J Schwarz, FJ Gildehaus and K Tatsch (2000) Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behavior disorder. Comparison with Parkinson´s disease and controls. *Brain* **123**, 1155-1160.

Elman I, M Sigler, J Kronenberg, JP Lindenmayer, A Doron, S Mendlovic and B Gaoni (1998) Characteristics of patients with schizophrenia successive to childhood attention deficit hyperactivity disorder. Isr. *J. Psychiatry Relat. Sci.* **35**, 280-286.

Faraone SV and J Biederman (1998) Neurobiology of attention-deficit hyperactivity disorder. *Biol. Psychiatry* **44**, 951-958.

Farmer AE and P McGuffin (1988) The pathogenesis and man-

agement of schizophrenia. *Drugs* **35**, 177-185.

Foley P and P Riederer (2000) The motor circuit of the human basal ganglia reconsidered. *J. Neural Transm.* (Suppl.) **58**, 97-110.

Francois C, D Grabli, K McCairn, C Jan, C Karachi, E-C Hirsch, J Feger and L Tremblay (2004) Behavioural disorders induced by external globus pallidus dysfunction in primates - II. Anatomical study. *Brain* **127**, 2055-2070.

Gainetdinov RR and MC Caron (2001) Genetics of childhood disorders: XXIV. ADHD, part 8: Hyperdopaminergic mice as an animal model of ADHD. *J. Am. Acad. Child. Adolesc. Psychiatry* **40**, 380-382.

Gerring J, K Brady, A Chen, C Quinn, E Herskovits, K Bandeen-Roche, MB Denckla and RN Bryan (2000) Neuroimaging variables related to development of secondary attention deficit hyperactivity disorder after closed injury in children and adolescents. *Brain Inj.* **14**, 205-218.

Gottesman II and TD Gould (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. *J. Am. Psychiatry* **160**, 636-645.

Graybiel AM (1990) Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neuosci.* **13**, 244-264.

Heiser P, S Friedel, A Dempfle, K Konrad, J Smidt, J Grabarkiewicz, B Herpertz-Dahlmann, H Remschmidt and J Hebebrand (2004) Molecular genetic aspects of attention-deficit/ hyperactivity dsisorder. *Neurosci. Biobehav. Rev.* **28**, 625-641.

Herzog J, J Reiff, P Krack, K Witt, B Schrader, D Müller and G Deuschl (2003) Manic episode with psychotic symptoms by subthalamic nucleus stimulation in a patient with Parkinson´s disease. *Mov. Disord.* **18**, 1382-1384.

Holroyd S, L Currie and GF Wooten (2001) Prospective study of hallucinations and delusions in Parkinson´s disease. *J. Neurol. Neurosurg. Psychiatry* **70**, 734-738.

Honer WG, LC Kopala and J Rabinowitz (2005) Extrapyramidal symptoms and signs in first-episode, antipsychotic exposed and non-exposed patients with schizophrenia or related psychotic illness. *J. Psychopharmacol.* **18**, 277-285.

Ismail MS and IH Richard (2004) A reality test: how well do we understand psychosis in Parkinson´s disease? *J. Neuropsychiatry Clin. Neurosci.* **16**, 8-18.

Janno S, M Holi, K Tuisku and K Wahlbeck (2004) Prevalence of neuroleptic-induced disorders in chronic schizophrenia patients. *Am. J. Psychiatry* **161**, 160-163.

Jellinger K (1989) Pathology of Parkinson´s syndrome, In: *Handbook of Experimental Pharmacology*, Vol. **88** (Calne DB, Ed.) (Springer:Berlin, Heidelberg), pp 47-112.

Jenkins BG, R Sanchez-Pernaute, AL Brownell, IC Yin-Ching and O Isacson (2004) Mapping dopamine function in primates using pharmacologic magnetic resonance imaging. *J. Neurosci.* **24**, 9553-9560.

Keshavan MS (1999) Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. *J. Psychiatr. Res.* **33**, 513-521.

Keshavan MS, M Sujata, A Mehra, DM Montrose and JA Sweeney (2003) Psychosis proneness and ADHD in young relatives of schizophrenia patients. *Schizophr. Res.* **59**, 85-92.

Klawans HL and R Rubovitz (1972) An experimental model of tardive dyskinesia. *J. Neural Transm.* **33**, 235-246.

Krause KH, SH Dresel, J Krause, HF Kung and K Tatsch (2001) Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. *Neurosci. Lett.* **285**, 107-110.

Kulisevsky J (2000) Role of dopamine in learning and memory: implications for the treatment of cognitive dysfunction in patients with Parkinson´s disease. *Drugs Aging* **16**, 365-379.

Laitinen LV (1995) Pallidotomy for Parkinson´s disease. *Neurosurg. Clin. N. Am.* **6**, 105-112.

Larisch R, W Sitte, C Antke, S Nikolaus, M Franz, W Tress and H-W Müller (2006). Striatal dopamine transporter density in drug naive patients with attention-deficit/hyperactivity disorder. *Nucl. Med. Commun.* **27**, 267-270.

Laruelle M, WG Frankle, R Narendran, LS Kegeles and A Abi-Dargham (2005) Mechanism of action of antipsychotic drugs: from dopamine D_2 receptor antagonism to glutamate NMDA facilitation. *Clin. Ther. (Suppl. A)* **27**, S16-S24.

Lencer R, G Eismann, M Kasten, K Kabakci, V Geithe, J Grimm and CH Klein (2004) Family history of primary movement disorders as a predictor for neuroleptic-induced extrapyramidal symptoms. *Brit. J. Psychiatry* **185**, 465-471.

Lencz T, CW Smith, A Auther, CU Correll and B Cornblatt (2004) Nonspecific and attenuated symptoms in patients at clinical high-risk for schizophrenia. *Schizophr. Res.* **68**, 37-48.

Limousin P, P Pollak, A Benazzouz, D Hoffmann, JF Le Bas, E Broussolle, JE Perrett and AL Benabid (1995) Effect on parkinsonian signs and symptoms of bilateral subthalamic stimulation. *Lancet* **345**, 91-95.

Lou HC, L Henriksen, P Bruhn, H Borner and JB Nielsen (1989). Striatal dysfunction in attention deficit and hyperkinetic disorder. *Arch. Neurol.* **46**, 48-52.

Marsden CD (1990) Parkinson´s disease. *Lancet* **335**, 948-952.

Marsh L, JR Williams, M Rocco, S Grill, C Munro and TM Dawson (2004) Psychiatric comorbidities in patients with Parkinson disease and psychosis. *Neurology* **63**, 293-300.

Max JE, PT Fox, JL Lancaster, P Kochunov, K Mathews, FF Manes, BA Robertson, S Arndt, DA Robin and AE Lansing (2002) Putamen lesions and the development of attention-deficit/ hyperactivity symptomatology. *J. Am. Acad. Child. Adolesc. Psychiatry* **41**(5), 563-571.

McCreadie RG, R Thara, TN Srinivasan and R Padmavathi (2003) Spontaneous dyskinesia in first-degree relatives of chronically ill, never-treated people with schizophrenia. *Br. J. Psychiatry* **183**, 45-49.

Mehler C and A Warnke (2002) Structural brain abnormalities specific to childhood-onset schizophrenia identified by neuroimaging techniques. *J. Neural Transm.* **109**, 219-234.

Narabayashi H, F Yokochi and Y Nakajima (1984) Levodopa-induced dyskinesia and thalatomy. *J. Neurol. Neurosurg. Psychiatry* **47**, 831-839.

Opler LA, DM Frank and PM Ramirez (2001) Psychostimulants in the treatment of adults with psychosis and attention deficit disorder. *Ann. NY Acad. Sci.* 297-301.

Pappert EJ, GG Goetz, FG Niederman, R Raman and S Leurgans (1999) Hallucinations, sleep fragmentation, and altered dream phenomena in Parkinson's disease. *Mov. Disord.* **14**, 117-121.

Pauletto G, E Belgrado, R Marinig and P Bergonzi (2004) Sleep disorders and extrapyramidal diseases: a historical review. *Sleep Med.* **5**, 163-167.

Perry E, M Walker, J Grace and R Perry (1999) Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends Neurosci.* **22**, 273-280.

Pine DS, RG Klein, DC Lindy and RD Marshall (1994) Attention-deficit hyperactivity disorder and comorbid psychosis: a review and two clinical presentations. *J. Clin. Psychiatry* **54**, 312-313.

Riederer P and S Wuketich (1976) Time course of nigrostriatal degeneration in Parkinson´s disease. A detailed study of influential factors in human brain amine analysis. *J. Neural Transm.* **38**, 277-301.

Riederer P, KW Lange, J Kornhuber and W Danielczyk (1992) Glutamatergic-dopaminergic balance in the brain. Its importance in motor disorders and schizophrenia. *Arzneimittelforsch*. **42**, 265-268.

Rubia K, S Overmeyer, E Taylor, M Brammer, SCR Williams, A Simmons and ET Bullmore (1999) Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am. J. Psychiatry* **156**, 891-896.

Sanchez-Ramos JR, R Ortoll R and GW Paulson (1996) Visual hallucinations associated with Parkinson disease. *Arch. Neurol.* **53**(12), 1265-1268.

Schafer D and W Greulich (2000) Effects of parkinsonian medications on sleep. *J. Neurol.* **247**, 24-27.

Shafritz KM, KE Marchione, JC Gore, SE Shaywitz and BA Shaywitz (2004) The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. *Am. J. Psychiatry* **161**, 1990-1997.

Sian J, M Gerlach, MBH Youdim and P Riederer (1999) Parkinson´s disease: a major hypokinetic basal ganglia disorder. *J. Neural Transm.* **106**, 443-476.

Srinivasan TN, R Thara, R Padmavathi and RG McCreadie (2001) Relationship of extrapyramidal symptoms to age at onset and drug treatment in middle-aged and elderly schizophrenic patients. *Schizophr. Res.* .**47**, 69-75.

Steen VM, R Lovlie and T McEwan (1997) Dopamine D_3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenic patients. *Mol. Psychiatry* 2, 139-145.

Sullivan RM and WG Brake (2003) What the rodent prefrontal cortex can teach us about attention-deficit/hyperactivity disorder: the critical role of early developmental events on prefrontal function. *Behav. Brain Res.* **146**, 43-55.

Takakusaki K, K Saitoh, H Harada, T Okumura and T Sakamoto (2004) Evidence for a role of basal ganglia in the regulation of rapid eye movement sleep by electrical and chemical stimulation for the pedunculopontine tegemental nucleus and the substantia nigra pars reticulata in decerebrate rats. *Neuroscience* **124**, 207-220.

Thanvi BR, SK Munshi, N Vijaykumar and TCN Lo (2003) Neuropsychiatric non-motor aspects of Parkinson´s disease. Review. *Postgrad. Med. J.* **79**, 561-565.

The Deep-Brain Stimulation for Parkinson´s Disease Study Group (2001) Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson´s disease. *N. Engl. J. Med.* **345**, 956-963.

Thompson PM, C Vidal, JN Giedd, P Gochman, J Blumenthal, R Nicolson, AW Toga and JL Rapoport (2001) Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early onset schizophrenia. *Proc. Natl. Acad. Sci. USA* **98**, 11650-11655.

Vaidya CJ, G Austin, G Kirkorian, HW Ridlehuber, JE Desmond, GH Glover and JDE Gabrieli (1998) Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proc. Natl. Acad. Sci. USA* **95**, 14494-14499.

Volkow ND, GJ Wang, JS Fowler, J Logan, M Gerasimov, L Maynard, YS Ding, SJ Gatley, A Gifford and D Franceschi (2001) Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J. Neurosci.* **2**, U1-U5.

Wint DP, MS Okun and HH Fernandez (2004) Psychosis in Parkinson´s diesease. *Psychiatry Neurol.* **17**, 127-136.

Wonody I, HM Adami, SL Cassady, JD Sherr, MT Avila and GK Thaker (2004) Ethnicity and the course of tardive dyskinesia in outpatients presenting to the motor disorders clinic at the Maryland Psychiatric Research Center. *J. Clin. Psychopharm-acol.* **24**, 592-598.