

From THE DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

PARKINSON'S DISEASE AND DEPRESSION

- **CLINICAL AND NEUROBIOLOGICAL
STUDIES**

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To my patients,

in great respect and admiration

of your courageousness and endurance

struggling for an active life

ABSTRACT

Parkinson's disease (PD) is a progressive degenerative movement disorder. PD patients also suffer from several non-motor symptoms including autonomic disturbances, cognitive decline and neuropsychiatric conditions. In this thesis, studies were conducted to increase our knowledge on the pathophysiology and treatment of major depression (MD) in patients with PD. Clinical rating studies on the prevalence as well as neurological and psychiatric symptoms in patients with PD and MD, solely PD and solely MD were performed. The therapeutic responsiveness towards the commonly used antidepressant, citalopram, in PD + MD and MD patients was investigated. In parallel with these clinical studies, imaging studies were made and cerebrospinal fluid (CSF) collected.

These studies showed that MD in PD is not as frequent in Sweden as has been previously reported. PD patients with a comorbid MD had more severe neurological symptoms than PD patients without depression, indicating an advanced and widespread neurodegenerative process. Treatment with citalopram in PD patients with MD on stable dopaminergic therapy reduced the depressive symptoms as effective as in MD patients without PD. The antidepressive effect occurred earlier in the PD patients. The PD symptoms of hypokinesia and rigidity as well as involuntary movements were reduced during treatment with citalopram. On the other hand, tremor increased during this treatment, possibly a result of increased serotonergic neurotransmission. Imaging studies showed that regional cerebral blood flow differs between PD patients with and without MD, as well as between MD patients with and without PD, both at baseline and regarding the response to treatment with citalopram. However, treatment with citalopram "normalizes" the mood-related abnormal rCBF pattern in both "only" MD and PD + MD patients, although in different ways. Biochemical studies of CSF showed that PD patients with MD have significantly lower baseline levels of MHPG, corticosterone and IL-6 when compared to solely MD patients. Moreover, in response to citalopram treatment, patients with solely MD exhibited an expected decrease in 5-HIAA and MHPG levels which was not found in PD patients with MD. Moreover, the levels of BDNF and IL-6 were lower in PD + MD patients compared to solely MD patients after treatment with citalopram in both groups.

Taken together, these data suggest that MD in PD could be an indication of a more advanced and widespread neurodegenerative process. These data have also provided imaging and biochemical evidence that there is a different antidepressant response towards SSRI medication in PD patients with MD compared to MD patients without PD, indicating diverse underlying pathophysiological mechanisms

Keyword: Parkinson's disease. Major depressive disorder, SSRI, rCBF, CSF-biomarker.

LIST OF PUBLICATIONS

- I. **Pålhagen SE.**, Carlsson M., Curman E., Wålinder J., Granéus A-K. Depressive illness in Parkinson´s disease – indication of a more advanced and widespread neurodegenerative process? *Acta Neurol Scand*, 2008 May; 117(5):295-304.
- II. **Pålhagen SE.**, Carlsson M., Wålinder J., Granéus A-K. Treatment of major depression in Parkinson´s disease improves depressive as well as motor symptoms – indicating a more extensive neurodegenerative process? *Submitted*.
- III. **Pålhagen SE.**, Ekberg S., Wålinder J., Granéus A-K., Granéus G. HMPAO SPECT in Parkinson´s disease (PD) with major depression (MD) before and after antidepressant treatment. *J Neurol* (2009) 256:1510–1518
- IV. **Pålhagen SE.**, Qi H., Mårtensson B., Wålinder J., Granéus A-K., Svenningsson P. Monoamines, BDNF, IL-6 and corticosterone in CSF in patients with Parkinson´s disease and major depression. *Submitted*.

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LIST OF ABBREVIATIONS

CSF	Cerebrospinal fluid
BDNF	Brain derived-neurotrophic factor
COMT	Catechol-O-metyltransferase
DSM	Diagnostic and Statistical Manual of Mental Disorders
H&Y	Hoehn and Yahr scale
HAM-D-17	Hamilton Depression Rating Scale with 17 items
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamin (serotonin)
HPA	Hypothalamic-pituitary-adrenal
HVA	Homovanillic acid
IL-6	Interleukin 6
MADRS	Montgomery-Åsberg Depression Rating Scale
MD	Major depression
MHPG	3-methoxy-4-hydroxyphenylethylenglycol
MMD	Major depressive disorder
MMSE	Mini Mental State Examination
99mTc-HMPAO	Technetium-99mlabeled hexamethylpropylenamine oxid
PD	Parkinson´s disease
rCBF	regional cerebral blood flow
SPECT	Single Photon Emission Computer Tomography
SSRI	Selective Serotonin Reuptake inhibitor
UK-PDS-BB	United Kingdom Parkinson´s Disease Society Brain Bank
UPDRS	Unified Parkinson´s Disease Rating Scale

1. INTRODUCTION AND BACKGROUND

Parkinson's disease (PD) is a progressive degenerative disorder with several clinical manifestations including motor system dysfunction, autonomic disturbances, cognitive decline but also a range of neuropsychiatric expressions.

Depression is commonly associated with PD and have clinical and biochemical similarities. The clinical likenesses include akinesia, psychomotor retardation while the biochemical similarities consist of not functioning dopaminergic, noradrenergic and serotonergic systems.

A neurochemical hypothesis of major depressive disorder is generally accepted. But recent research studies suggest that dysfunctional circuits in the brain constitute the neurobiology of depression. Functional neuroimaging studies examining regional metabolic and blood flow changes in depression give support for a “modulating dysfunctional limbic-cortical circuits” in depression (Mayberg H, 2003)

PD is now recognized as more than just a motor disease and the nigrostriatal dopamine system is just one of many pathways involved.

PARKINSON'S DISEASE

As James Parkinson (1755-1824) in his famous Essay on Shaking Palsy 1817 states in the Chapter I -Definition – “Shaking Palsy. (Paralysis Agitans). Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured”. This was solely based on reports of six patients, of whom three were only “causally met on the street” or “only seen at a distance”. Even if James Parkinson did not distinguish any psychiatric or behavioural changes he noted later when he discussed more advanced disease that the patients may suffer “with slight delirium”. In 1861-62 Jean Marie Charcot (1825-1893) “founder of the modern neurology” added more symptoms (rigidity) to James Parkinson's clinical description and attached the name Parkinson's disease to the syndrome. Charcot also included mood changes

as part of the syndrome. (Charcot JM et al 1861). The knowledge of the pathology and clinical spectrum of this disease has greatly increased since then.

Pathophysiology

Friedrich Heinrich Lewy first described the inclusion bodies, which now bear his name, in the dorsal vagal nucleus and the nucleus basalis in the brains of parkinsonian patients and considered this as a pathologic hallmark of idiopathic PD (Levy FH, 1912). Konstantin Nikolaevich Tretiakoff (Tretiakoff KN, 1919) then reported loss of pigmented cells in the substantia nigra pars compacta (SNc) these came to be called 'corps de Lewy'. Arvid Carlsson (Carlsson, A 1957) demonstrated that reserpine reduced brain dopamine and reserpine induced bradykinesia in rabbits reversed with levodopa. Arvid Carlsson (Carlsson, A 1958, 1959) also observed that 80% of the dopamine in the brain was localised in the basal ganglia and suggests the relation between loss of dopamine and PD. The dopamine-depletion theory was then confirmed by several post-mortem studies of PD patients (Hornykiewicz O, 2006). The degeneration of dopaminergic neurons in the midbrain plays a key role in the pathology of PD although cell loss is found to exist also in the locus coeruleus, dorsal nuclei of the vagus, raphe nucleus, and nucleus basalis of Meynert and ventro tegmental area (Damier P, 1999).

The distinct sites of neurodegeneration and neurochemical pathways involved in PD is schematic drawn in Fig 1 (Lang AE, 1998) where the most important changes in the *dopaminergic* pathways is in the SNc which is the origin of the nigrostriatal tract to the caudate nucleus and putamen and also in the ventral tegmental area (VTA) which projects dopaminergic connections to the entorhinal cortex, olfactory tubercle, cingulate gyrus and frontal cortex. The *noradrenergic* connections start in locus coeruleus and have widespread connections upstreams to cerebellum, central gray matter of the midbrain, amygdala, substantia innominata, thalamus, limbic cortex and neocortex and downstreams to the spinal cord. *Serotonergic* pathways project from raphe nuclei to cerebellum, substantia nigra, amygdala, striatum and cortex, also descending fibres to spinal cord. The *cholinergic* inputs come from the basal nucleus of Meynert substantia innominata and go to prefrontal cortex, basal forebrain, thalamus, hypothalamus, amygdala and hippocampus.

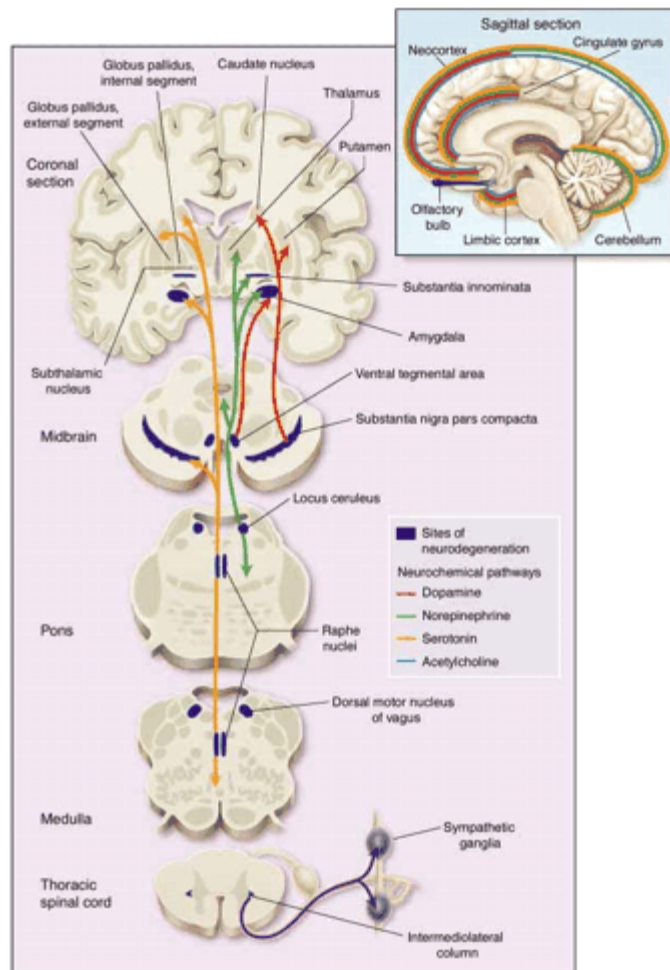


Fig 1.
 Sites of neurodegeneration and neurochemical pathways involved in PD
 (Lang AE, 1998) (Reprint with kind permission of N Engl J Med)

Simple classification of PD as strict a basal ganglia disease is no longer satisfactory but the role of the circuit anatomy of the basal ganglia in the pathophysiology of Parkinsonism is essential. The knowledge of the dopaminergic nigrostriatal system is still evolving. The basal ganglia-thalamocortical pathways have a parallel functional arrangement in brain motor control circuits. The Basal ganglia consists of four principal nuclei: 1) Striatum. 2) globus pallidus (or pallidum) .3) substantia nigra (pars reticulata and pars compacta) and 4) subthalamic nucleus (Fig 1). Striatum which is the major recipient of inputs to the basal ganglia from cerebral cortex, thalamus and brain stem, consisting of putamen, nucleus caudatus and nucleus accumbens

All these structures operate in anatomically and functionally segregated loops in a parallel fashion with a number of somatotopic channels which connect specific thalamic and cortical areas, (Alexander G, 1990, 1994) through distinct parts of the basal ganglia.

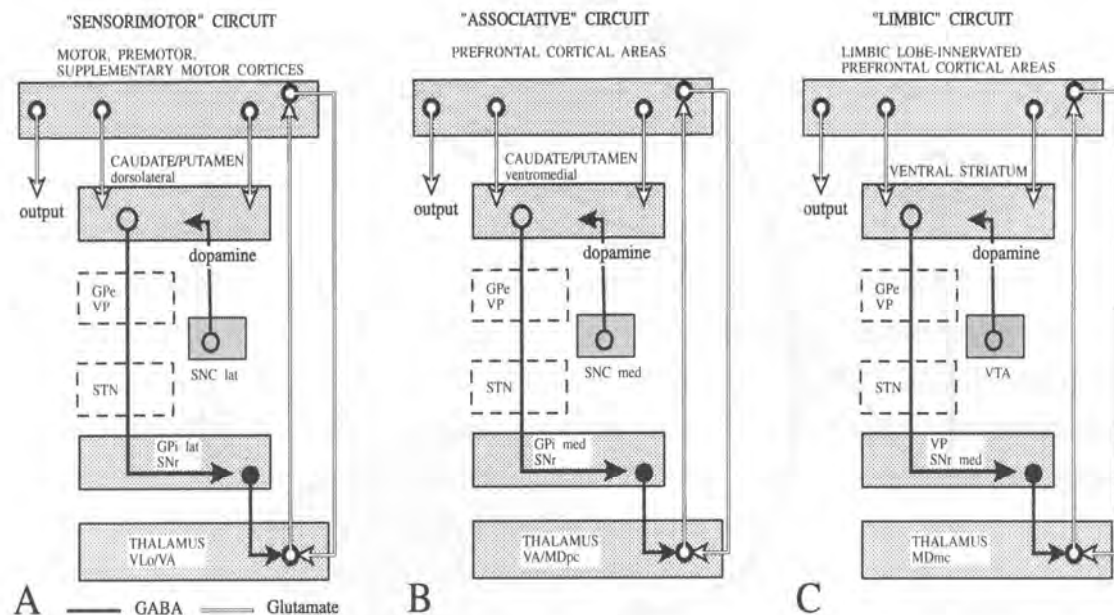


Fig 2.

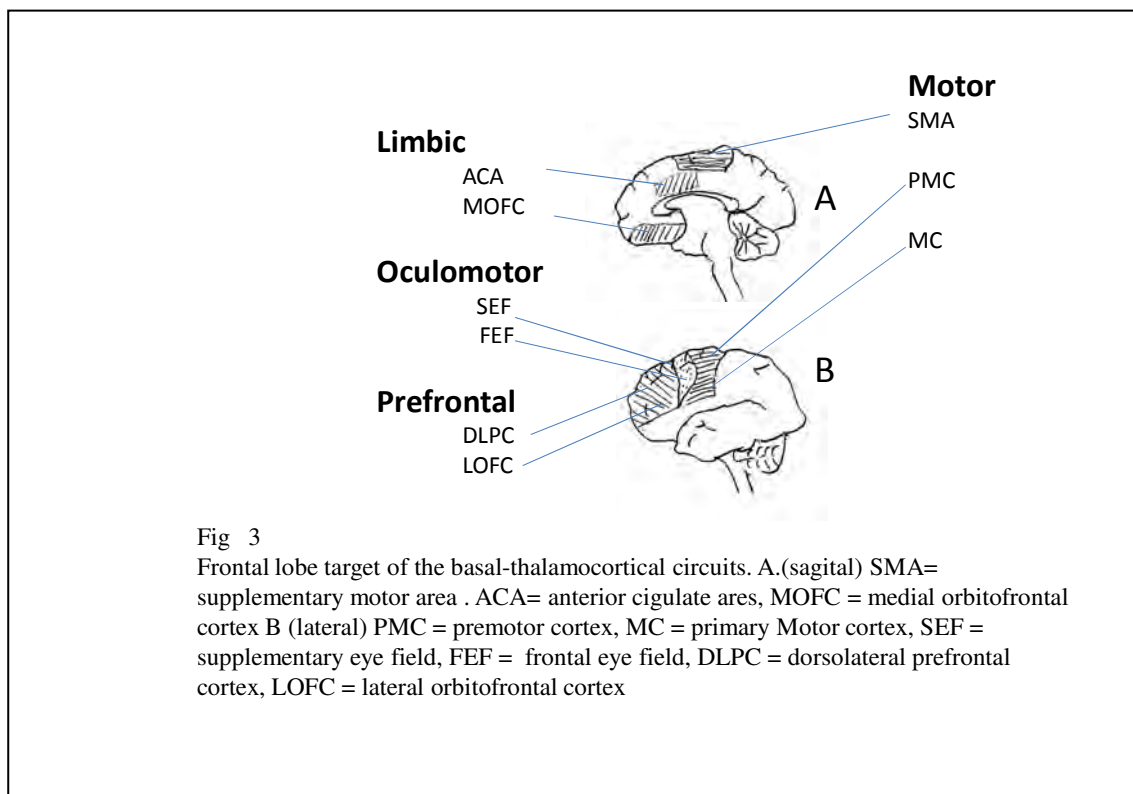
Schematic representation of the three main basal ganglia-thalamocortical circuits.

(Groenewegen HJ 1993. Reprint with kind permission from Eds.) For abbreviations see text.

The drawings shown in Fig 2 propose that these three basal ganglia-thalamocortical circuits involve different parts of the striatum, the pallidum and the substantia nigra via different ventral and medial thalamic nuclei. In this scheme also the input structures are striatum and output structure GPi (globus pallidum internus) and SNr (reticular part of the substantia nigra) are indicated by a single arrow –Fig 4 for more details.

This functional organization of the basal ganglia with key brain regions contributes to a range of behaviours besides voluntary movement, such as skeletomotor, oculomotor, cognitive and emotional functions. Fig 3 points out the frontal lobe targets of the basal ganglia-thalamocortical circuits which match prefrontal areas by *mesocortical* pathways as dorsolateral prefrontal cortex (DLPFC) which have a role in cognitive functioning and lateral orbitofrontal cortex (LOFC) as well as ventromedial prefrontal cortex (VMFC) are

involved in emotional processing. The *mesolimbic* projections to anterior cingulate cortex are involved both in selective attention and emotional regulation.



The utmost important and also best understood anatomically and physiologically circuit are the “motor circuit” which mainly are responsible for the cardinal features of PD, hypokinesia, rigidity, resting tremor and gait abnormalities (Albin RI, 1989, DeLong MR, 1990 and 2007) .The two output nuclei of the basal ganglia, GPi and SNr tonically inhibit their target nuclei in the thalamus and brainstem (fig 4) .

The connections between input and output structures are organized in two main pathways; both are projections of medium-size spiny striatal neurons and have GABA as a transmitter. But the ‘*direct*’ pathway contains the tachykinin neuropeptides substance P and projects to GPi and/or SNr and expresses predominantly dopamine D1 receptors. The ‘*indirect*’ pathway expresses mainly D2 receptors and contains the opoid peptide enkephalin and reaches first GPe and then STN by GABAergic projections, but from STN to GPi/ SNr it is by a glutaminergic projection.

Normal function of basal ganglia is necessary for the regulation of the neuronal excitability within each link. This is established by a complex organization of striatum where

every part is controlled by several pre- and postsynaptic systems including interneuron (Obeso J, 2008). Under regular circumstances there is a balance between the inhibition by the direct route and the excitation by the indirect route. This balance results in a tonic inhibition of the thalamic ventralis anterior and lateralis nuclei. (Fig 4 A).

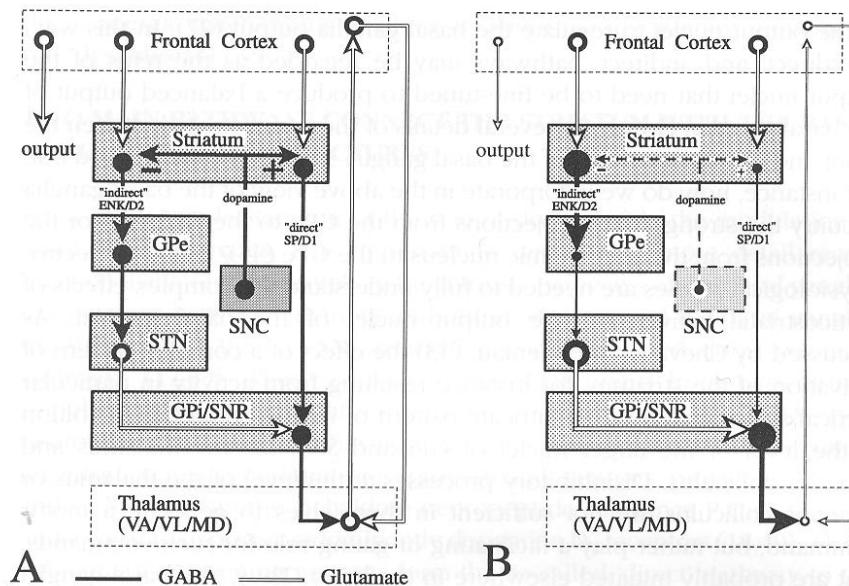


Fig 4.

Schematic representation of the main connection of the “sensorimotor” pathways within a model of basal ganglia-thalamocortical circuit. A. Normal status with the two output routes (‘indirect’ and ‘direct’ in balance’ at the level of the output structure. B. Presumed disturbances in Parkinson’s disease: depletion of dopamine in the striatum leads to dysbalance in the two output routes and a suppression of the thalamocortical activity. (Groenewegen HJ 1993. Reprint with kind permission from Eds.)

In Parkinson’s disease, (Fig 4 B) with dopamine depletion, the internal balance is disturbed which results in an increased inhibition of thalamocortical and brainstem motor nuclei. The higher activity in of GPi and SNr neuron is supposed to be result of reduced inhibitory activity in the ‘direct’ circuit and a higher activity in the ‘indirect’ circuit which results primarily in a higher neuronal firing on the STN and GPi /SNr. This concept was mainly first based on experimental studies in animals, MPTP monkeys (Bergman H. 1990, Azis TZ. 1991). Now a number of studies on PD patients demonstrated that blockade or lesion of the STN or GPi gives a marked clinical improvement of the motor symptoms (Rodriguez-Oroz MC 2005).

In recent years a lot of studies have focused on the pathological synchronization in PD and proposed models on cellular and network basis for the oscillations in the basal

ganglia (Hammond C.2007, Timmerman L. 2002). Excessive synchrony at low beta frequencies in basal ganglia-cortical circuits is supposed to impair motor processing in PD (Weinberger M 2006). There are conflicting results in experimental animals in comparison to clinical studies with PD patients (Rivlin-Etzion M, 2006, Silberstein P 2005). The mesostriatal dopamine denervation results in defects in cortico-striatal plasticity (Calabresi P. 2007) which also has impact on non-motor symptoms as cognitive impairment due to unbalanced DA/Ach interactions (Calabresi P. 2006) or sleep disturbances (Rye DB, 2004) and Restless legs (Cervenka S. 2006) due to altered dopaminergic activity in subthalamic and thalamic neurons. In a recent review (Wickens JR,2009) focus on dopamine dependent synaptic plasticity in the basal ganglia in terms of spike-timing dependent plasticity phenomena in terms of long-term depression (LTD) and long-term potentiation (LTP) but it still remains to understand the molecular and cellular mechanism behind.

Heikko Braak and colleagues (Braak H. 2000, 2003, 2006) have proposed stages in the development of Parkinson's disease related pathology and propose that the pathological process, accumulation of alpha-synuclein accumulation is not random but spreads along axonal pathways in a constant pattern. It starts outside CNS in the gastric autonomic plexus of Meissner and in the dorsal nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus. The degeneration progress in an ascending way through brainstem to cortical areas, beginning with the anteriomedial temporal mesocortex and then neocortex with prefrontal areas. There are very early conformation of presymptomatic evidence of Lewy bodies, the condition was named incidental Lewy body pathology and might be an early phase of PD. (Dickson DW, 2008).

The proposal from Braak et al has met great attention and its value has been confirmed, even though at least 15 % of patients with PD do not fulfill the pattern (Kalaitzakis ME, 2008). A reconsidered model for cortico-basal ganglia-cortical circuitry in PD is now published (Braak H. 2008) based on a neuropathological staging with the spatio-temporal distribution of PD-related inclusions. This model now also incorporates and emphasized key non-dopaminergic connections in the lower brainstem as pedunculopontine tegmental nucleus (with cholinergic, glutamatergic and GABAergic cells and main component of the reticular activating system), lower raphe nuclei (serotonergic-) and the coeruleus complex (noradrenergic activity).

J.W. Langston some years ago (Langston JW, 2006) argued that Parkinsonism could “Just be the Tip of the Iceberg” and he reminded us that the neuronal degeneration and Lewy body and neuritic pathology is widespread in the central and peripheral nervous systems. Parkinsonism/Substantia nigra degeneration is the tip of the iceberg and under water level is pons, basal forbrain, medulla, amygdala, hypothalamus and olfactory bulb but also so spinal cord (intermediolateral column), peripheral autonomic nervous system (heart, intestinal track, bladder), olfactory cortex, temporal cortex as well as neocortex. Langston suggests the name ‘*Parkinson’s Complex*’ when referring to the entire constellation of signs and symptoms.

MAJOR DEPRESSIVE DISORDER

Current diagnostic framework.

(Table 1 and appendix 4)

Depression is a complex and heterogeneous condition. It comprises a transient mood state as well as a clinical disorder or a syndrome. The terminology and diagnostic criteria used for this diverse group has changed over the years. World Health Organization WHO has since 1948 produced the International Classification of Diseases, Injuries and Causes of Death, ICD and now achieved the edition ICD-10 Classification of Mental and Behavioural Disorders (WHO 1992) including a comprehensive manual of the Mental and Behavioral Disorders; Clinical Descriptions and Diagnostic guidelines).

Over 50yrs ago, a US diagnostic approach was made by development of the Diagnostic and Statistical Manual of Mental Disorders, first edition (DSM –I) was published by American Psychiatric Association (APA 1952). Next edition DSM-II removed the concept of reactive conditions and proposed instead multiple diagnoses. In edition DSM-III (1980) with a major revision of the nomenclature more descriptive without regard to etiology. In DSM-III the APA for descriptions as clinical depression, major depression, unipolar depression or unipolar disorder proposed the term “*Major depressive disorder*” and describes “a mental disorder characterized by an all-encompassing low mood accompanied by low self- esteem, and loss of interest or pleasure in normally enjoyable activities”.

Table 1. Diagnostic criteria for depressive disorder

DSM IV	ICD-10 Depressive disorder
<i>Most of day, nearly every day for at least 2 weeks</i>	<i>A duration of at least 2 weeks is usually required for diagnosis for depressive episodes of all three grades of severity</i>
<i>Major depressive disorder</i>	<i>Depressive episode F</i>
<p><i>Five or more of following symptoms: At least one symptom is either depressed mood or loss of interest or pleasure:</i></p> <ol style="list-style-type: none"> <i>1. Depressed mood</i> <i>2. Loss of interest</i> <i>3. Significant weight loss or gain or decrease or increase of appetite</i> <i>4. Insomnia or hypersomnia</i> <i>5. Psychomotor agitation or retardation</i> <i>6. Fatigue or loss of energy</i> <i>7. Feelings of worthlessness or excessive or inappropriate guilt</i> <i>8. Diminished ability to think or concentrate, or indecisiveness</i> <i>9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or suicide attempt or a specific plan</i> 	<p><i>At least five of following symptoms: Main/Typical symptom:</i></p> <ol style="list-style-type: none"> <i>i. Depressed mood,</i> <i>ii. Loss of interest and enjoyment,</i> <i>iii. Reduced energy leading to increased fatigability</i> <i>v. Diminished activity in typical depressive episodes</i> <p><i>Additive/Other symptoms</i></p> <ol style="list-style-type: none"> <i>1. Reduced concentration</i> <i>2. Reduced self-esteem and self-confidence</i> <i>3. Ideas of guilt and unworthiness</i> <i>4. Bleak and pessimistic views of the future</i> <i>5. Ideas or acts of self-harm or suicide</i> <i>6. Disturbed sleep</i> <i>7. Diminished appetite</i> <p><i>Depression with somatic syndrome:</i></p> <ol style="list-style-type: none"> <i>1. Loss of interest or pleasure in activities that are normally enjoyable</i> <i>2. Lack of emotional reactivity to normally pleasurable surroundings and events</i> <i>3. Waking in the morning 2h or more before the usual time</i> <i>4. Depression worse in the morning</i> <i>5. Objective evidence of definite psychomotor retardation or agitation</i> <i>6. Marked loss of appetite</i> <i>7. Weight loss</i> <i>8. Marked loss of libido</i> <p><i>For mild depressive episode: Two of most typical symptoms of depression and two of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: with somatic symptoms.</i></p> <p><i>For moderate depressive episode: two of three of most typical symptoms of depression and at least three of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: with somatic symptoms.</i></p> <p><i>For severe depressive episode: All of the typical symptoms are present and at least four of the other symptoms of severe intensity are required. If four or more of the somatic symptoms are present, the episode is diagnosed: with somatic symptoms</i></p>

The general term depression is not preferred in clinical and research use because it often include other types of psychological depressive response. The diagnosis of major depressive disorder is based on patient's self-reported experience, revealed behavior and a mental status examination.

Other changes in DSM-III was incorporation of a multi-axial system for evaluation of other domains. Axis I disorders include major mental disorders as depression, anxiety disorders, bipolar disorders and Axis II underlying personality disorder. Relevant medical conditions and physical disorder have to be registered by Axis III. There were place for assessments of contributing psychosocial and environmental factors to the disorder in Axis IV. Global Assessment of functioning has to be coded in Axis V. This represents different principles used for depressive disorders than used in ICD-9 which now also incorporated a glossary which served as reference frame for clinicians.

DSM IV (APA 1994) is generally used in US but also depending on its specific operationalized criteria for diagnosis now used worldwide for research purpose. ICD-10 is used in generally in European countries.

Neurobiological mechanisms in major depressive disorder

The role of monoamines. (Fig 5)

The breakthrough in 1950s with discovery of antidepressant treatments strengthened the evidence of biochemical abnormality behind depressive disorders. A substance, Iproniazid, already in 1951 given for tuberculosis, also induced euphoria then regarded as a negative side effect. But after some years the mood stimulating effect was recognized and the drug was established as the first effective antidepressant drug. The mechanism behind was found to be an irreversible inhibition of the enzyme MAO, which leads to a secondary increase of transmitter in the noradrenergic neurons (Fillenz, M, 1981). 1958 an agent, imipramine, was discovered by chance to have antidepressive effect. Later it was found (Hertting et al 1961) that imipramine blocked the neuronal reuptake of noradrenaline from the synapse which prolonged the actions of released transmitter. Conclusion (Schildkraut JJ, 1965) was that depression was an effect of functional deficit of noradrenergic transmission in the brain.

Today's antidepressant drugs are still designed to increase monoamine transmission by inhibition of neuronal uptake; an excellent example is the selective serotonin reuptake inhibitor (SSRI); Fluoxetine (Fuller RW 1974), now prescribed worldwide (Fuller RW 1995)

was first investigated for an analgesic effect (Messing RB 1975); Zimelidine was available from Astra Sweden in the early 1980s (Carlsson A, 1999) but the drug was withdrawn already 1983 because of associated risk for Guillain-Barré syndrome. Other examples are selective noradrenaline reuptake inhibitors (SNRI) as reboxetine (Dencker SJ, 2000) and bupropion (Dhillon S, 2008) the latter a combination of specific dopamine and noradrenaline reuptake inhibition. Antidepressant effect could also be achieved by inhibition of degradation (monoamine oxidase inhibitor, (MAO-A) (Da Prada M, 1989).

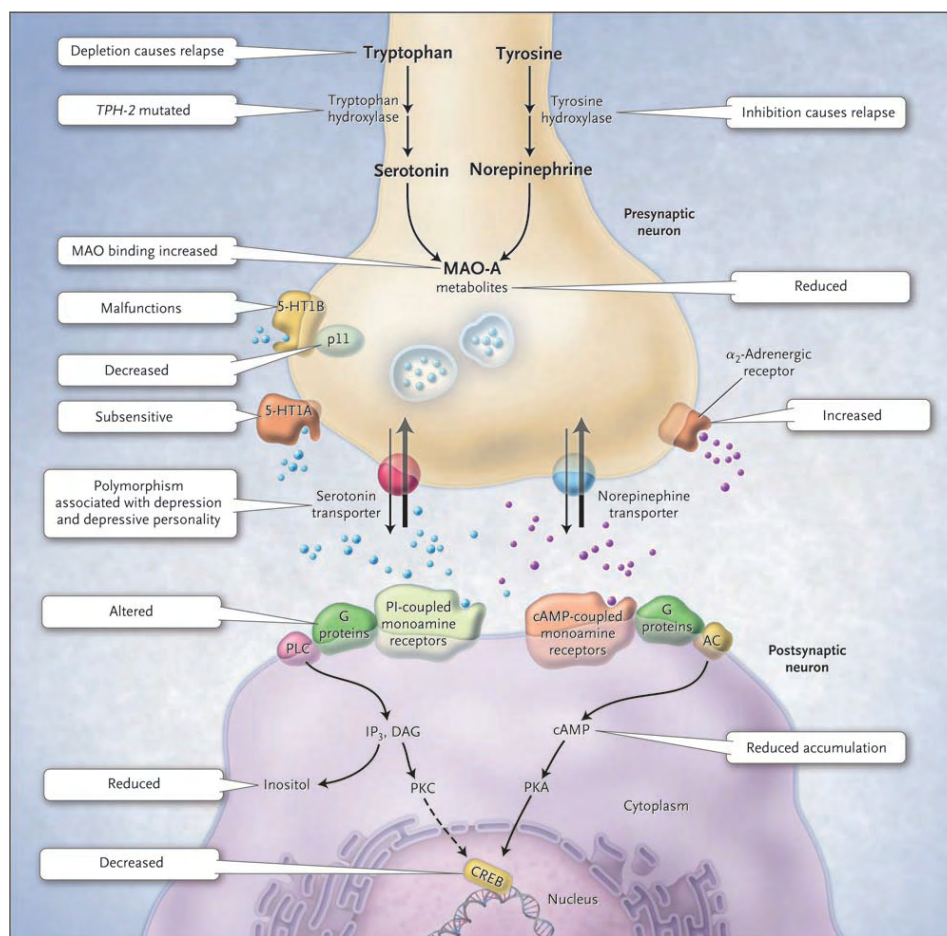


Fig 5.
The Monoamine-Deficiency Hypothesis. See text.
(Belmarker RH and Agam G, 2008.
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There are numerous direct and indirect evidences associated with the monoaminergic neurotransmitter systems in major depressive disorder:

a) Serotonergic system.

- i. Reduced CSF 5-HIAA (Jonkinen J,2007)
- ii. Reduced 5HT_{1A}receptor binding in living brain (Savitz J, 2009)
- iii. Antidepressant efficacy of agents which increase intra synaptic 5-HT (Maes M,1995).

b) Noradrenergic system

- i. Reduced CSF and urinary MHPG (Sheline Y,1997)
- ii. Elevated plasma NE (Veith ,1994, Carney RM, 1999)
- iii. Antidepressant effect of drugs whose effect will increase NE (Schatsberg AF,1995)

c) Dopaminergic

- i. Reduced CSF HVA (Engström G 1999)
- ii. Antidepressant effect of drugs whose effect will increase DA. (Willner P,1995)

All these mono-amine based drugs are powerful antidepressants. But they require in many cases weeks of treatment before effect although the drugs immediately amplify the monoamine transmission. Experimental serotonin manipulation in healthy controls with ingestion of tryptophan-deficit amino acid mixture, which transiently decreases serotonin levels in the brain, results in no alteration of the mood (Ruhe HG, 2007). Individuals with a personal or family history of major depressive disorder experienced under the same circumstances a notable relapse of their depressive symptoms. It means that the vulnerability, at least of the serotonin system, is depending on several possible factors as genes or impact of stress or a combination (Jans, LAW,2006).

Genes

In a review and metaanalysis (Sullivan PF,2000) comparing concordance rates for major depression between monozygotic and dizygotic twins a heritability of about 37% were found which is much lower than for bipolar disorder or schizophrenia. But there are risk factors as early onset, severe and recurrent depression with higher penetrance for relatives (Kendler KS, 1999). No specific gene(s) are convincingly identified as a risk factor. The serotonin transporter

gene contains a polymorphism (short and long alleles) in the serotonin- transporter –linked polymorphic region (5-HTTLRP). The short allele causes reduced synthesis of the serotonin transporter (Lesch KP, 1996). If this has a direct relation to depression is unclear. Individuals with this short variant have greater probability to have depressive symptomatology after tryptophan depletion (Neumeister A.2002).

Stress and the Hypothalamic-Pituitary-Adrenal (HPA) Axis (Fig 6)

Is stress per se a “depressogenic” factor? This question is of considerable importance both clinically and scientifically. Stress is often precipitating depression (Kendler KS, 2006). A large prospective epidemiologic study found interestingly that 5-HTTLPR only predicted depression in association with defined life stress (Caspi A, 2003). Studies support that psychosocial misfortune in childhood can alter the reactivity of the HPA-axis by modifications in genes by epigenetic changes (Tsankova N,2007). The epigenetic process is extremely long lasting and may be a part of the explanation for the extensive disturbances later in the neuroendocrine system (Wong ML, 2000).

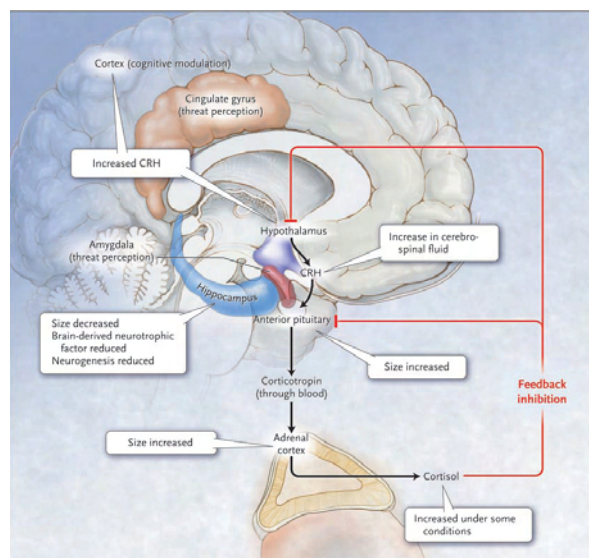


Fig 6

The Hypothalamic-Pituitary-Cortisol System in Depression

For details see text.

(Belmarker RH and Agam G, 2008.

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A *dysfunctional HPA-axis* is postulated to have a role in the pathophysiology of depression through abnormalities in the cortisol response to stress. (Parker KJ, 2003). The response to stress gives hypercortisolemia and a resistance to feedback inhibition (Raison CL, 2003). This leads to a stimulating local synthesis and release of cortico-tropin-releasing factor (CRF) into the brain including the frontal and the limbic regions (Merali Z, 2004, Makino S, 2002) and a measureable increase in CSF (Merali Z, 2004). Hippocampal size is reduced (the subgranular zone (SGZ) probably as an indirect effect of excess glucocorticoids. This atrophy reflects a diminished neurogenesis due to reduced brain-derived neurotrophic factor as a consequence of elevated levels of glucocorticoids. This volumetric reduction in hippocampus and other parts of the forebrain (subgenual prefrontal cortex, dorsolateral prefrontal cortex) found in depressed patients (MacQueen GM, 2003, Rajkowska G, 2000) together with published animal studies, which found that stress reduce brain-derived neurotrophic factor (BDNF)-mediated signaling in hippocampus (Nestler EJ, 2002), has supported a popular hypothesis for depression, '*BDNF hypothesis*'. Postmortem studies of patients with depression who have committed suicide have shown reduction of BDNF in the hippocampus (Karege F, 2005). Results from chronic treatment with antidepressants in animal models give support for an increased BDNF-signaling. (Nestler EJ, 2002). But in recent medical literature this BDNF-hypothesis is considered as an oversimplification.

Neural Circuitry of depression

The phenomenology of depression started with a concept of empirical observations and currently the most used nosological classifications are DSM-IV or ICD-10. Aggregation of symptoms could give some information of clinical course but make no definite reference to etiology or pathophysiology.

Depression is for sure a complex and heterogeneous disorder. It is unlikely result of a disease in a single neurotransmitter system or a specific brain region. Neuroscience has during the last 25 yrs significant expanded the knowledge of the pathophysiology of depression. Immense efforts are produced to define neurobiological mechanisms, predisposing genetic factors which in combination with certain environmental factors influences mood disorders. Several studies have also associated depression with cerebral structures in a functional way. In vivo neuroimaging has shown dysfunction in specific neuronal networks in patients with

depressive disorders. Organization within these integrated pathways as well as their ability to perform adaptive plasticity is crucial.

Helen S Mayberg published 1997, (Mayberg, 1997a) a model of depression as a consequence of limbic-cortical dysregulation and based on in vivo structural and functional imaging techniques of patients with depressive disorder. The proposed working model is a multi component model. Depressive illness are associated with downregulation of dorsal limbic (anterior and posterior cingulated) but also neocortical regions as prefrontal, premotor, parietal cortex and relatively increases in ventral paralimbic area (subgenual cingulated, anterior insula, hypothalamus caudate). Remission shows normalization of hypofunctioning cortical sites and concurrent inhibition of overactive paralimbic regions. The research group also published identified biomarkers which might improve diagnostic accuracy and treatment effect (Mayberg HS, 1997 b, Mayberg HS 2003) (Fig 7).

Other research groups have in parallel studies published the same results where they elegantly shown by imaging the functional abnormalities in limbic and prefrontal cortical structures in major depression (Drevets WC, 1997, 2000 and 2008).

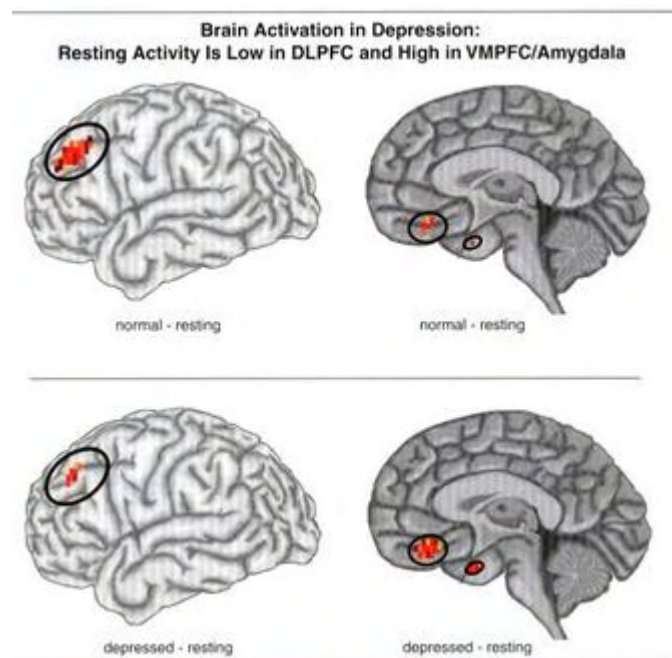


Fig 7.

Neuroimaging of brain activation in depression.

See above text.

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MAJOR DEPRESSION / MAJOR DEPRESSIVE DISORDER IN PARKINSON'S DISEASE

Non-motor symptoms of Parkinson's disease

Non-motor symptoms (NMS) were already described by James Parkinson in his famous *Essay on Shaking Palsy 1817* “the expulsion of the feces from the rectum sometimes requiring mechanical aid” and “the bowels, which had all long been torpid, now in most cases, demand stimulating medications of considerable power”.

Constipation is a common symptom in PD it will often be recognized as a consequence to lack of activity or dehydration. In fact, however, it could be a consequence of the underlying pathology of PD. Lewy bodies has been found in the myenteric plexus of colon (Kupsky WJ 1987).

The knowledge of underlying neuropathology for the NMS in PD is increasing and both the central and peripheral nervous systems are involved (Braak H. 2003, 2008, Langston JW 2006). For more details see 1.1

NMS in PD include: 1) *Neuropsychiatric* symptom; as depression, apathy, anhedonia, anxiety, dementia, impulse control disorder, hallucinations. 2) *Sleep dysfunction*: disorders of sleep initiation and maintenance, parasomnias, excessive day time sleepiness. 3) *Autonomic system dysfunction*: bladder, orthostatic dysfunction, hyperhidrosis, sexual dysfunction. 4) *Gastrointestinal symptoms*: constipation, hypersalivation, dysphagia. 5) *Sensory symptoms*: pain, olfactory dysfunction, visual symptoms 6) Other symptoms as fatigue, weight loss.

Studies regarding health related quality of life (HRQOL) (Kuopio AM. 2000, Schrag A. 2000) illustrate that non-motor manifestations in PD significantly impair QOL and often are depression the major factor. It is now established that NMS occur in over 85% of the PD patients (Shulman LM 2001).

It is essential to recognize NMS for adequate treatment and comprehensive care. In order to facilitate this, a multidisciplinary group developed an NMS screening questionnaire with 30 items (Chaudhuri KR, 2006) which provide as the authors said “not an overall score of disability, and is not a graded or rating instrument. Instead, it is a screening tool designed to draw attention to the presence of NMS and initiate further investigation”. A PD NMS Questionnaire (NMSQuest) and a Non-Motor Symptom assessment scale for Parkinson's

disease (NMSS) are available for use in the clinic (Chaudhuri KR, 2008). The NMSS has recently been used as a valuable instrument to show that continuous dopaminergic stimulation by intrajejunal levodopa infusion in PD is beneficial for NMS (Hoening H, 2009).

Major depression in Parkinson's disease

Prevalence and Diagnose

Reported incidence and prevalence rates vary widely due to inconsistent methodology of the definitions, assessments instrument and the study population. In a review (Slaughter JR, 2001) of all published studies 1922-1998 found in 45 studies an average prevalence rate for depression of 31% but only a few, 10 studies, used DSM criteria. Recent systematic review of prevalence studies on depression in PD (Reijnders J, 2008) from 1990 to 2006 found when accepted quality criteria was applied in the remaining 36 articles of from the beginning 104 articles, a weighted *prevalence of major depressive disorder of 17%*. The quality assessment criteria (Aarsland D, 2005), which were applied in the article, scored type of case identification, diagnostic criteria for PD and even diagnostic criteria for depression as if use of structured interview to establish a diagnose by DSM or ICD, or if only used cut-off score on a depression rating scale. Maximum quality score are 9 and all included studies have a mean of 5.1.

In earlier studies different assessment tools were used, study design and patient criteria varies, and most studies do not discriminate between major depression, minor depression and dysthymia. Therefore a NIH-sponsored workshop set up to reduce this bias recommended changes in the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for PD. It recommended an *inclusive approach to symptom assessment*, i.e. that all symptoms are taken into account, regardless of their overlap with PD or other medical conditions, as well as the inclusion of subsyndromal depression in clinical studies and specification of timing of assessments for PD patients with motor fluctuations (Marsh L, 2006).

Depression in PD is doubtless underdiagnosed. In a study (Shulman LM, 2002) to test diagnostic accuracy of depression in PD, the treating neurologist found a prevalence of 21% but a standardized test showed 44% which give a diagnostic accuracy of 35%, in the same study

the figures for anxiety was 41% and fatigue 25%. It is therefore easy to conclude that depression in PD also is undertreated (Weintraub D, 2003).

Symptomatology of depression in PD

Much of the difficulty to diagnose the two disorders, PD and MMD correctly is the dilemma with overlapping symptoms. General symptoms as sleep disturbances, difficulties concentrating and fatigue occur in both. Depressive symptomatology of mood disorders associated with PD generally resembles those of non-PD as major depression (Pålhagen SE, 2008, Merschdorf U, 2003).

Risk factors for depression in PD are early-onset PD, advanced PD, female gender, cognitive impairment. A recent validation study of depressive syndromes in PD (Starkstein S, 2008) give strong support for association of MD with more advanced PD. This study also confirm earlier findings that PD patients with depression tend to experience less guilt and self blame and suicidal acts but greater rates of anxiety, dysphoria, irritability and suicidal ideation without suicidal behavior.

Etiology - Is depression a risk factor of neurologic disease?

Recent published study about the spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease (Aarsland D, 2009) shows convincingly that early drug naive young PD patient have a characteristic pattern where depression, anxiety, sleep disturbances and apathy were the most common. 25% of the patients had at least clinically significant one of these symptoms and 13% had two. Although the neuropsychiatric symptoms expand with more advanced disease, it is notable that this occurs at this early stage when the motor symptoms usually are mild. Both depression and anxiety can develop before the onset of PD has been shown in several register studies (Nilsson, FM 2001. Schuurman AG, 2001. Leentjens AFG 2003) powerfully support than the brain changes which occur very early in a subtype? of patients results in neuropsychiatric symptoms seen in advanced disease.

From the classic theory – the Monoamine hypothesis – towards a neurocircuitry model of depression in PD.

The parallel dysfunction in PD not only affect the dopaminergic neurons but also the serotonergic, the noradrenergic and the acetylcholinergic (Lang A, 1998. Jellinger KA, 1999) as described earlier. Especially interesting for origin of mood disturbances in PD is the dysfunction in the limbic circuits by dopaminergic as well as noradrenergic neurons (Remy, 2005).

Reduced noradrenergic activity is associated with anhedonia, reduced motivation, reduced emotional memory, loss of energy, and loss of libido – a good picture of the depressive symptomatology in PD. Reduced serotonergic activity is associated with anxiety and panic, reduced impulse control, reduced aggression regulation, sleep disturbances, reduced appetite, and loss of libido.

In mood disorders, many different mechanisms interact. A concept of neurocircuitry models underlying depression has been proposed, involving the prefrontal cortex, amygdala and related parts of the striatum, pallidum and medial thalamus.(Maybeg HS, 1997 a). In PD, major depression could be the result of a more advanced, widespread degenerative disease – a dysfunction between reduced catecholaminergic (dopamine and norepinephrine) and serotonergic systems. (Go to section 1.3.4 for more details)

Therapeutic approaches

Treatment with levodopa improves most cognitive and behavioural functions in the ON state, but it does not remedy all depressive symptoms, and concomitant anti-depressive treatment is indicated.

Many open-label studies show positive effects of tricyclic antidepressants and SSRIs, but very few randomised clinical trials. Furthermore, some studies have shown negative results, primarily owing to high placebo response. However, two recently published randomised, placebo-controlled studies have compared the effects of an SSRI and a tricyclic anti-depressant.

The largest placebo-controlled trial up to date in PD with MD (Menza M, 2009) compared the effects of paroxetine CR (SSRI), nortriptyline(tricyclic antidepressant and placebo in 52 patients – Primary outcomes were change in the Hamilton Depression Rating Scale (HAM-D) and number of responders at 8 weeks. The results showed that nortriptyline was superior to placebo for the change in HAM-D already at 2 weeks and the effect remains at week 8, while paroxetine CR was not superior to placebo at any point.

The short-term efficacy of citalopram, desipramine and placebo were compared in 48 patients measured with the Montgomery Asberg Depression Rating Scale (MADRS) score. (Devos A, 2008) After 14 days, desipramine showed an improvement compared with citalopram and placebo. Both treatments produced significant improvements after 30 days. The

authors concluded that desipramine's more intense short-term effect was outweighed by its lower tolerability

Dopamine agonists seem to have a positive effect on depressive symptoms in some PD patients, but published studies on their effects on PD depression are lacking. According to a recently published meta-analysis, pramipexole had a beneficial effect on mood and motivational symptoms in PD patients without a major depressive disorder (Leentjens AFG, 2009). The clinical value of pramipexole in the treatment of depressive and apathetic syndromes requires, however, further investigation

“DSM-IV Malfunctioning Brain Circuits” - How to Match?

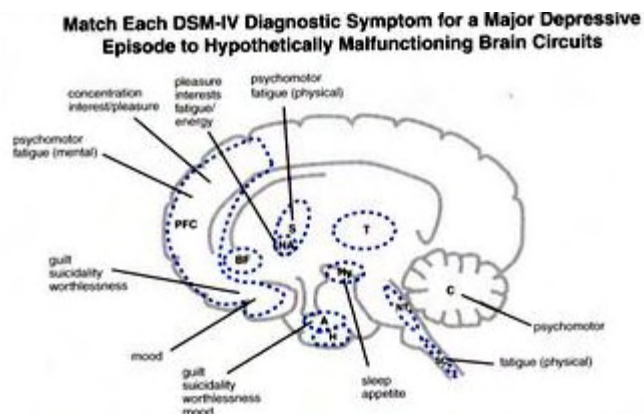


Fig 8.

Matching depression symptoms to circuits.

Alterations in neuronal activity and in efficiency of information processing within each of the eleven brain regions shown here can lead to symptoms of a major depressive episode.

Functionality in each region in each region is hypothetically associated with a different constellation of symptoms.

PFC=prefrontal cortex, BF=basal forebrain, S=striatum, NA= nucleus accumbens. T=thalamus, HY=hypothalamus, A= amygdala, H=hippocampus, NT=brainstem neurotransmitter centers, SC=spinal cord, C=cerebellum.

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Stephen M Stahl (Stahl SM, 2008) who has extensive experience of teaching psychopharmacology - argues in his latest textbook from a theoretical point of view and then of course oversimplify, to start “mapping” onto each brain region the specific symptoms. For a DSM-IV diagnose of a major depressive episode numerous symptoms are required and also a

variety of neuronal circuits which act by different monoaminergic transmitter system. Each of the nine symptoms (see appendix 4) is "mapped" in Fig 8, to specific regions where also sets of monoamines are active. Targeting these pathways would give an appropriate base for further information how to reduce or eliminate the mood disorder.

For example depressive episode is shown to be disorganized processing in amygdala and prefrontal cortex known as ventromedial prefrontal areas (VMPFC) (Mayberg HS, 2003. Drevets WC, 2000). Each of the three monoamine neurotransmitters innervates these areas. See Fig I- III in Appendix 7.

The presented "technique" or "approach" is a method of *deconstructing syndromes* into localizations in brain and/or matching to presumptive circuits. Then for treatment you may use a symptom-based selection for antidepressants. In some patients serotonergic action alone by SSRI is not enough then a SNRI with its norepinephrine effect could be used.

Interestingly, as earlier mentioned and stressed again, a report from the NINDS/NIMH group with Jeffery Cummings as chair (Marsch L, 2006) pointed out and recommended an *inclusive model* for depression in PD i.e. considers all symptoms as related to depression, regardless of their overlap with PD or other medical conditions and inclusion of *subsyndromal depression* in clinical research studies of depression of PD. This is towards and compatible with a broadened neurocircuitry model of major depressive disorder.

Pathways/projections of the major monoaminergic, Dopamine, Serotonergic, Norepinephrine and Acetylcholine (appendix7).

2. GENERAL AIMS

To gain further knowledge on the pathophysiology and treatment of depression in patients with Parkinson's disease the following studies were conducted.

1. To determine the prevalence and clinical picture of patients with Parkinson's disease and concomitant major depression using neurological and psychiatric rating scales and comparisons with patients with solely Parkinson's disease or solely major depression.
2. To determine the therapeutic responsivity towards citalopram in patients with Parkinson's disease and major depression and in patients with solely major depression.
3. To utilize imaging methodology to identify brain regions with altered regional cerebral blood flow in patients with Parkinson's disease and major depression, solely Parkinson's disease or solely major depression and effects of citalopram.
4. To analyze cerebrospinal fluid in patients with Parkinson's disease and major depression, solely Parkinson's disease or solely major depression with regards to monoamine metabolites, BDNF, orexin, IL-6 and corticosterone under baseline conditions and following treatment with citalopram.

3. MATERIAL AND METHODS

SUBJECTS

PD patients

Recruitment of PD patients was carried out during years 1997-1999 at Jönköping county with a population of 345 000 inhabitants. The county was expected with an estimated PD prevalence of 1.5/1000 to have about 515 individuals with PD. Most of PD population were diagnosed and followed at the outpatient department connected to the neurological centre at County Hospital Ryhov with overall responsibility for the county .Only a minority of patients, mostly patients who after definite diagnosis showed a stable symptomatology with given treatment and those PD patients in the palliative phase living at nursing home, were referred back to the local hospitals in the county.



Fig 9.
Map over the population's area
(Jönköping County).

The study population was consecutively included according to the following inclusions- and exclusions criteria.

Inclusions criteria

- idiopathic PD which meet UK PD Society Brain Bank criteria (Hughes AJ,1992)
- stabilized antiparkinson therapy for 6 month
- with or without unipolar depression by DSM IV criteria (American Psychiatric Association, 1994)
- no antidepressant treatment for the last 6 months
- informed consent signed

Exclusions criteria

- age < 50 yrs
- other neurologic disease than PD
- other psychiatric disease than depression
- patients with suicidal behaviour or psychotic depression which motivated treatment at a psychiatric clinic
- clinical dementia diagnosis or MMSE <24 points
- clinical significant or unstable somatic diseases
- diabetes mellitus (type I/II)
- essential hypertension (>160/90 mm Hg)
- ongoing anticoagulation therapy
- previous or ongoing treatment with neuroleptics

Logistic aspects

The intention of this study was to have 15 patients included in each PD group with and without major depression. When planning the study 1996 we assumed according to current opinion in the literature that prevalence for depressive illness in PD was as high as 50-80% and major depression at least 25-30% (Cummings JL. 1992). We therefore supposed that the recruitment would take about 8-12 month and that was the truth for PD without MD. For the

study group PD with MD, the true prevalence, as later was confirmed in the literature, is in fact only 7.7 – 17% (Tandberg E, 1996. Reijnders J 2008) which lead up to a recruitment period of almost 3 years.

MD patients

This patient group with 15 patients with solely MD was recruited during 2 years (2000-2001) by general practitioners in the central district of Östergötland County and referred to our study team at University Hospital in Linköping.

Inclusions criteria

- unipolar depression by DSM III-IV criteria (American Psychiatric Association, 1994)
- no antidepressant treatment for the last 6 months
- informed consent signed

Exclusions criteria

- age < 50 yrs
- other psychiatric disease than depression
- patients with suicidal behaviour or psychotic depression which motivated treatment at a psychiatric clinic
- sign of PD
- clinical dementia diagnosis or MMSE <24 points
- clinical significant or unstable somatic diseases
- diabetes mellitus (type I/II)
- essential hypertension (>160/90 mm Hg)
- ongoing anticoagulation therapy
- previous or ongoing treatment with neuroleptics

Study groups

	N	Main group	Control groups for	
			Parkinsonian symptoms	Depressive symptomatology
	total	PD pts with depression	PD pts without depression	Non-PD pts with depression
Planned	45	15	15	15
Screening	128	93	19	16
Inclusion	37	11	14	12
Completed	37	11	14	12

Demographics and clinical data at inclusion for the study groups

Group	A PD + MD	B PD	C MD	Group comparison	
	PD pts with depression n=11	PD pts without depression n=14	Non-PD pts with depression n=12	p-value A-B A-C	analysis
Sex					
Men	6	8	7	0.85	#
Women	5	6	5	0.89	
Age (yrs)	64.3 + 10.1 median 68,0	65.3 + 7.2 median 67,2	62.7 + 9.3 median 61,0	0.78 0.69	†
Cognition MMSE	29.1 + 1.1 range 26 -30	28.5 + 1.7 range 25 -30	28.8 + 0.9 range 27 -30	0.45 0.95	§

PD=patients with Parkinson's disease. MD = patients with major depression.
MMSE= Mini Mental State Examination # = Chi-Square analysis, † Independent Samples T test Sig 2-tailed,
α = Fisher's exact probability test. § = Mann Whitney U -test.

At inclusion, there were no statistical differences in age or sex between the three patient groups. Mini mental status examination (MMSE) (Folstein MF 1975) test revealed no difference between the groups.

METHODS

INSTRUMENT FOR ASSESSMENT

Parkinsonian symptoms

There are two different systems for diagnosing and define Parkinson's disease according to symptoms and neuropathological findings:

- a) United Kingdom Parkinson's Disease Society Brain Bank (UK-PDS-BB) criteria (Hughes A. 1992).
- b) National Institute of Neurological Disorders and Stroke (NINDS) Diagnostic Criteria for Parkinson Disease (Gelb DJ. 1999).

The discrepancies are very small between the two systems and there are up to now no comparing studies evaluating sensitivity or specificity. In this study we used a).

UK PDS Brain Bank clinical diagnostic criteria (Hughes A. 1992)

Already in 1988 researchers, funded by the Parkinson's disease Society, developed the UK PDS Brain Bank Criteria, a guide for diagnosing Parkinson's, which remains the global standard for diagnosis today for the purpose to maximise the accurate diagnosis of Parkinson's:

Step 1 Diagnosis of Parkinsonian syndrome

- * Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- * And at least one of the following: muscular rigidity, 4-6 Hz rest tremor, postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2 Exclusion criteria for Parkinson's disease

- * History of repeated strokes with stepwise progression of parkinsonian features
- * History of repeated head injury
- * History of definite encephalitis
- * Oculogyric crises
- * Neuroleptic treatment at onset of symptoms

- * More than one affected relative
- * Sustained remission
- * Strictly unilateral features after 3 years
- * Supranuclear gaze palsy
- * Cerebellar signs
- * Early severe autonomic involvement
- * Early severe dementia with disturbances of memory, language, and praxis
- * Babinski sign
- * Presence of cerebral tumor or communicating hydrocephalus on CT scan
- * Negative response to large doses of levodopa (if malabsorption excluded)
- * MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- * Unilateral onset
- * Rest tremor present
- * Progressive disorder
- * Persistent asymmetry affecting side of onset most
- * Excellent response (70-100%) to levodopa
- * Severe levodopa-induced chorea
- * Levodopa response for 5 years or more
- * Clinical course of 10 years or more

(adapted from Hughes AJ. 1992)

United Parkinson Disease Rating Scale (UPDRS)

(Fahn S. 1987) Appendix 1

UPDRS is a widely used scale for evaluation of clinical impairment in PD. The scale was introduced in 1987 as an overall assessment scale that would quantify the signs and symptoms of PD. Permits both an overall measure of disability and individual subscores. Include earlier rating scales: Hoehn and Yahr staging scale (Hoehn MM, Yahr MD 1967) and the modified Schwab and England activities of daily living (ADL) scale (Schwab RS, England AC Jr.1968).

The Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess I: Mentation, Behavior and Mood (4 items), II: Activities of Daily Living (ADL) (13 items), III: Motor symptoms (14 items) and IV: Complications of dopaminergic therapy (11 items). Each item scored 0 – 4. Higher scores imply more severe PD symptoms or more pronounced complications. The scores increase with worsening of symptoms and decrease when improvement.

Hoehn and Yahr scale (H & Y scale) (Hoehn MM, Yahr MD 1967)

H&Y scale is commonly used system for describing how the symptoms of Parkinson's disease progress and is an attempt staging of the disease. A rating scale from 0 to 5, where 5 is most disabling. In the 70-ies it was estimated that the progression between stages takes about 2 to 2.9 years (Marttila RJ. 1977). For an optimally treated PD patient at present the progression is much slower. An average non-demented PD patient with onset at age 62 yrs treated appropriately progresses by one stage in approximately six years (Rajput AH. 1997). It must be stressed that the progression rate varies widely from patient to patient.

We used the Modified Hoehn and Yahr staging scale

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aide

Webster scale

(Webster DD. 1968)

Appendix 2

Webster rating scale is a scale for patients with Parkinson's disease based on 10 clinical findings. The Webster scale indicates the severity of disease and the clinical impairment with minimum score 0 and maximum score 30. Higher score implies more severe PD symptoms.

Depressive illness

Diagnostic and Statistical Manual of Mental Disorders (DSM)

(American Psychiatric Association, 1994)

Appendix 4

Diagnostic and Statistical Manual of Mental Disorders (DSM) is published by the American Psychiatric Association and provides diagnostic criteria for mental disorders. The DSM-IV organizes each psychiatric diagnosis into five levels (axes) relating to different aspects of disorder or disability. Axes I include major mental disorder as depression and anxiety disorders.

In the screening process a DSM IV diagnosis of major depression was made in a structured interview with aid of the Structural Clinical Interview for DSM-III-R (SCID-D) (Spitzer R, 1987) if our patients meet the criteria for a major depressive episode.

Hamilton Depression Rating Scale with 17 items (Hamilton M. 1960) Appendix 5

The HAM-D-17 was used to estimate severity of depressive symptoms and has a minimum score 0 and a maximum score 53 points; 20 points cover depressed moods, 18 points cover anxiety and sleep and 15 points cover somatic symptoms. High scores imply more severe depressive symptoms. HAM-D-17 has demonstrated sufficient validity in PD (Leentjens AFG. 2000, Starkstein SE.1998, Naarding P. 2002).

Indeed the HAM-D scale is recommended for screening as well as for measurement of severity of depressive symptoms in the Depression Scale Assessment Program by Parkinson's Disease Rating Scales Task Force Steering in Movement Disorder Society (Schrug A. 2007).

To identify clinically significant depressive symptoms, cut-off scores of ≥ 12 were chosen. A study (ref 34) 2002 confirmed that combination of DSM-IV criteria for major depression and HAM-D-17 justified coexisting high validity and anticipated disease specific properties of HAM-D-17. The authors suggested for dichotomize study population into depressed and non-depressed patients a cutoff 12/13 which give a maximum of sensitivity (0.80) and specificity (0.92).

Montgomery-Åsberg Depression Rating Scale (Montgomery SA 1979) Appendix 6

The MADRS is an observer-rated scale which covers almost all the DSM-IV criteria of a major depressive episode, apart from retardation/agitation and the reverse neuro-vegetative symptoms e.g. hypersomnia and increased appetite. But compared to HAM-D the MADRS has relatively few somatic items.

The MADRS with 10 items score from 0 to 60:42 points cover depressed moods and 18 points cover anxiety, reduced sleep and appetite. To identify clinically significant depressive symptoms, cut-off scores of ≥ 12 were used. MADRS has demonstrated sufficient validity in PD (Leentjens AFG 2000, 2003).

Even MADRS is recommended for screening as well as for measurement of severity of depressive symptoms in the Depression Scale Assessment Program by Parkinson's Disease Rating Scales Task Force Steering in Movement Disorder Society (Schrug A. 2007).

Others

Mini mental status examination (MMSE) (Folstein MF. 1975) Appendix 3

The MMSE is still one of the most widely used clinical instruments for detecting and monitoring cognitive impairment and changes over time in PD (Bronnick K, 2007, Aarsland 2009). Global cognitive function was assessed MMSE with range 0–30, where maximum score is 30 and implies a normal cognitive function. We choose a cut off score <24 as abnormal with increased odds of dementia and these patients were excluded from the study.

Methods

Lumbar puncture

The patients were not allowed to leave bed from 11 pm on the day of hospitalization and until the LP had been performed the next morning. A standardized procedure for LP was used and performed at the L4-5 level with the patient in a supine position. Between 12 and 15 ml CSF from the first portion was collected in order to minimize the gradient influence on the proteins, peptides and neurotransmitters. The procedure was repeated 12 weeks later. All CSF samples were aliquoted and stored in an hour at -80°C until assayed.

HMPAO SPECT

The anti-Parkinsonian medication was given in the morning to assure “on” phase during the SPECT acquisition. The rCBF scintigraphy was performed with the technique used for the reference brain study (Björkstén KS 2004). The patients arrived at about 10 a.m. to rest supine in a quiet room with dim light for 30 min. An intravenous bolus injection of 10 MBq kg⁻¹ ^{99m}Tc-HMPAO (hexamethylpropylene amine oxime) was given with the patient’s eyes open and focusing at a point on the ceiling. After an additional 5 min of rest, the patient was moved to the camera table. The patient’s head was carefully positioned vertical to the canthomeatal plane and two laser positioning lights were used for the other two planes. The head was held with fixation strips attached to a specially constructed carbon fiber head holder, which allowed the camera detector to rotate very close to the head. An elliptic tomographic acquisition started about 15 min after injection.

SPECT images were acquired using a single detector rotating gamma camera (General Electric XRT with a Starcam 3000 computer) with a low-energy high-resolution collimator. There were 64 planar images collected over a 360° orbit in 128 × 9 × 128 matrix with a zoom of 1.6 (pixel size 2.7 mm). The spatial resolution of the images was calculated at 14 mm by phantom measurement. Data processing and quantitative analysis of rCBF were performed as described earlier in detail (Wallin A. 2007). Transaxial slices were reconstructed by filtered back-projection and transformed into a single parametric image by dividing each slice in sectors and let the max counts/pixel value in the peripheral cortical part of each sector form a horizontal row in the new image with sector numbers from right frontal to left frontal on the x-axis (columns) and slice numbers from the vertex to the basal parts of the brain on the y-axis (rows). This new image was expanded to a 64 × 9 × 16 pixel matrix by interpolation, which meant normalization of all patient studies to the same size.

The parametric image can be looked upon as a circular screen on which the max counts/pixel values are projected (Fig. 1a). The screen also corresponds to the orbit of rotation made by the gamma camera detector during the acquisition. The borders between the main cerebral lobes were reconstructed on this image from the normal anatomy of the brain surface (Fig. 10).

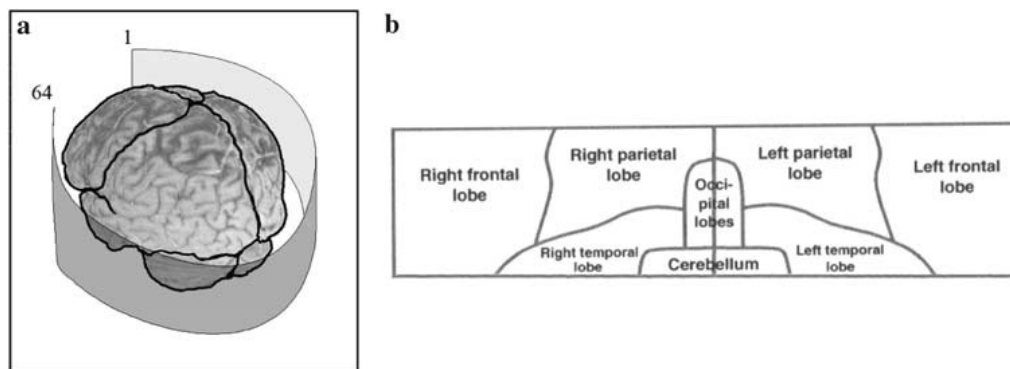


Fig. 10

a The parametric image can be described as a planar screen on which the cortical structures are projected. That means that the upper parts of the hemispheres are displayed more and more on an expanded scale in the parametric image. The figures refer to the columns 1–64 representing right frontal to left frontal areas.

b The projections of the main lobes in the final normalized parametric image.

Monoamine metabolism measurement

Mass fragmentographic methods for levels of HVA, 5-HIAA and HMPG

The levels of HVA, 5-HIAA and HMPG were determined as previously described by a mass fragmentographic method using the deuterated metabolites as internal standards.

Previous studies (Blennow K 1993) have shown that body height and age are confounding factors for accurate values of monoamine metabolites. This is thought to depend upon a larger surface area for monoamine metabolite transport from the subarachnoid space in taller than in shorter individuals. To correct the monoamine metabolite values for these parameters, the following formula were used:

$$\text{HVA corr} = \text{HVA} / [1233 - (5.6 \times \text{length})] \times 100$$

$$\text{5-HIAA corr} = \text{5-HIAA} / [(514 + (0.79 \times \text{age}) - (2.5 \times \text{length}))] \times 100$$

$$\text{HMPG corr} = \text{HMPG} / [(117 - (0.40 \times \text{length}))] \times 100$$

EIA and RIA technique for measurement of BDNF, Orexin, IL-6 and corticosterone.

CSF samples (100 µl) were analyzed with commercially available enzyme immunoassays (EIAs) for measurements of BDNF (Chemicon), interleukin-6 (Fitzgerald Industries) and corticosterone (Assay Design) according to the manufacturer's instructions. For measurements of orexin-A a commercially radioimmunoassay (Phoenix Pharmaceuticals) was employed according to the manufacturers instruction. Small aliquots of the CSF were also retained for protein determination by the BCA protein assay method (Pierce, Rockford, IL) using bovine serum albumin as a standard. Data from EIA and RIA analyses were normalized to these protein measurements.

STATISTICS

Study I

Quantitative data are shown as mean \pm standard deviation ($M \pm SD$, when applicable also median value and range). Dichotomy and nominal data were tested by chi squared analysis and Fisher's exact probability test for small-sample categorical data. Independent samples t-test Sig two tailed were applied for interval or ratio scale. The nonparametric tests for two independent samples Mann Whitney U-test were used for comparison of groups. Statistical evaluations for an analysis of variance for repeated measures were performed by one-way ANOVAs complemented by post hoc test of Bonferroni for multiple comparisons. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 10, 0.5 (SPSS Inc., Chicago, IL, USA).

Study II

Quantitative variables are summarized by mean \pm standard deviation ($M \pm SD$) or when applicable by median and range. Dichotomy data were tested by chi-square analysis. Independent samples T test Sig 2 tailed were applied for interval or ratio scale. For quantitative variables Wilcoxon Mann-Whitney Rank Sum Test was used for comparisons between the PD patient with depression and the PD patients without depression and the patients with depression without PD respectively. Wilcoxon Signed Rank Test was used to assess outcome at consecutive visits within patient groups for quantitative data. Post Hoc Tests for multiple comparisons including Bonferroni were then used with mean difference significant at the 0.05 level when multiple comparisons were performed. Categorical variables were compared using Fischer's exact test. A two-sided p-value less than 5% was considered statistically significant. All analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 10, 0.5 (SPSS Inc., Chicago, 1999).

Study III

Statistical analyses: The parametric image obtained from each patient study was normalized to the peak intensity in the occipital area of the activity profile from our reference brain and a SD map (Björkstén KS 2004) was constructed according to the formula:

$$\frac{(\text{normalized patient image}) - (\text{mean reference image})}{(\text{SD reference image})}$$

when comparing the three patient groups (MD with PD, PD and MD) with the reference brain (Fig. 2a–c in paper III) significant hypoperfusion was defined as > 2SD reduction relative to the reference brain.

To make the statistical comparisons between the three groups of patients the Mann–Whitney U-test was applied to the SD values of each pixel but for the comparison before and after treatment paired Student's t-test was used (Statistica Ver 6.0 StatSoft). For an easily accessible visual demonstration of the rCBF group differences another parametric image was constructed based on the calculated p-values (Figs. 2, 4 in paper III). The p-values were not corrected for the number of pixels because the conclusions were not based on single pixels. Instead results were based on the existence of clusters of pixels with $p < 0.05$ in each pixel, a minimum cluster size of 3 x 2 pixels (width x height) and that clusters had to be located in the mid part of the parametric image. We consider this sector (rows 5–12) as the region of interest due to the technical difficulties to acquire useful data from the upper and lower parts of the brain with our technique (Wallin A. 2007).

For the frequency analysis Fisher exact test was used to calculate the percentage number of individuals necessary for a significant difference ($p < 0.05$ in each pixel). Assuming that 10% of the control subjects could differ more than 2SD in all 16 9 64 pixels the calculations gave a $p < 0.05$ if 60% or more of the patients differed >2SD compared to the reference brain.

Acronyms used for the different patient groups in the statistical evaluation:

PD +MD is depressed PD patients (n = 11)

“only” PD is PD patients without MD (n = 14)

“only” MD is MD patients without PD (n = 12)

All PD is PD patients with and without MD (n = 25)

All MD is MD patients with and without PD (n = 23)

Study IV

Data from biochemical analyses of baseline levels of PD+MD, PD and MD patients, were analyzed with one-way ANOVAs followed by Newman-Keul's test for pairwise comparisons. Concerning levels of orexin A, an unpaired two-tailed Student's T-test was used to compare MD patients with pooled PD and PD+MD patients. Data from the MD patients with or without PD that underwent treatment with citalopram were also analyzed with two-way ANOVAs (treatment x diagnosis) followed by Bonferroni's test for pairwise comparisons to identify whether specific diagnosis and/or treatment effects could be found. Statistical differences in patient populations on clinical rating scales are indicated in tables and explained in detail (Pålhagen SE. 2008).

STUDY DESIGN

Flow chart

After a screening procedure for inclusion and exclusion criteria, the patients had a baseline investigation with somatic-neurological examination (SEP) and a psychiatric assessment (JW and/or MC). Later, the same day, the patients were hospitalized until the next day.

Prescribed drugs were allowed before 11 pm on the day of hospitalization and after the LP and the SPECT had been performed the next day.

The standardized LP implied a minimum of 8 h of fasting and strict bed rest until the LP was performed at the L4–5 level with the patient in a supine position. The SPECT investigation was carried out later the same day.

At week 12, the patients were again hospitalized and a second LP and SPECT were performed. The patients were rated for somatic, neurological and psychiatric symptoms at

	Visit	Screening	Baseline	W2	W4	W8	12
Medical history & Demographics		X					
Physical examination		X	X				X
Vital signs			X	X	X	X	X
12-lead ECG		X	X				X
Clinical chemistry and hematology		X	X	X	X	X	X
DSM III-IV		X					
MMSE		X	X				X
Hoehn and Yahr rating		X	X	X	X	X	X
Webster		X	X				X
UPDRS		X	X	X	X	X	X
HAM D-17		X	X	X	X	X	X
MADRS		X	X	X	X	X	X
Inclusions / exclusions criteria		X					
Informed consent		X					
Hospitalized			X				X
Lumbar punctio ^e			X				X
SPECT			X				X
Adverse event recording			X	X	X	X	X
Concomitant medication recording ^l		X	X	X	X	X	X

weeks 2, 4, 8 and 12 (see Methods). Initial symptoms at the onset of PD were obtained from the patient's medical records. All parkinsonian patients were examined in "on" phase, i.e. the period with most effect on PD symptoms during the dopaminergic treatment. The depressed patients without PD were examined at baseline to exclude any sign of parkinsonian symptoms.

Drug treatment

All PD patients had stable antiparkinsonian treatment including levodopa for at least six months. . The number of patients treated with a COMT-inhibitor, a MAO-B inhibitor and a dopamine receptor agonist as well as anxiolytic and hypnotic drugs are shown presented (Pålhgen SE 2008).

Antidepressant treatment started after the first LP and the first SPECT with a dose of 10 mg citalopram, which at week 2 was increased to 20 mg. During the study the citalopram doses were individually adjusted according to therapeutic response to a maximum of 30 mg per day.

Logistic aspects

The screening process needed 128 visits. With visits at baseline, week2, 4, 7 and 12 for the 37 patients who were included and fulfilled the study, there were an additional amount of 210 visits plus 84 “nights” at hospital. The clinical evaluation scales include a lot of time consuming items; UPDRS 42 items, Webster 10 items, MMSE 10 items, HAM D with 17 items and MADRS with 10 items.

All together 338 patient visits and for each included patient in the study 731 variables were registered in the database i.e. about 27 000 data.

4.RESULTS AND DISCUSSION

Study I: Depressive illness in Parkinson's disease – indication of a more advanced and widespread neurodegenerative process?

In order to evaluate any relationship between PD and depressive illness we studied three groups of patients: PD-patients with depression were compared to PD-patients without depression and PD-patients with depression were compared to depressed patients without PD. To our knowledge no such comparisons between such three groups have been published previously.

Result:

Positive family history of PD was seen in both parkinsonian groups but in none of the depressed non-parkinsonian patients. Family history of depression was found in one third of the depressed non-parkinsonian patients but in none of the PD groups, not statistically significant difference.

At the debut of PD the patient with a later depression were younger than the patients without development of depression. Disease duration defined as the time since the onset of symptoms was consequently longer for the depressed PD patients as well as the duration of L-dopa treatments with a later depression were younger than the patients without development of depression.

None of the parkinsonian patients had a MD before the debut of PD or the start of levodopa treatment. The levodopa dose was higher in the depressed PD patients compared with PD patients without depression. At the debut of PD tremor was the first symptom almost twice as often in non depressed patients compared with PD patients with a later depression, while the depressed PD patients from start seemed to be akinetic-rigid. There was no difference between the two PD groups regarding laterality.

At inclusion depressed PD patients were more disabled than PD patients without depression, according to the H&Y scale. The depressed PD patients had more

involuntary movements according to UPDRS IV ($p < 0.01$). Motor fluctuation according to UPDRS item 32-38 was seen in 64% of the depressed PD patients compared to 43% in the non-depressed patients ($p < 0.001$). In the depressed PD-group some depressive symptoms were less severe compared with the depressed patients without PD. Sleep disturbances were significantly more often found among depressed PD patients than with PD patients without depression. Reduced sleep was more pronounced in depressed patients without PD compared to depressed PD-patients.

No differences between the patient groups concerning analysis of laboratory tests. However, the subgroup of PD patients with COMT-inhibitor ($n=7$) had a lower Hcy ($10.4 + 1.3$ $\mu\text{mol/l}$) compared to those without this drug ($13.2 + 3.2$) ($p < 0.05$).

Discussion:

Several issues have to be taken into account when depression in PD is discussed: Short episodes, lasting only minutes – hours, with depressive feelings of anxiety and hopelessness often correlates with “off” phase, i.e. when PD symptoms are severe, but these depressive symptoms disappear during “on” phase. However, all patients were examined in the “on” phase,

As the burden of a chronic disease itself has to be recognized, a comparable group of PD patients, but without depression, was included. If there were no significant motor differences between PD patients with and without depression, the depressive symptoms should not be related to physical disability. However, the depressed PD patients had a somewhat more advanced PD symptoms.. Thus, it cannot be excluded that the motor problems had some impact on the depressive symptoms.

It is known that dopaminergic dysfunction per se can cause not only motor problems but also depressive illness (Goodwin F, 1990). If so, depressive symptoms may improve during treatment with dopaminergic treatment. However, the higher doses and the longer duration of levodopa treatment in the depressed PD patients, compared with the PD patients without depression, seem to contradict this assumption. Furthermore, a study of the effect of long term levodopa therapy in de novo patients with PD did not improve their depressive symptoms (Choi C, 2000).

After many years of levodopa treatment the general PD symptoms in patients without depression were less pronounced compared with the PD-patients with depression. This is especially notable as they were treated with lower L-dopa doses than the depressed patients,

but, on the other hand, some of them were treated with COMT- and MAO-B-inhibitor, with added dopaminergic effect. As the depressed PD patients were found to have more severe neurological PD symptoms and a longer duration of the disease than the patients without depression it is possible that depression in PD reflects a more advanced and widespread neurodegeneration.

This may include serotonergic as well as dopaminergic neurons, also related to a longer duration of PD. Furthermore it could be discussed if tremor reflects the activity in serotonergic neurons as tremor as initial symptom was seen twice as often in non-depressed PD-patients compared to depressed PD patient. Such a relationship has been discussed by others (Doder M, 2005).

The finding that the PD patients with depression had more dyskinesias than non-depressed patients may be due to their somewhat higher levodopa doses but may also indicate that depression is a component of a more advanced PD disease. Furthermore, depression induces stress, which could trigger the occurrence of involuntary movements. In addition, as stress has been shown to increase neuronal loss it cannot be excluded that depression, leading to stress, could cause an increased neuronal loss, including dopaminergic neurons (Lucas LR, Celen Z, Tamashiro KL, et al. 2004, Remy P, Doder M, Lees A, Turjanski N, Brokks D. 2005).

It has been under debate if the high prevalence of depression in PD is misinterpretation of apathy (Richard IH. 2006). In fact patients with PD can be apathetic without being depressed (Kirsch-Darrow L, Fernandez HF, Marsiske M, Okun MS, Bowers D. 2006). Mood in apathy is neutral but in depression causes emotional distress and apathy has been shown to be associated with cognitive impairment (Pluck GC, Brown RG. 2002). In our study the patients were cognitive well-functioning why apathy probably was not prominent. In the present study the patient also met the criteria for MD according to DSM IV which probably avoids misdiagnosing (Kirsch-Darrow L, Fernandez HF, Marsiske M, Okun MS, Bowers D. 2006).

Study II: Treatment of major depression in Parkinson's disease improves depressive as well as motor symptoms – indicating a more extensive neurodegenerative process?

The objectives of the present study were to compare in an exploratory and a hypothesis-generating approach the therapeutic response to a SSRI treatment in two groups of patients with MD: patients with and without Parkinson's disease. The drug chosen was citalopram, at that time the most used SSRI. PD symptoms as well as mental symptoms were assessed during the antidepressive treatment and also compared to PD patients without depression.

Result: (assessment by MADRS)

Depressed patients with PD showed already after two weeks of antidepressive treatment a statistically significant improvement in total scores of depressive symptoms ($p < 0.05$). A significant decrease of the symptom insomnia was seen at week 2 ($p < 0.05$), and of the items for apparent and reported sadness, insomnia, as well as fatigue at week 4 ($p < 0.05$).

Depressed patients without PD have a delay in response. At visit week 4 an improvement was seen ($p < 0.05$), which was even more marked after eight weeks of antidepressive treatment ($p < 0.01$). Although the total MADRS scores seemed to increase at week 12, they were still lower than during the first month of treatment ($p < 0.01$). Significant reductions were registered for insomnia ($p < 0.01$) at week 4 and for apparent and reported sadness, inner tension, concentration difficulties and fatigue/apathy ($p < 0.05$, respectively) as well as at week 8 ($p < 0.05$, respectively).

Comparison between depressed patients with and without PD. At the start of the study the MADRS scores did not differ significantly between depressed PD patients and depressed patients without PD. During treatment with citalopram the PD patients scored significant lower than the patients without PD at the first 4 weeks of treatment ($p < 0.05$). At week 12 there was no statistically significant difference between the two patient groups.

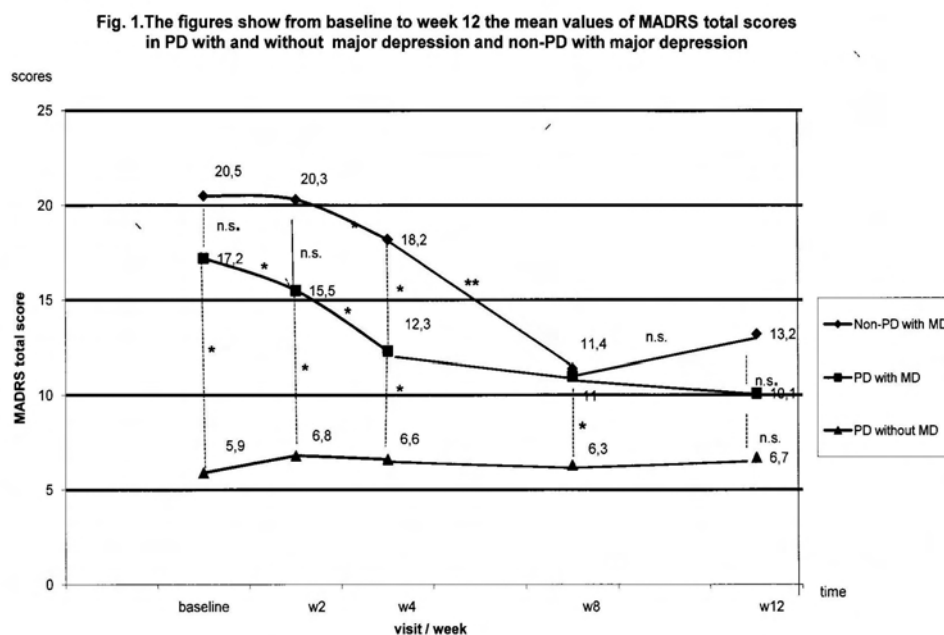


Fig 1 (from Paper II)

PD= patients with Parkinson's disease. MD = Major Depression. MADRS= Montgomery-Åsberg Depression Rating Scale. Statistics: Wilcoxon Signed Test for related samples test within groups. Post Hoc Tests multiple comparisons incl. Bonferroni with mean difference significant at the 0.05 level. **= p value < 0.01, *= p value < 0.05. n.s.= non significant

Result: (assessment by HAM-D-17)

Depressed patients with PD. After 2 weeks of antidepressive treatment a statistically significant ($p < 0.01$) improvement in depressive symptoms was seen. The HAM-D-17 scores then gradually decreased and at week 12 approached the level for the non-depressed PD group. After the first two weeks of treatment a significant reduction on several symptoms were observed: depressed mood (Q1), insomnia middle (Q5), anxiety somatic (Q11) ($p < 0.001$, respectively), insomnia initial (Q4), insomnia delayed (Q6), mental retardation (Q8), agitation (Q9) and anxiety psychic (Q10) ($p < 0.01$, respectively). At week 12 all symptoms were significantly reduced in comparison to baseline.

Depressed patients without PD. A reduction in depressive symptoms was not seen before week 4 but then substantial effects were seen on several items: depressed mood ($p < 0.001$), insomnia initial, insomnia middle, insomnia delayed, agitation and anxiety psychic ($p < 0.05$, respectively). Further improvement in the total HAM-D 17 score was seen at week 8 ($p <$

0.05) and 12 compared to values at inclusion. However, at week 12 the depressed patients without PD had not reached the level for depressed patients with PD ($p < 0.05$).

Comparison between depressed patients with and without PD. At baseline the PD-patients with depression had lower HAM-D-17 scores ($p < 0.05$) compared to depressed patients without PD.

Fig. 2. The figures show from baseline to week 12 the mean value of Hamilton D-17 total score in PD with and without major depression and non-PD with major depression

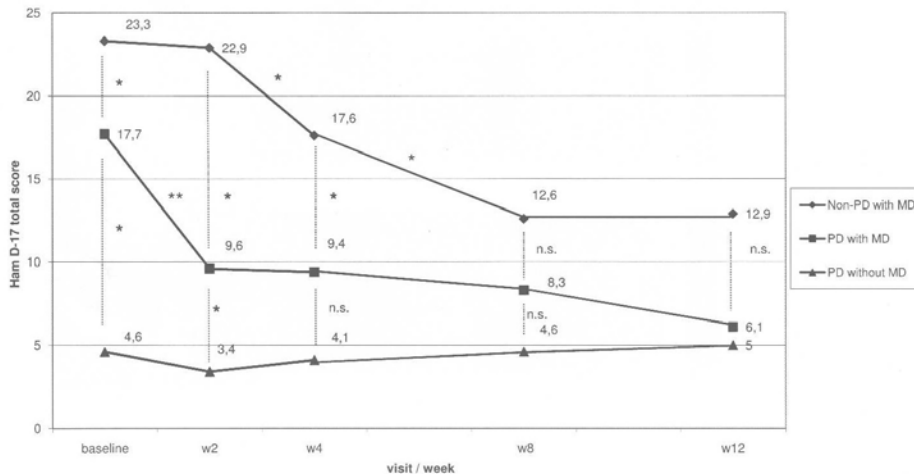


Fig 2, from Paper II

PD= patients with Parkinson’s disease. MD = Major Depression. HAM-D-17 = Hamilton depression scale with 17 items. Statistics: Wilcoxon Signed Rank Test for related samples test within groups. Post Hoc Tests multiple comparisons incl. Bonferroni with mean difference significant at the 0.05 level. **= p value < 0.01, *= p value < 0.05. n.s.= non significant

Result: (assessment by UPDRS):

PD symptoms. The antiparkinsonian treatment remained unchanged during the study. At the start of the study the PD patients with depression had more advanced PD symptomatology according to H&Y ($p < 0.05$) and UPDRS part IV “Complications of therapy” ($p < 0.01$) compared to the PD patients without depression (Pålhagen SE, 2008). However, UPDRS part III, “Motor”, was not significantly changed with exception for occurrence of tremor measured as item 20 in UPDRS was lower ($p < 0.01$) at baseline for PD with depression compared to PD without depression, and increased significantly during treatment with

citalopram ($p < 0.01$). At baseline the degree of hypokinesia was similar in the two groups of PD patients (Fig 3). During treatment with citalopram *hypokinesia* decreased ($p < 0.01$) and became significantly lower in depressed PD patients compared to PD patients without MD ($p < 0.001$). Also some improvement of *rigidity* was seen during antidepressant treatment ($p < 0.05$). Involuntary movements decreased during treatment with citalopram ($p < 0.01$).

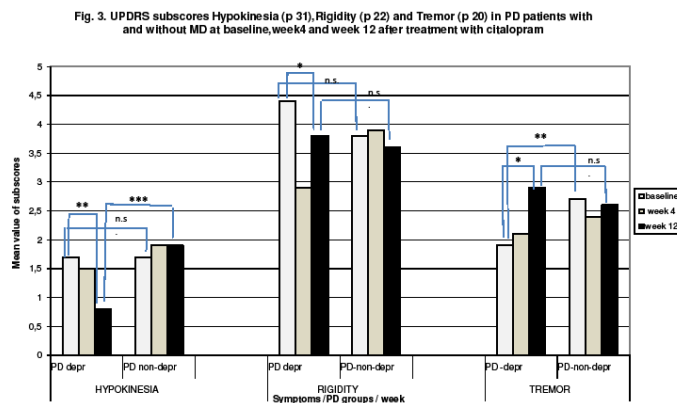


Fig 3 from Paper II

UPDRS = Unified Parkinson's Disease Rating Scale. PD = patients with Parkinson's disease. MD = Major Depression. Wilcoxon Signed Rank Test for related samples within groups. Mann Whitney U-test for independent samples test between groups. . ***= p value < 0.001, **= p value < 0.01, *= p value < 0.05. n.s.= non significant

Discussion:

The treatment response of SSRI on specific depressive or neurological symptoms could possibly enlighten underlying mechanisms. A multi-neurotransmitter perspective is needed due to the complex pathophysiology of PD and depressive symptomatology.

Numerous studies have examined interactions between the serotonin and dopamine system and in some animal studies serotonin have been shown to inhibit striatal dopamine release (Jenner P, 1983 and Jacobs BL, 1993), whereas others have found that serotonergic stimulation potentially release dopamine (Parsons LH, 1996). It is possible that such serotonin-dopamine interactions also underlie some of the both antidepressant and antiparkinsonian effects following citalopram seen in the PD patients.

A controlled study (Devos D, 2008) with comparison of desipramine and citalopram in depressed PD patients showed a significant improvement in MADRS scores after 30 days treatment for both drugs. This therapeutic time-profile for citalopram is also in line with the findings in our present study and support the early effect.

A “serotonergic hypothesis” for depression in PD was proposed (Mayeux R., 1990). It was supported by findings of degeneration of serotonergic neurons post mortem in patients with Parkinson’s disease (Jellinger KA, 1991). This theory was recently maintained by findings of a reduction in serotonin levels in CSF, measured as its metabolite 5-hydroxyindoleacetic acid (5-HIAA), as well as the serotonin transporter and tryptophan hydroxylase, the rate-limiting enzyme for serotonin production (Kish SJ, 2008). Decreased levels of the serotonin metabolite 5-HIAA in CSF has also been observed (Mayeux R, 1984 and Kostic VS, 1987). The fact that enhancement of central serotonergic neurotransmission by citalopram treatment rapidly reversed several depressive symptoms may speak in favour of a primary serotonergic hypofunction in depressed PD patients. However, a placebo controlled study showed that PD patients who were on a tryptophan-reduced diet, showed no changes in mood (Leentjens AFG, 2006).

To be noted is that the antidepressant treatment seemed to improve some parkinsonian symptoms. Hypokinesia and rigidity were thus significantly reduced in the depressed PD patients while treated with citalopram, also shown by others (Rampello L, 2002 and Tesei S, 2000). On the other hand it cannot be excluded that decreased PD symptoms contribute to improvement of depressive symptoms. Hypokinesia might also be an expression of depression itself, which, however, was contradicted by the fact that the degree of hypokinesia at baseline was similar in the PD patients with and without concomitant depression. It thus seems as treatment with citalopram could decrease some PD symptoms.

Our finding that tremor increased during treatment with SSRI is in line with other reports (Weintraub D, 2006 and Kulisevsky J, 2008) and indicates that enhance of tremor relates to an increased serotonin activity. Furthermore, we observed that involuntary movements decreased during antidepressant treatment. The occurrence of involuntary movements might be a result of decreased serotonergic effect (Bara-Jimenez W, 2005) and as treatment with SSRI improves the serotonergic activity, the disposition for involuntary movements could be reduced.

Study III: HMPAO SPECT in Parkinson's disease (PD) with major depression (MD) before and after antidepressant treatment

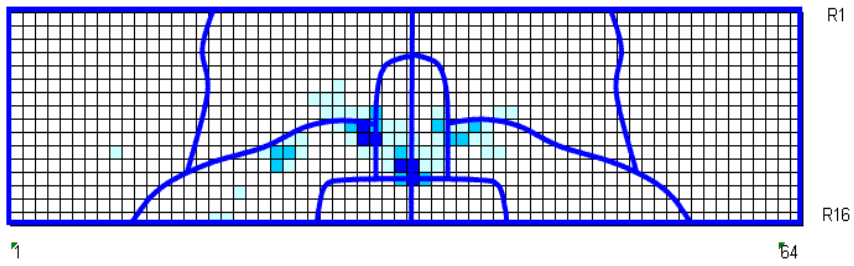
Investigations using single-photon emission computed tomography (SPECT), measuring regional cerebral blood flow (rCBF), may contribute to enlighten the neurobiological substrates linked to depressive symptoms. SPECT was performed in order to compare rCBF in MD patients with and without PD. The study included 11 MD patients with PD, 14 non-depressed PD patients and 12 MD patients without PD. All patients were followed for 12 weeks with repeated evaluation of depressive as well as PD symptoms. Antiparkinsonian treatment remained unchanged during the study. Antidepressant treatment with SSRI (citalopram) was given to all patients with MD. SPECT was performed before and after 12 weeks of antidepressant treatment

Result:

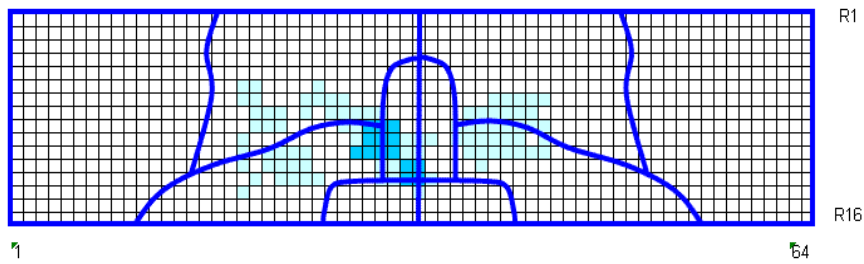
i. *Comparison with the reference brain.* (Fig 2 paper III)

By use of common statistics for group comparisons (the unpaired Student's t-test) no significant difference in rCBF was found in any part of the cortex in any group of patients compared with the reference brain. However, using a more sensitive statistical method, the frequency analysis, giving the percentage number of patients in each group with a reduction of rCBF > 2SD in individual pixels, some group differences were visible. Among the PD patients with MD there were generally (frequency around 70%) distinct small areas with significantly reduced rCBF localized in the preoccipital area (cuneatum) and in the basal central part of the occipital lobe in relation to the reference brain. The reduction was most evident in the right preoccipital cortex. In the PD patients without MD the same pattern of reduced cortical perfusion was seen, although less frequent (about 50%), while in the group of patients with only MD this pattern was seldom present (<30%). On the other hand, in patients with only MD "spotted" hypoperfusion on the right side was noticed, most evident in the lower parts of the frontal lobe

a) PD + MD



b) PD



c) MD

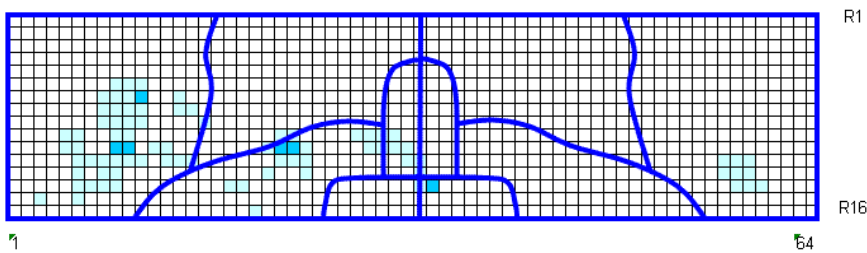


Fig 2. (From Paper II) *Comparison with the reference brain*

Parametric images for the three groups of patients showing in blue colour cortical areas with reductions of regional blood flow (rCBF) compared with the reference brain. The reductions are visualized by the percentage number of patients in each group with a reduction of rCBF $>2SD$ in individual pixels (dark blue 60-100% of the patients, medium blue 40-60%, light blue 20-40% and white pixels $<20\%$). On the x-axis are 64 columns and on the y-axis 16 rows. Blue lines outline the boundaries between the main lobes of the cerebral hemispheres according to Fig. 1b

- ii. *Comparison between patient groups before treatment with SSRI.* (Fig 3 paper III)

Patients with PD + MD compared to patients with “only” MD (Fig 3 a). In patients with PD + MD the rCBF was higher in several regions compared to patients with “only” MD (or lower in MD compared to PD + MD). The differences in rCBF were statistically significant in two right frontal regions and in one left frontoparietal region. Preoccipitally on the right side there was a significantly lower rCBF in PD + MD relative to “only” MD.

All patients with PD (with and without MD) compared to patients with “only” MD (Fig. 3b). In the patients with PD reductions of rCBF were seen in the preoccipital regions bilaterally and in the basal central part of the occipital lobe compared to patients with “only” MD. In the patients with PD the rCBF was higher in the basal part of the right frontal lobe, compared to patients with “only” MD. The differences were significant in the two regions on the right side.

Patients with PD + MD compared to patients with “only” PD (Fig 3 c). In patients with PD + MD the rCBF was statistically higher bilaterally in the frontoparietal areas, in the right dorsolateral area and in the left anterior frontal area compared to patients with “only” PD. In the basal occipital and preoccipital regions no difference was seen between these two groups.

All patients with MD (with and without PD) compared to patients with “only” PD (Fig 3d). In all MD patients as a group significantly higher rCBF was found only in the right dorsolateral area in the frontal lobe compared to patients with “only” PD. In the occipital and preoccipital regions no difference was seen between these two groups.

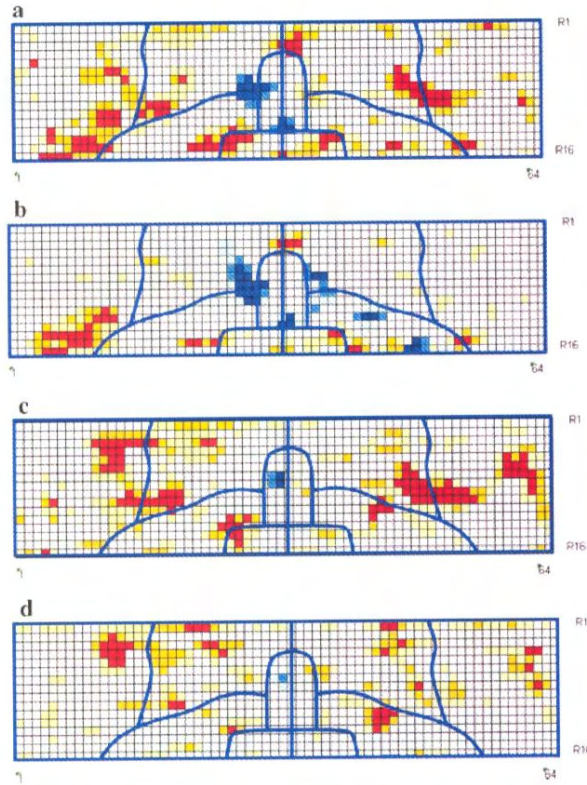
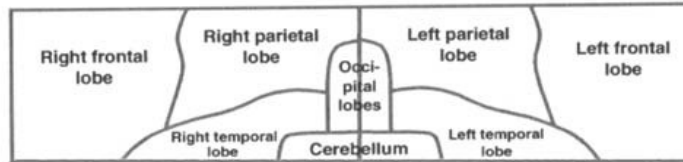


Fig. 3 Comparison between patient groups before treatment with SSRI. These four parametric images are based on p -values and visualise the calculated statistical group differences in the individual pixels. The p -values are indicated in colour (white $p > 0.20$), higher CBF in the first group compared to the second group red, orange and yellow colours ($p < 0.05$, $p < 0.10$ and $p < 0.20$, respectively), lower CBF in the first group compared to the second group dark, medium and light blue colours ($p < 0.05$, $p < 0.10$ and $p < 0.20$, respectively). **a** PD + MD compared to MD. **b** All PD (with and without MD) compared to MD. **c** PD + MD compared to PD. **d** All MD (with and without PD) compared to PD

Fig 3 paper III

- i. *Comparison before and after treatment with SSRI for 12 weeks in MD patient groups* (Fig 4 Paper III)

Patients with PD + MD (Fig. 4a). After treatment with SSRI a reduction of the previously increased rCBF (Fig. 3a, c) was seen in several areas in both hemispheres, although only significant in the left frontal dorsolateral region. No change was seen in rCBF in the preoccipital area.

Patients with “only” MD (Fig. 4b). After treatment with SSRI an increase of the previously “spotted” and widespread reductions in rCBF in the right hemisphere (Fig. 2c) was seen. In the left hemisphere there was instead a decrease after treatment. Neither the increased flow values nor the decreased values reached statistical significance.

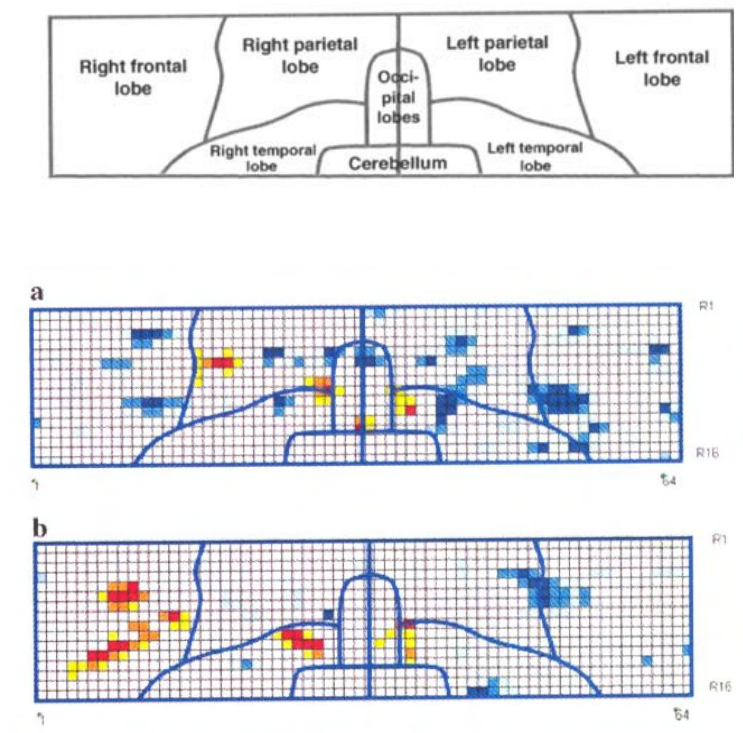


Fig. 4 Comparison before and after treatment with SSRI for 12 weeks in MD patient groups. These parametric images are based on p -values and visualise the calculated statistical group differences in individual pixels as indicated by colours. Higher rCBF after treatment compared to before treatment red, orange and yellow colours ($p < 0.05$, $p < 0.10$ and $p < 0.20$, respectively), lower rCBF after SSRI treatment dark, medium and light blue colours ($p < 0.05$, $p < 0.10$ and $p < 0.20$, respectively). **a** PD + MD before and after SSRI treatment. **b** MD before and after SSRI treatment

Discussion:

In the present study our clinical observation of different therapeutic responses in MD patients with and without PD has been supplemented with a SPECT analysis of the cortical blood flow (rCBF). The aim was to obtain further support for our hypothesis of an underlying, more widespread neurodegenerative disease in PD patients with MD compared to PD patients without MD. Furthermore, a second SPECT was performed after 12 weeks of antidepressant treatment with SSRI (citalopram) in order to analyze if the pattern of rCBF would change differently in MD patients with and without PD. SPECT only allows the calculation of relative values of the regional cortical perfusion normalized to an internal reference, here the max value in the occipital lobe. Thus, in the comparison with the reference brain, as well as in the comparison between the groups of patients, differences in the cortical blood flow distribution can be evaluated but not the absolute blood flow values. Furthermore, our SPECT technique only measures the cortical blood flow in the lateral parts of the cerebral hemispheres.

The interindividual variation in cortical blood flow pattern was striking despite clinically homogenous patient groups concerning diagnose as well as treatment. Except for a reduced rCBF in and close to the occipital lobe in the PD patients, our SPECT results did not show any diagnosis specific differences in the distribution of cortical CBF in any of the three groups of patients in comparison with our reference group of healthy individuals. The occipital and preoccipital hypoperfusion in the PD patients was more evident in PD patients who also had MD (Fig. 2a), which may be an indication of more advanced neurodegenerative disease in PD + MD.

In mood disorders rCBF abnormalities are very variable when evaluated with SPECT. In our group “only” MD (without PD) some of the patients showed a “spotted” reduction of rCBF at baseline, mainly in the frontal region on the right side (Fig. 2c), compared to the reference brain. However, when comparing “only” MD with PD + MD or all PD patients (Fig. 3a, b) a significant lower rCBF in the basal part of the right frontal lobe was observed. The areas involved in Figs. 2c and 3a, b are not exactly overlapping but are probably related.

After treatment with citalopram for 12 weeks there was an increase of rCBF in these areas, i.e., towards normalization. In the concept of neurocircuitry models in mood disorders a circuit involving the prefrontal cortex, amygdala and related parts of the striatum, pallidum and medial thalamus has been suggested in depression (Drevets WC, 2000). If so, cortical activity abnormalities, as revealed by SPECT, might reflect underlying dysfunction in the basal ganglia or the limbic system. Often there seems to be reciprocal functional

relationships between cortical and deeper structures and our results may support an effect on cortical brain areas in circuits of importance for depression. In depression combined with an organic/neurologic disease (sometimes named “secondary depression”) the anatomical circuits implicated in PD involve the limbic–cortical–striatal–pallidal–thalamic structures (Drevets WC, 2000). Organic disease may affect the circuitry in different ways, implying imbalances within these circuits rather than overall increased or decreased synaptic activity within a particular structure, giving rise to the depressive syndrome (Drevets WC, 1997). In the comparison of depressed and non-depressed PD patients at least four cortical regions with significantly higher rCBF appear in the depressed PD patients: fronto-parietally on both sides, dorsolaterally in the right frontal lobe and in the anterior left frontal lobe (Fig. 3c). All these areas with increased rCBF had a more or less normalized perfusion after SSRI treatment (Fig. 4a), suggesting that in these areas the blood flow is mood related. The higher rCBF fronto-parietally seems to be rather typical for our depressed PD patients as higher rCBF is found regardless of whether the comparison is made against “only” MD or “only” PD (Fig. 3a, c), and not at all seen in the comparison between all PD patients and “only” MD (Fig. 3b). In contrast, the two frontal regions in our depressed PD patients do not show higher blood flow in comparison with “only” MD (Fig. 3a), which could be interpreted as an increased rCBF in these areas and is more related to the depressive state per se.

To our knowledge there are no previous studies concerning rCBF in PD patients with MD before and after long-term antidepressant treatment with citalopram. Earlier studies have included PD patients with minor depression (Mayberg HS, 1990, Mentis MJ, 2002 and Matsui H, 2006) or moderately severe depression according to DSM-III-R (Ring HA, 1994). In our study all depressed patients met DSM-III-IV criteria for MD. In contrast to these earlier studies which report hypoperfusion in various prefrontal cortex structures, we found hyper perfusion in these areas in our depressed PD patients before treatment with citalopram. The cortical hyper perfusion in PD patients with untreated MD could be a result of modulating and compensatory mechanisms including prefrontal structures like right DLPFC (Drevets WC, 2008), and/or an expression of a cortical activation due to dopaminergic treatment. However, our SPECT results also indicate activation of cortical structures located fronto-parietally on both sides not related to MD alone. This observation draws attention to these regions as specific areas for MD in PD.

Interestingly, treatment with citalopram “normalizes” the mood-related abnormal rCBF pattern in both “only” MD and PD + MD patients, although in different ways: the mainly right frontal areas showing hypoperfusion initially in “only” MD have higher/increased rCBF after treatment, while all four areas with hyperactivity initially in PD + MD show lower/decreased rCBF after treatment with SSRI. This may suggest substantial diverse underlying abnormalities in MD with and without PD, and the outcome of treatment an expression of a modulating activity within relevant neurocircuitry structures being effective whether MD is a separate entity or combined with PD. Clinically both groups with MD responded well to citalopram, although somewhat different. Our SPECT findings may help explain the antidepressant response. It is possible that the previously increased rCBF in PD with MD reflects compensatory mechanisms in the circuitry which are changed after treatment with citalopram.

Study IV: Monoamines, BDNF, IL-6 and corticosterone in CSF in patients with Parkinson's disease and major depression.

To improve our understanding of the biochemical basis of MD in PD patients, we examined the levels of the monoamine metabolites homovanillic acid (HVA), 5-hydroxyindole-3-acetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylethylenglycol (MHPG), as well as brain-derived neurotrophic factor (BDNF), the hypothalamic neuropeptide orexin-A, interleukin-6 (IL-6) and corticosterone in CSF. The study include patients with PD with or without concurrent MD and patients with solely MD (i.e. PD+MD, solely PD and solely MD, respectively). The abovementioned biochemical assays were also made in depressed patients (PD+MD and solely MD) after 12 weeks of treatment with citalopram.

Results:

The classical monoamine deficiency hypothesis of depression suggest that a dysfunction of the noradrenergic/serotonergic function leads to depression and there is, indeed, evidence for a reduction of both NA and 5-HT in brain samples and/or cerebrospinal fluid (CSF) from depressed PD patients. However, it has also been reported that there are no changes of these monoamines in CSF from depressed PD patients. We wanted to study monoamine metabolite levels in our patient groups.

Levels of the monoamine metabolites; HVA, 5-HIAA and MHPG.

Consistent with the fact that the PD patients were treated with L-DOPA significant differences in baseline levels of HVA were found when compared to patients with solely MD (Fig XX). Treatment with citalopram did not affect the levels of HVA in patients with PD+MD or patients with solely MD.

At baseline, no significant differences in 5-HIAA were found between the PD+MD, PD or solely MD patients. However, when the solely MD and the PD+MD patients who were treated with citalopram were compared, there were both a diagnosis and treatment effects, The diagnosis can be explained by the higher levels of 5-HIAA in PD+MD patients than solely MD patients seen both before and after treatment with citalopram. The treatment effect

can be ascribed to a reduction of 5-HIAA in solely MD patients, but not in PD+MD patients, after citalopram treatment. MHPG levels were significantly lower in the PD+MD patients compared to solely MD patients. Moreover, these patient groups responded differently to citalopram treatment. There was a reduction in MHPG in solely MD patients in response to citalopram treatment which could not be seen in PD+MD patients.

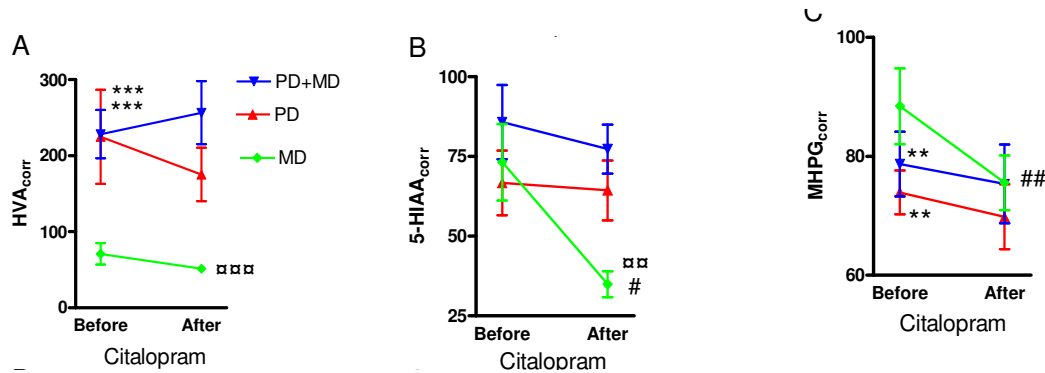


Fig 1 from paper IV

Corrected levels of the monoamine metabolites, (A) HVA, (B) 5-HIAA and (C) MHPG, in cerebrospinal fluid from Parkinson's disease (PD) patients with no major depression (MD), PD with MD (PD+MD) and solely MD patients. Baseline values were compared with one-way ANOVA followed by Newman Keul's test for pairwise comparisons: ** P<0.01; *** P<0.001 versus MD. Citalopram-treated MD patients with or without PD were also evaluated by two-way (treatment x diagnosis) ANOVA followed by Bonferroni's test for pairwise comparison. Citalopram treatment effects are indicated by # P<0.05; ## P<0.01 and diagnosis effect by αα P<0.01; ααα P<0.001.

Levels of BDNF, orexin-A, IL-6 and corticosterone

All monoamine-based antidepressants require some weeks of administration before they become clinically effective. It is unlikely that the enhanced monoaminergic transmission, *per se*, is antidepressant, but rather initiates cellular adaptations that ultimately lead to an antidepressant action. Indeed, depression is a multifactorial disease with changes in many different biochemical parameters not only involving monoamines. Stress hormones (e.g. cortisol and corticosterone), immune responses (e.g. interleukins), neurotrophic factors (e.g. BDNF, VEGF) and neuropeptides (e.g. SP, NPY, orexin) are also involved. We therefore studied the levels of some of these parameters in our patient groups.

There were no significant differences in the baseline levels of BDNF between any of the treatment groups. However, when also values from the citalopram treatment was included, there were lower levels of BDNF in PD+MD patients than solely MD patients (Fig 2).

Likewise, no significant differences were seen in the baseline levels of orexin-A between any of the treatment groups (Fig 2). However, a significant reduction of PD diagnosis was found when PD and PD+MD patients were pooled and compared with solely MD patients.

There were no significant differences in the baseline levels of IL-6 between the patient groups. However, when values both before and after citalopram treatment was evaluated there was a diagnosis effect. The diagnosis effect can be explained by the lower levels of IL-6 in PD+MD patients than solely MD patients seen both before and after treatment with citalopram.

Interestingly, the baseline levels of corticosterone differed between the studied groups and the corticosterone levels was significantly lower in PD + MD compared to solely MD patients (Fig 2).

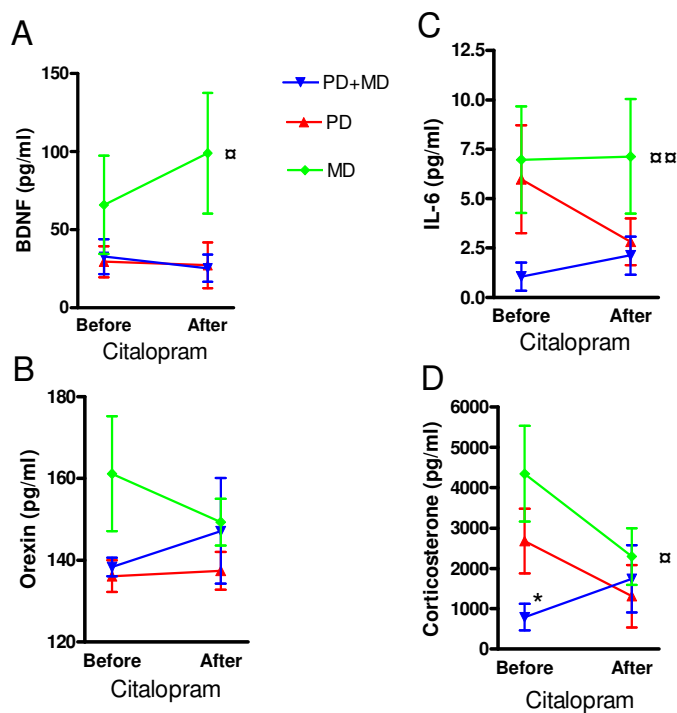


Fig 2 from paper IV

Levels in pg/ml of (A) BDNF, (B) orexin, (C) IL-6 and (D) corticosterone in cerebrospinal fluid from Parkinson's disease (PD) patients with no major depression (MD), PD with MD (PD+MD) and solely MD patients. Samples are taken at baseline and after 12 weeks. Note that solely MD patients and PD+MD patients, but not solely PD patients, received citalopram treatment during the 12 weeks of study. Baseline values were compared with one-way ANOVA followed by Newman Keul's test for pairwise comparisons: * $P < 0.05$ versus MD. Citalopram-treated MD patients with or without PD were also evaluated by two-way (diagnosis x treatment) ANOVA followed by Bonferroni's test for pairwise comparison. Diagnosis differences are indicated by □ $P < 0.05$; □□ $P < 0.01$.

Discussion:

This study has provided novel evidence that the biochemical composition of CSF in PD patients with concurrent MD differs from that of MD patients without PD with regards to monoamine metabolites, BDNF, IL-6 and corticosterone.

In accordance with previous work, the levels of the noradrenaline metabolite, MHPG, were lower in the PD+MD patients than in solely MD patients. In contrast to some previous reports (Mayeux, 1984, Kish, 2008), no difference in 5-HIAA levels was found between PD and PD+MD patients before treatment.

However, a difference in 5-HIAA concentration was found between PD+MD patients versus solely MD patients in response to treatment with citalopram. In agreement with previous studies in MD patients using various SSRIs, including citalopram and fluoxetine, citalopram reduced 5-HIAA levels in solely MD patients. This decrease in 5-HIAA is considered to be due to an increased autoinhibition of the firing of serotonin neurons by elevated extracellular levels of serotonin. Interestingly, we found no similar reduction of 5-HIAA levels after citalopram treatment in the PD patients with MD, indicating a different serotonin turnover after citalopram in PD+MD patients compared to solely MD patients. There are strong serotonin-noradrenaline interactions. It is therefore interesting that the regulation of MHPG after citalopram treatment mirrors that of 5-HIAA with a reduction in solely MD patients but not in PD+MD patients. Since the citalopram treatment was clinically effective not only in solely MD patients, but also in PD+MD patients, our data indicate that the regulation of MHPG and 5-HIAA does not correlate to clinical responsivity towards citalopram in depressed PD patients.

To find biochemical parameters in CSF that are characteristic for PD patients with MD and/or correlate to the clinical responsivity towards antidepressant treatment, we also studied the levels of BDNF, orexin-A, IL-6 and corticosterone. Our data show that BDNF levels were significantly lower in PD patients with MD compared to solely MD patients after treatment with citalopram, maybe an expression of more advanced neurodegeneration in the former group. However, there was no significant difference in the BDNF levels between these patient groups during citalopram treatment.

A previous study has reported reduced orexin-A in CSF from PD patients (Drouot, 2003). In the present study, we could only detect lower orexin-A when all PD patients, regardless whether they were depressed or not, were compared to solely MD patients. No significant effects on orexin-A was found after citalopram treatment

It is well-known that the stress response and the hypothalamic-pituitary-adrenal (HPA) axis is altered in depression, with a hyperactivity in MD patients.. Such changes are reflected in peripheral levels of cortisol and corticosterone and has consequences not only for brain function but also on the immune system. Here, we found that baseline corticosterone and IL-6 levels were significantly lower in PD+MD patients compared to solely MD patients indicating that the stress responses, HPA axis and/or neuroimmune systems may be differentially regulated in PD+MD and solely MD patients. The levels of corticosterone converged between PD+MD and solely MD patients after citalopram treatment, perhaps reflecting a favourable homeostatic response.

5. SUMMARY OF FINDINGS AND COMMENTS

Study I: Depressive illness in Parkinson's disease – indication of a more advanced and widespread neurodegenerative process?

PD patients with a comorbid Major Depression had more severe neurological symptoms than PD patients without depression, indicating an advanced and widespread neurodegenerative process. However, tremor as an initial symptom seemed to be more common in PD patients without a later depression, maybe reflecting a more favorable serotonergic activity.

Our findings favour the hypothesis that depression and PD to some extent are clinically different entities but with common central neurotransmissions pathways. Sleep disturbances is common in PD and could be overlooked as an expression of depression.

Study II: Treatment of major depression in Parkinson's disease improves depressive as well as motor symptoms – indicating a more extensive neurodegenerative process?

Treatment with a SSRI (citalopram) in PD patients with MD on stable dopaminergic therapy reduced the depressive symptoms at least as effective as in MD patients without PD. The antidepressive effect even seemed to occur earlier in the PD patients.

Furthermore, the PD symptoms of hypokinesia and rigidity as well as involuntary movements were reduced during treatment with citalopram. On the other hand, tremor increased during this treatment, possibly a result of increased serotonergic neurotransmission. The interaction between central serotonergic and dopamine systems and their clinical representations are stressed and discussed.

Study III: HMPAO SPECT in Parkinson's disease (PD) with major depression (MD) before and after antidepressant treatment

We have shown that the rCBF differs between PD patients with and without MD, as well as between MD patients with and without PD, both at baseline and regarding the response to treatment with SSRI (citalopram).

Most conspicuous findings in PD patients with MD were an increased rCBF fronto-parietally in an area symmetrically located on both sides and a decreased rCBF pre-occipitally and occipitally. Thus, larger cortical areas are involved in depressed PD patients with hyperactivity (reciprocal to basal degeneration in PD and maybe dopaminergic treatment) and with hypoactivity (probably due to organic lesions leading to hypoperfusion).

Interestingly, treatment with citalopram “normalizes” the mood-related abnormal rCBF pattern in both “only” MD and PD + MD patients, although in different ways: the mainly right frontal areas showing hypoperfusion initially in “only” MD have higher/increased rCBF after treatment, while all four areas with hyperactivity initially in PD + MD show lower/decreased rCBF after treatment with SSRI.

These observations indicate a more advanced and widespread neurodegenerative disorder in PD combined with MD.

Study IV: Monoamines, BDNF, IL-6 and corticosterone in CSF in patients with Parkinson's disease and major depression.

The major findings of this study are that PD patients with MD have significantly lower baseline levels of MHPG, corticosterone and IL-6 when compared to solely MD patients.

In response to citalopram treatment, patients with solely MD exhibited an expected decrease in 5-HIAA and MHPG levels which was not found in PD patients with MD. Moreover, the levels of BDNF and IL-6 were lower in PD + MD patients compared to solely MD patients after treatment with citalopram in both groups.

It appears that the biochemical basis and responsivity towards citalopram differs between PD patients with MD and MD patients without PD.

These biochemical data provide support that PD+MD patients have a differential stress responsivity and a more widespread neurodegeneration than solely MD patients.

6. General Conclusions

From the data presented in this thesis some general conclusions can be drawn:

- MD in PD is not as frequent in Sweden as has been reported in some studies conducted in other countries.
- PD patients with a comorbid MD had more severe neurological symptoms than PD patients without depression, indicating an advanced and widespread neurodegenerative process
- Treatment with a SSRI (citalopram) in PD patients with MD on stable dopaminergic therapy reduced the depressive symptoms at least as effective as in MD patients without PD. The antidepressive effect even seemed to occur earlier in the PD patients.
- The PD symptoms of hypokinesia and rigidity as well as involuntary movements were reduced during treatment with citalopram. On the other hand, tremor increased during this treatment, possibly a result of increased serotonergic neurotransmission.
- rCBF differs between PD patients with and without MD, as well as between MD patients with and without PD, both at baseline and regarding the response to treatment with citalopram.
- Treatment with citalopram “normalizes” the mood-related abnormal rCBF pattern in both “only” MD and PD + MD patients, although in different ways
- PD patients with MD have significantly lower baseline levels of MHPG, corticosterone and IL-6 when compared to solely MD patients.
- In response to citalopram treatment, patients with solely MD exhibited an expected decrease in 5-HIAA and MHPG levels which was not found in PD patients with MD. Moreover, the levels of BDNF and IL-6 were lower in PD + MD patients compared to solely MD patients after treatment with citalopram in both groups.

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10.APPENDIX

Appendix 1

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

Reference : Fahn S, Elton R, Members of the UPDRS Development Committee.

In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information 1987, pp 15 3-163, 293-304

<http://www.mdvu.org/library/ratingscales/pd/updrs.pdf>

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite

impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems.

Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression Thought Disorder

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (nonroutine) activities.

3 = Loss of initiative or disinterest in day to day (routine) activities.

3 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech

0 = Normal.

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

5 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

- 0 = Normal.
- 1 = Rare choking.
- 2 = Occasional choking.
- 3 = Requires soft food.
- 3 = Requires NG tube or gastrostomy feeding.

8. Handwriting

- 0 = Normal.
- 1 = Slightly slow or small.
- 2 = Moderately slow or small; all words are legible.
- 3 = Severely affected; not all words are legible.
- 4 = The majority of words are not legible.

9. Cutting food and handling utensils

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can cut most foods, although clumsy and slow; some help needed.
- 3 = Food must be cut by someone, but can still feed slowly.
- 4 = Needs to be fed.

10. Dressing

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Occasional assistance with buttoning, getting arms in sleeves.
- 3 = Considerable help required, but can do some things alone.
- 4 = Helpless.

11. Hygiene

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Needs help to shower or bathe; or very slow in hygienic care.
- 3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
- 4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can turn alone or adjust sheets, but with great difficulty.
- 3 = Can initiate, but not turn or adjust sheets alone.
- 4 = Helpless.

13. Falling (unrelated to freezing)

- 0 = None.
- 1 = Rare falling.
- 2 = Occasionally falls, less than once per day.
- 3 = Falls an average of once daily.
- 4 = Falls more than once daily.

14. Freezing when walking

- 0 = None.
- 1 = Rare freezing when walking; may have start hesitation.
- 2 = Occasional freezing when walking.
- 3 = Frequent freezing. Occasionally falls from freezing.
- 4 = Frequent falls from freezing.

15. Walking

- 0 = Normal.
- 1 = Mild difficulty. May not swing arms or may tend to drag leg.
- 2 = Moderate difficulty, but requires little or no assistance.
- 3 = Severe disturbance of walking, requiring assistance.
- 4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Moderate; bothersome to patient.
- 3 = Severe; interferes with many activities.
- 4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism

- 0 = None.
- 1 = Occasionally has numbness, tingling, or mild aching.
- 2 = Frequently has numbness, tingling, or aching; not distressing.
- 3 = Frequent painful sensations.
- 4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech

- 0 = Normal.
- 1 = Slight loss of expression, diction and/or volume.
- 2 = Monotone, slurred but understandable; moderately impaired.
- 3 = Marked impairment, difficult to understand.
- 4 = Unintelligible.

19. Facial Expression

- 0 = Normal.
- 1 = Minimal hypomimia, could be normal "Poker Face".
- 2 = Slight but definitely abnormal diminution of facial expression
- 3 = Moderate hypomimia; lips parted some of the time.
- 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
- 3 = Moderate in amplitude and present most of the time.
- 4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

- 0 = Absent.
- 1 = Slight; present with action.
- 2 = Moderate in amplitude, present with action.
- 3 = Moderate in amplitude with posture holding as well as action.
- 4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

- 0 = Absent.
- 1 = Slight or detectable only when activated by mirror or other movements.
- 2 = Mild to moderate.
- 3 = Marked, but full range of motion easily achieved.
- 4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally,

with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least

3 inches.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

0 = Normal.

1 = Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient

erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)

- 0 = None
- 1 = 1-25% of day.
- 2 = 26-50% of day.
- 3 = 51-75% of day.
- 4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)

- 0 = Not disabling.
- 1 = Mildly disabling.
- 2 = Moderately disabling.
- 3 = Severely disabling.
- 4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?

- 0 = No painful dyskinesias.
- 1 = Slight.
- 2 = Moderate.
- 3 = Severe.
- 4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)

- 0 = No
- 1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?

- 0 = No
- 1 = Yes

37. Are "off" periods unpredictable?

- 0 = No
- 1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?

- 0 = No
- 1 = Yes

39. What proportion of the waking day is the patient "off" on average?

- 0 = None
- 1 = 1-25% of day.
- 2 = 26-50% of day.
- 3 = 51-75% of day.
- 4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?

- 0 = No
- 1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

- 0 = No
- 1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

- 0 = No
- 1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING

Reference: Hoehn M, Yahr M. Parkinsonism: Onset, progression and mortality. Neurology 1967. 17:427-42.

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal.

Unaware of any difficulty.

90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment.

Might

take twice as long. Beginning to be aware of difficulty.

80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% = Not completely independent. More difficulty with some chores. Three to four times as long in some.

Must spend

a large part of the day with chores.

60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% = More dependent. Help with half, slower, etc. Difficulty with everything.

40% = Very dependent. Can assist with all chores, but few alone.

30% = With effort, now and then does a few chores alone or begins alone. Much help needed.

20% = Nothing alone. Can be a slight help with some chores. Severe invalid.

10% = Totally dependent, helpless. Complete invalid.

0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

Appendix 2

Webster's Parkinson's Disease Rating Scale (WPDRS)

Reference: Webster DD. Critical analysis of the disability in Parkinson's Disease. Mod Treatment 1968. 5:257-82.

This scale was developed as a simple rating scale that can be used to evaluate the degree of total parkinsonian disabilities. It applies a gross clinical rating to each of the 10 listed items, assigning value rating of 0–3 for each item, where 0 = no involvement and 1, 2, and 3 are equated to early, moderate, and severe disease, respectively. Scores range from 0 to 30, and decline represents decrease in severity of PD signs. Values of 1 to 10 indicate early illness; 11 to 20, moderate disability; and 21 to 30, severe or advanced disease.

1. Bradykinesia of Hands - Including Handwriting

0 = No involvement.

1 = Detectable slowing of the supination-pronation rate, evidenced by beginning difficulty in handling tools, buttoning clothes, and with handwriting.

2 = Moderate slowing of supination-pronation rate, one or both sides, evidenced by moderate impairment of hand function. Handwriting is greatly impaired, micrographia present.

3 = Severe slowing of supination-pronation rate. Unable to write or button clothes. Marked difficulty in handling utensils.

2. Rigidity

0 = Non-detectable.

1 = Detectable rigidity in neck and shoulders. Activation phenomenon is present. One or both arms show mild, negative, resting rigidity.

2 = Moderate rigidity in neck and shoulders. Resting rigidity is positive when patient not on medication.

3 = Severe rigidity in neck and shoulders. Resting rigidity cannot be reversed by medication.

3. Posture

0 = Normal posture. Head flexed forward less than 4 inches.

1 = Beginning poker spine. Head flexed forward up to 5 inches.

2 = Beginning arm flexion. Head flexed forward up to 6 inches. One or both arms raised but still below waist.

3 = Onset of simian posture. Head flexed forward more than 6 inches. One or both hands elevated above the waist. Sharp flexion of hand, beginning interphalangeal extension. Beginning flexion of knees.

4. Upper Extremity Swing

0 = Swings both arms well.

1 = One arm definitely decreased in amount of swing.

2 = One arm fails to swing.

3 = Both arms fail to swing.

5. Gait

0 = Steps out well with 18–30 inch stride. Turns about effortlessly.

1 = Gait shortened to 12–18 inch stride. Beginning to strike one heel. Turn around time slowing. Requires several steps.

2 = Stride moderately shortened - now 6–12 inches. Both heels beginning to strike floor.

3 = Onset of shuffling gait, steps less than 3 inches. Occasional stuttering-type or blocking gait. Walks on toes-turns around very slowly.

6. Tremor

0 = No detectable tremor found.

1 = Less than one inch of peak-to-peak tremor movement observed in limbs or head at rest or in either hand while walking or during finger to nose testing.

2 = Maximum tremor envelope fails to exceed 4 inches. Tremor is severe but not constant and patient retains some control of hands.

3 = Tremor envelope exceeds 4 inches. Tremor is constant and severe. Patient cannot get free of tremor while awake unless it is a pure cerebellar type. Writing and feeding himself is impossible.

7. Facies

0 = Normal. Full animation. No stare

1 = Detectable immobility. Mouth remains closed. Beginning features of anxiety or depression.

2 = Moderate immobility. Emotion breaks through at markedly increased threshold. Lips parted some of the time. Moderate appearance of anxiety or depression. Drooling may be present.

3 = Frozen facies. Mouth open ¼ inches or more. Drooling may be severe.

8. Seborrhea

0 = None.

1 = Increased perspiration, secretion remaining thin.

2 = Obvious oiliness present. Secretion much thicker.

3 = Marked seborrhea, entire face and head covered by thick secretion.

9. Speech

0 = Clear, loud, resonant, easily understood.

1 = Beginning of hoarseness with loss of inflection and resonance. Good volume and still easily understood.

2 = Moderate hoarseness and weakness. Constant monotone, unvaried pitch. Beginning of dysarthria, hesitancy, stuttering, difficult to understand.

3 = Marked harshness and weakness. Very difficult to hear and to understand.

10. Self-Care

0 = No impairment.

1 = Still provides full self-care but rate of dressing definitely impeded. Able to live alone and often still employable.

2 = Requires help in certain critical areas, such as turning in bed, rising from chairs, etc. Very slow in performing most activities but manages by taking much time.

3 = Continuously disabled. Unable to dress, feed himself, or walk alone.

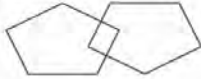
Appendix 3

Mini Mental Status examination (MSSE)

Reference:

Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: A practical method for grading the state of patients for the clinician. *J Psychiat Res* 1975. 12:189-98.

Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. *Hosp Pract*. 1987;22(1A):99, 103, 106, 110.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

Appendix 4

DSM IV

Reference: American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th edition. Washington, DC: American Psychiatric Association, 1994.

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Major Depressive Episode

Single Episode

A. Presence of a single Major Depressive Episode

B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode.

Note: This exclusion does not apply if all the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

Recurrent

A. Presence of two or more Major Depressive Episodes.

Note: To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.

B. The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects or a general medical condition.

Appendix 5

Hamilton Rating Scale for Depression (HAM D-17)

Reference: Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.

Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:276-96.

1. Depressed mood (Sad, hopeless, helpless, worthless)

0 = Absent

1 = Gloomy attitude, pessimism, hopelessness

2 = Occasional weeping

3 = Frequent weeping

4 = Patient reports highlight these feelings states in his/her spontaneous verbal and non-verbal communication.

2. Feelings of guilt

0 = Absent

1 = Self-reproach, feels he/she has let people down

2 = Ideas of guilt or rumination over past errors or sinful deeds

3 = Present illness is punishment

4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations. Delusions of guilt.

3. Suicide

0 = Absent

1 = Feels life is not worth living

2 = Wishes he/she were dead, or any thoughts of possible death to self

3 = Suicide, ideas or half-hearted attempt

4 = Attempts at suicide (any serious attempt rates 4)

4. Insomnia, initial

0 = No difficulty falling asleep

1 = Complaints of occasional difficulty in falling asleep i.e. more than half-hour

2 = Complaints of nightly difficulty falling asleep

5. Insomnia, middle

0 = No difficulty

1 = Patient complains of being restless and disturbed during the night

2 = Walking during the night – any getting out of bed rates 2 (except voiding bladder)

6. Insomnia, delayed

0 = No difficulty

1 = Waking in the early hours of the morning but goes back to sleep

2 = Unable to fall asleep again if he/she gets out of bed

7. Work and Interests

0 = No difficulty

1 = Thoughts and feelings of incapacity related to activities: work or hobbies

2 = Loss of interest in activity – hobbies or work – either directly reported by patient or indirectly seen in listlessness, in decisions and vacillation (feels he/she has to push self to work or activities)

3 = Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities

4 = Stopped working because of present illness. In hospital rate 4 if patient engages in no activities except supervised ward chores

8. Retardation (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

- 0 = Normal speech and thought
- 1 = Slight retardation at interview
- 2 = Obvious retardation at interview
- 3 = Interview difficult
- 4 = Interview impossible

9. Agitation

- 0 = None
- 1 = Fidgetiness
- 2 = Playing with hands, hair, obvious restlessness
- 3 = Moving about; can't sit still
- 4 = Hand wringing, nail biting, hair pulling, biting of lips, patient is on the run

10. Anxiety, psychic

- 0 = No difficulty
- 1 = Subjective tension and irritability
- 2 = Worrying about minor matters
- 3 = Apprehensive attitude apparent in face or speech
- 4 = Fears expressed without questioning

11. Anxiety, somatic (Physiological concomitants of anxiety) such as:

- gastrointestinal: dry mouth, wind, indigestion, diarrhea, cramps, belching
- cardiovascular: palpitations, headaches
- respiratory: hyperventilation, sighing
- urinary frequency
- sweating

- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Incapacitating

12. Somatic symptoms: gastro-intestinal

- 0 = None
- 1 = Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen
- 2 = Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms

13. Somatic symptoms: general

- 0 = None
- 1 = Heaviness in limbs, back or head; backaches, headaches, muscle aches, loss of energy, fatigability
- 2 = Any clear-cut symptom rates 2

14. Genital Symptoms (Symptoms such as: loss of libido, menstrual disturbances)

- 0 = Absent
- 1 = Mild
- 2 = Severe

15. Hypochondriasis

- 0 = Not present
- 1 = Self-absorption (bodily)
- 2 = Preoccupation with health
- 3 = Strong conviction of some bodily illness
- 4 = Hypochondriac delusions

16. Loss of Weight (Rate either 'A' or 'B')

A. When rating by history:

- 0 = No weight loss
- 1 = Probable weight loss associated with present illness
- 2 = Definite (according to patient) weight loss

B. Actual weight changes (weekly):

- 0 = Less than 1 lb (0.5 kg) weigh loss in one week
- 1 = 1-2 lb (0.5 kg-1.0 kg) weight loss in week
- 2 = Greater than 2 lb (1 kg) weight loss in week
- 3 = Not assessed

17. Loss of Insight

- 0 = Acknowledges being depressed and ill
- 1 = Acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc.
- 2 = Denies being ill at all

Appendix 6

Montgomery Asberg Depression Rating Scale (MADRS)

Reference: Montgomery SA, Åsberg M. A new depression scale, designed to be sensitive to change. Br J Psychiatry 1979; 134:382–9.

1 - APPARENT SADNESS - *Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.*

- 0 No sadness
- 1
- 2 Looks dispirited but does brighten up without difficulty
- 3
- 4 Appears sad and unhappy most of the time
- 5
- 6 Looks miserable all the time. Extremely despondent.

2 - REPORTED SADNESS - *Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.*

- 0 Occasional sadness in keeping with the circumstances.
- 1
- 2 Sad or low but brightens up without difficulty.
- 3
- 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
- 5
- 6 Continuous or unvarying sadness, misery or despondency.

3 - INNER TENSION - *Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.*

- 0 Placid. Only fleeting inner tension.
- 1
- 2 Occasional feelings of edginess and ill-defined discomfort
- 3
- 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
- 5
- 6 Unrelenting dread or anguish. Overwhelming panic.

4 - REDUCED SLEEP - *Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.*

- 0 Sleeps as usual.
 - 1
 - 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep
 - 3
 - 4 Sleep reduced or broken by at least two hours.
 - 5
 - 6 Less than two or three hours sleep.
-

5 - REDUCED APPETITE - *Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.*

- 0 Normal or increased appetite.
- 1
- 2 Slightly reduced appetite
- 3
- 4 No appetite. Food is tasteless.
- 5
- 6 Needs persuasion to eat at all.

6 - CONCENTRATION DIFFICULTIES - *Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.*

- 0 No difficulties in concentrating.
- 1
- 2 Occasional difficulties in collecting one's thoughts.
- 3
- 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- 5
- 6 Unable to read or converse without great difficulty.

7 - LASSITUDE - *Representing a difficulty getting started or slowness initiating and performing everyday activities.*

- 0 Hardly any difficulties in getting started. No sluggishness.
- 1
- 2 Difficulties in starting activities.
- 3
- 4 Difficulties in starting simple routine activities, which are carried out with effort.
- 5
- 6 Complete lassitude. Unable to do anything without help.

8 - INABILITY TO FEEL - *Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.*

- 0 Normal interest in the surroundings and in other people.
- 1
- 2 Reduced ability to enjoy usual interests.
- 3
- 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- 5
- 6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9 - PESSIMISTIC THOUGHTS - *Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.*

- 0 No pessimistic thoughts.
- 1
- 2 Fluctuating ideas of failure, self-reproach or self-depreciation.
- 3

- 4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
- 5
- 6 Delusions of ruin, remorse and unredeemable sin. Self-accusations which are absurd and unshakable.

10 - SUICIDAL THOUGHTS - *Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide. Suicidal attempts should not in themselves influence the rating.*

- 0 Enjoys life or takes it as it comes.
- 1
- 2 Weary of life. Only fleeting suicidal thoughts.
- 3
- 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- 5
- 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Appendix 7

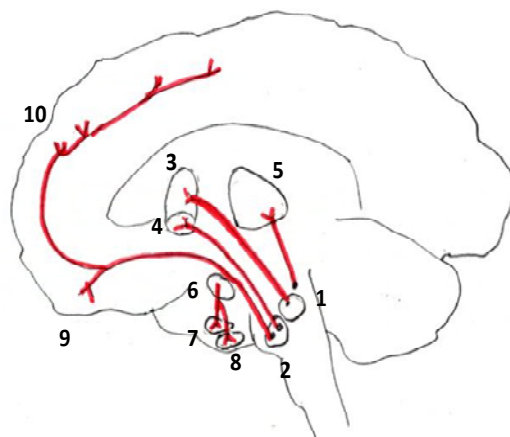


Fig the major Dopamine pathways

1. SN = substantia nigra. 2. VTA = ventral tegmental area. 3. Striatum. 4. NA= nucleus accumbens. 5. Thalamus. 6. Hypothalamus. 7. Amygdala 8. Hippocampus. Prefrontal cortex with 9. VMFC = ventromedial prefrontal cortex. 10. DLPFC = dorsolateral prefrontal cortex.

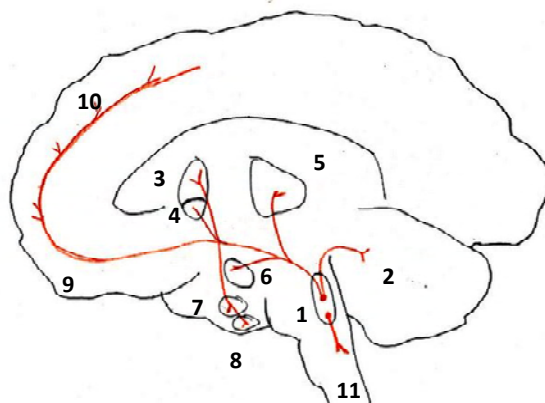


Fig major serotonergic projections

1. The upper rostral nuclei; dorsal and medial raphe, n linearis and raphe pontis
 2. Cerebellum 3. Striatum 4. n accumbens 5. Thalamus 6. Hypothalamus 7. Amygdala 8. Hippocampus 9. VMFC = ventromedial prefrontal cortex 10. DLPFC = dorsolateral prefrontal cortex 11. spinal cord

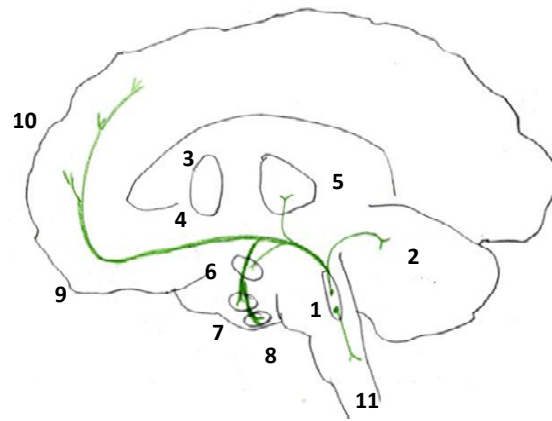


Fig major norepinehrine pathways

1. LC = locus coeruleus. 2.Cerebellum 3. Striatum 4. Nucleus accumbens 5. Thalamus 6. Hypothalamus 7. Amygdala 8. Hippocampus 9. VMFC = ventromediala prefrontala cortex 10. DLPFC = dorsolateral prefrontal cortex 11. spinal cord

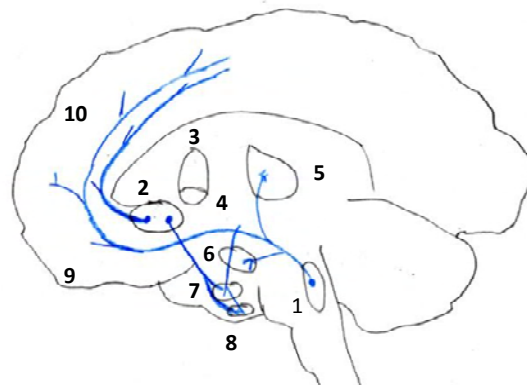


Fig Major acetylcholine projections via brainstem and basal forebrain

1. Brainstem 2. BF= basal forebrain with a complex of basal nucleus , n basalis of Meynert 3. Striatum 4. Nucleus accumbens 5. Thalamus 6. Hypothalamus 7. Amygdala 8. Hippocampus 9. VMFC=ventromedial prefrontal cortex 10. DLPFC = dorsolateral prefrontal cortex