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Functional and structural brain correlates of memory and verbal functions

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Psychology
Department of Psychology and Logopedics
Abo Akademi University
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Supervised by

Docent Mira Karrasch, PhD, Clinical Neuropsychologist
Department of Psychology and Logopedics
Abo Akademi University
Finland

Reviewed by

Dr. Jaime Kulisevsky, MD, PhD
Associate Professor of Neurology
Universitat Autònoma de Barcelona
Director at the Institute of Biomedical Research
Sant Pau Hospital, Barcelona
Spain

Professor Kathy Dujardin, PhD
Professor in Neurosciences
Neurology and Movement Disorders Department
Lille University Medical Center
France

Opponent

Dr. Jaime Kulisevsky, MD, PhD
Associate Professor of Neurology
Universitat Autònoma de Barcelona
Director at the Institute of Biomedical Research
Sant Pau Hospital, Barcelona
Spain

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To Birgit & Erik, and to all who are affected by Parkinson's disease

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SWEDISH SUMMARY-SVENSK SAMMANFATTNING

Parkinsons sjukdom är en neurodegenerativ sjukdom som numera är känd för att ha betydande effekter på den kognitiva funktionsförmågan. Emedan Parkinson-demens (PDD) och Parkinson-mild kognitiv svikt (PD-MCI) nyligen har blivit etablerade koncept, har de tidigaste kognitiva symptomen och deras neurala korrelat uppmärksammats sparsamt trots att det är känt att kognitiv funktionsnedsättning existerar under hela sjukdomsförloppet.

Syftet med föreliggande avhandling var att studera kognitiva funktioner och deras neurala bakgrund hos icke-dementa, medicinerade Parkinsonpatienter i ett tidigt stadium av sjukdomen. Specifika kognitiva uppgifter studerades i relation till elektrofysiologiska (EEG) och strukturella (MRI) hjärnavbildningsmetoder. Studien fokuserade på olika aspekter av minne och verbala funktioner, eftersom dessa har associerats med cortikal degeneration och demens vid Parkinsons sjukdom. De studerade minnesaspekterna var inkodning och retention under en korttidsminnesuppgift samt fri minnesretention i en incidentell och en intentionell kontext. Verbala funktioner studerades med semantiska, fonemiska och alternerande ordfluensuppgifter. I **Studie I** mättes händelserelaterade modulationer (ERD/ERS) i elektrofysiologiska responser under en korttidsminnes-/igenkänningsuppgift. Resultaten påvisade avvikande oscillatorisk aktivitet hos Parkinsonpatienter under minnesinkodningsfasen i uppgiften. Inkodning av auditiv information framkallade inte alfasynkronisering (ERS) i bakre delar av hjärnbarken i patientgruppen. I patientgruppen fattades också en pre-stimulus alfasynkronisering som observerades i kontrollgruppen. Frånvaron av specifika elektrofysiologiska responser kan tolkas som en neural manifestation av subtila minnesinkodningsproblem, möjligen innefattande komponenter av abnormal inhibitorisk kontroll. **Studie II** visade att patientgruppen presterade sämre än kontrollgruppen i fri minnesretention oavsett om inkodningskontexten var intentionell eller incidentell. Sämre minnesprestationer var relaterade till kognitiv/psykomotorisk långsamhet, men inte till attentiv/exekutiv belastning. Patientgruppen uppvisade också mera subjektiva minnesproblem än kontrollgruppen. Subjektiva minnesproblem var inte relaterade till minnesprestationer, och kan därför reflektera en metakognitiv medvetenhet om generella funktionshinder som härstammar från flera andra kognitiva domäner. **Studie III** visade att sämre prestationer i en incidentell minnesuppgift var associerade med förminskad volym av grå hjärnmassa i höger parietallob i patientgruppen. Sedvanliga intentionella visuella och verbala minnesuppgifter var inte relaterade till hjärnvolym. Eftersom både cortikala och subcortikala neurala

nätverk antas medverka i både intentionell och incidentell minnesprocessering, behövs fortsatta studier för att klargöra sambandet mellan strukturell degeneration och försämrad fri minnesretention hos patienter som är i ett tidigt skede av Parkinsons sjukdom. **Studie IV** visade att fonemisk, men inte semantisk eller alternerande ordfluens, var relaterad till hjärnvolym i patientgruppen. De associerade hjärnstrukturerna fanns i högra svanskärnan (nucleus caudatus). Över hela gruppen fanns ett samband mellan sämre semantisk fluens och förminskad vänster parietal hjärnvolym, samt på trendnivå bilateralt mindre cerebellumvolym. På behavioral nivå presterade patientgruppen sämre än kontrollgruppen endast i den alternerade ordfluensuppgiften. Resultaten tyder på att olika ordfluensuppgifter är relaterade till olika neurala substrat och att alternerande ordfluens är mera försämrad än semantisk och fonemisk fluens vid tidig Parkinsons sjukdom.

Centrala resultat:

- Parkinsonpatienter påvisar abnormala ERD/ERS-responser under minnesinkodning, vilket kan reflektera subtila inkodningsproblem.
- Parkinsonpatienter har försämrad fri minnesretention oavsett intentionalitet under minnesinkodning, vilket kan reflektera en generell försämring i fri retention.
- Höger parietal cortikal volym är relaterad till försämrad fri retention vid tidig Parkinsons sjukdom, men endast under incidentella inkodningsbetingelser med visuellt material.
- Parkinsonpatienter har försämrad alternerande fluens, men endast fonemisk, inte semantisk eller alternerande fluens, är relaterad till höger caudatus volymreduktion.
- Studien påvisar neurala manifestationer av både subtila och objektivt mätbara förändringar i minnes- och verbala funktioner redan hos icke-dementa, medicinerade patienter i ett tidigt skede av Parkinsons sjukdom. De preliminära resultaten bör etableras i fortsatta studier med större sampel.

Nyckelord: Parkinsons sjukdom, minne, fri retention, incidentellt minne, verbal fluens, EEG, ERD/ERS, MRI, VBM

ABSTRACT

Parkinson's disease (PD) is a multisystem neurodegenerative disorder, which has been acknowledged to have significant impact on cognitive functioning. Whilst Parkinson's disease dementia (PDD) and Parkinson's disease mild cognitive impairment (PD-MCI) have recently become established concepts, the earliest neuropsychological symptoms and their neural correlates have received little attention although cognitive impairment is known to affect patients throughout the course of the disease.

The general aim of this thesis was to study cognitive functions and their neural basis in early-stage, non-demented, medicated PD patients. Specific cognitive tasks were examined in combination with electrophysiological (EEG) and structural brain imaging (MRI) methods. The main interest was different aspects of memory and verbal functioning. These functions have been associated with cortical degeneration and dementia in PD. The memory components of interest were short-term memory encoding and retrieval, as well as free recall in incidental and intentional task conditions. The verbal tasks of interest were semantic, phonemic, and alternating fluency. **Study I** showed that PD patients exhibited abnormal brain oscillatory activity (as measured by ERD/ERS modulations of the EEG) during the encoding phase of a working memory/recognition memory task. Encoding of auditory information did not elicit posterior alpha ERS in PD patients. A pre-stimulus alpha ERS seen in the control group was also absent in the PD group. Absent responses in PD patients may be a neural manifestation of covert memory encoding impairment, possibly comprising components of abnormal inhibitory control. **Study II** showed that PD patients were impaired on immediate free recall regardless of the intentionality of the encoding condition. Recall performances were associated with cognitive/psychomotor slowing, and not with attentive/executive task demands. PD patients also had more subjective memory complaints than controls. Complaints were not related to memory performances, thus memory complaints may reflect metacognitive awareness of general impairment stemming from mild deficits in several cognitive domains. **Study III** showed that worse free recall on an incidental visual memory task was associated with reduced right parietal gray matter volume in PD patients. Conventional, intentional visual and verbal memory tasks were not associated with gray matter volumes. Whilst both cortical and subcortical neural networks are believed to be involved in both intentional and incidental memory in healthy humans, further studies are needed to establish the role of brain volumetric degeneration in free recall deficits in early PD. **Study IV** showed that phonemic

fluency, but not semantic or alternating fluency, was related to brain gray matter volume in PD patients. The associated volume reductions were located in the right caudate. Worse semantic fluency was related to smaller left parietal gray matter volume and at trend level to smaller bilateral cerebellar gray matter volume over the whole group. On the behavioral level, PD patients performed worse than controls only on the alternating fluency task. The results indicate that different verbal fluency tasks are related to different neural substrates, and that alternating fluency is more impaired than semantic and phonemic fluency in early-stage, non-demented PD.

Principal findings:

- PD patients have abnormal ERD/ERS responses during memory encoding, possibly reflecting covert memory encoding deficits.
- PD patients are impaired on free recall irrespective of the intentionality of encoding, possibly reflecting a general free recall deficit.
- Right parietal cortical gray matter volume is related to free recall memory deficits in PD, but only in conditions not involving an intention to memorize visual items.
- PD patients are impaired on alternating fluency, but only phonemic fluency, not alternating or sematic fluency, is related to right caudate gray matter volume reduction.
- These findings reveal subtle neural manifestations of overt and covert dysfunctions in memory and verbal functioning in early-stage, non-demented and medicated PD patients. The preliminary results need to be established in further studies with larger samples.

Keywords: Parkinson's disease, memory, free recall, incidental memory, verbal fluency, EEG, ERD/ERS, MRI, VBM

ABBREVIATIONS

AD	Alzheimer's disease
BDI	Beck Depression Index
EEG	Electroencephalogram
ERD	Event-related desynchronization
ERP	Event-related potential
ERS	Event-related synchronization
GDS-15	Geriatric Depression Scale, 15 item short form
H&Y stage	Disease severity staging according to Hoehn & Yahr
L-dopa	Levodopa
LEDD	Levodopa equivalent daily dose
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PD-MCI	Parkinson's disease mild cognitive impairment
TMT	Trail Making Test
TFR	Time-frequency representations
VBM	Voxel-based morphometry
UPDRS-III	Unified Parkinson's Disease Rating Scale motor section
CFQ	Cognitive Failures Questionnaire

1 INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease affecting the elderly population (Schapira, 2009). The essential pathophysiological process involves the gradual loss of dopaminergic neurons in deep midbrain structures. Dopaminergic pathways connecting the basal ganglia with different regions of the brain are disrupted, resulting in a complex symptom picture including motor and cognitive symptoms (Obeso et al., 2008). Multifocal lesions also occur in nondopaminergic systems, including Lewy body pathology resulting from the deposition of the protein marker α-synuclein (Jellinger, 2012). The cardinal motor symptoms (tremor, rigidity, akinesia, postural impairments) are the most visible and best recognized, and they respond well to dopamine replacement treatments (mainly levodopa, L-dopa) (Ferreira et al., 2013; Jankovic, 2008). There is insufficient information on treatment effects on cognition, and reported effects have been mixed and mostly modest (Seppi et al., 2011). The etiology of dopaminergic neuronal degeneration is unknown, thus no treatment is yet available to prevent or to reverse the disease process.

In recent years, it has been widely recognized that PD comprises progressive cognitive and neuropsychiatric symptoms, which eventually result in PD dementia (PDD) in a vast majority of patients (Aarsland & Kurz, 2010; Hely, Reid, Adena, Halliday, & Morris, 2008). The neuropathological mechanisms underlying cognitive impairment and dementia are not well understood, but cortical Lewy pathology and Alzheimer's disease (AD) related changes have been proposed to contribute to cognitive decline (Jellinger, 2012). The publication of Movement Disorders Society (MDS) Task Force diagnostic criteria for PDD (Emre et al., 2007) has initiated extensive research covering the nature and progression of the neurocognitive deficits in PD, providing emerging evidence of non-dopaminergic systems involvement in cognitive decline. Structural and functional brain imaging evidence suggests that PDD is associated with widespread cortical and hippocampal atrophy (Weintraub et al., 2011) as well as abnormal electrophysiological brain responses (Klassen et al., 2011). The MDS recommendations have recently been extended to include PD mild cognitive impairment (PD-MCI) (Litvan et al., 2012), which may represent a transitional state between normal cognition and dementia.

It has become increasingly apparent that the study of cognition at different disease stages is essential for the understanding of the full neurocognitive trajectory of PD. Based on findings from cross-sectional studies, it has been estimated that

approximately 27% of all PD patients have PD-MCI (Aarsland et al., 2010; Litvan et al., 2011) and that approximately 30% have PDD (Aarsland, Zaccai, & Brayne, 2005). Longitudinal studies have been scarce, but it has been estimated that after 10 years approximately 75-80% eventually develop PDD (Aarsland & Kurz, 2010; Hely et al., 2008). More specific subtyping of cognitive phenotypes has identified five clinical presentations ranging from no cognitive impairment (19%), no impairment but slight mental slowing (41%), moderate impairment in most cognitive domains except recognition memory and visual ability (13%), severe cognitive impairment in all domains including mental slowing (24%), and very severe overall cognitive impairment (2.5%) (Dujardin et al., 2013). Cognitive performance may vary as a consequence of age, education, apathy (Dujardin et al., 2013), the presence of visual hallucinations (Hobson & Meara, 2004), or REM sleep disorders (Gagnon et al., 2009). Risk factors associated with PDD have been reported to be older age, akinetic-rigid motor type and axial symptoms, and cognitive impairment at early stages (Emre et al., 2007).

1.1 Cognitive impairment in early-stage PD

Despite a lively research interest in cognitive impairment in the mid- and late stages of PD, the earliest neurocognitive changes have received little attention. Cognitive deficits have, however, been reported to be present throughout the course of PD. At the initial stages, patients themselves may report difficulties in maintaining attention and performing simultaneous operations, word-finding problems, and difficulties in the recollection of recent episodic events (Pagonabarraga & Kulisevsky, 2012). Objectively measurable impairments in memory, executive functioning, psychomotor speed, visuospatial functioning, and specific aspects of language functioning have been reported in large, newly diagnosed cohorts (Muslimovic, Post, Speelman, & Schmand, 2005). Impairments in executive functions, as well as working memory and attention, have been suggested to be the earliest and most evident neuropsychological symptoms, and they have been proposed to reflect functional changes in fronto-striatal circuits (Kehagia, Barker, & Robbins, 2010). Some aspects of the early dysexecutive syndrome, such as selective attention, cognitive flexibility, planning ability, working memory, and visuospatial processing have been reported to become alleviated by dopaminergic medication (Kulisevsky et al., 2000; Macdonald & Monchi, 2011). However, others have found positive medication effects only on simple attention tasks, suggesting a non-dopaminergic pathology underlying impairment on more complex attentive/executive tasks (Hanna-Pladdy, Jones, Cabanban, Pahwa, & Lyons, 2013).

It has been suggested that cognitive impairment with posterior-cortical basis may be more vulnerable to rapid cognitive decline than frontal-based executive impairment (Pagonabarraga & Kulisevsky, 2012). Longitudinal data on the symptom progression beginning from the earliest stages in PD has implied that initially impaired semantic fluency and figure copying performances predict dementia, while frontally based tasks such as phonemic fluency are not associated with dementia risk (Williams-Gray et al., 2009).

1.1.1 Memory impairment

While severe temporal lobe-dependent memory consolidation problems (forgetting what one has learned after a delay) resembling the hallmark symptoms of Alzheimer's disease (AD) are rarely reported in early-stage PD, impairments in immediate and delayed free recall are frequent (Brønnick, Alves, Aarsland, Tysnes, & Larsen, 2011; Elgh et al., 2009; Muslimovic et al., 2005). When compared to impairments in other cognitive domains (language, performance on simple attention tasks, and visuospatial function), free recall memory impairment has been reported to be of the largest magnitude (Hanna-Pladdy et al., 2013; Muslimovic et al., 2005). Findings from studies with drug-naïve patients have suggested that the memory impairment is due to a deficit of encoding/learning rather than a deficit of retrieval (Brønnick et al., 2011). Impaired free recall performances have also been suggested to be mediated by primary working memory deficits (Higginson et al., 2003), which may hinder encoding (Lewis, Slabosz, Robbins, Barker, & Owen, 2005). In early-stage PD, neither episodic memory nor all working memory performances seem to be improved by dopaminergic treatment (Hanna-Pladdy et al., 2013), suggesting non-dopaminergic involvement also in early-stage memory impairment.

The neural background and evolution of the free recall impairment in PD has been sparsely studied. In contrast to the structural changes in the hippocampal and entorhinal cortex corresponding to early memory decline in AD (Reiman & Jagust, 2012), the pathology in early PD initially involves brainstem nuclei and other subcortical structures (Braak et al., 2003). It has been suggested, that recall deficits in PD may be due to impairments both in encoding, related to structural degeneration of the hippocampus and temporo-parietal cortex, as well as to retrieval, which in turn is believed to be associated with dysfunctions in striatal-cortical connections (Ibarretxe-Bilbao, Junque, Marti, & Tolosa, 2011; Weintraub et al., 2011; Weintraub, Moberg, Culbertson, Duda, & Stern, 2004). It is not entirely clear how and when the suggested fronto-striatal dysexecutive free recall deficit turns into a cortical free recall

deficit, and the issue remains unresolved until explanatory functional and structural information from patients at all disease stages is available. However, in many recent structural imaging studies on PD, memory has been addressed as a uniform concept not taking into account the differences between separate memory processes and their underlying neural substrates. Thus, it remains to be established whether distinct memory processes such as encoding and retrieval might be differently affected in early PD, and whether their structural correlates are different at different disease stages. Structural imaging techniques are, however limited to the measurement of static structural correlates of the memory outcome (for instance recall success), and are therefore not optimal for capturing ongoing 'on-line' processes occurring during encoding.

1.1.2 Verbal fluency impairment

Verbal fluency impairments are also among the earliest and most common cognitive deficits in PD (Henry & Crawford, 2004b; Muslimovic et al., 2005) and semantic fluency impairment has been associated with an increased risk of dementia (Evans et al., 2011; Williams-Gray et al., 2009). Semantic fluency (words belonging to a semantic category, often animals) has in general been reported to be more impaired than phonemic fluency (words beginning with a specific letter) in PD (Henry & Crawford, 2004b; Koerts et al., 2013), although some studies with non-demented PD patients have reported reverse patterns (Ibarretxe-Bilbao, Zarei, et al., 2011), or even no differences in relation to healthy controls (Fine, Delis, Paul, & Filoteo, 2011; Herrera, Cuetos, & Ribacoba, 2012; Piatt, Fields, Paolo, Koller, & Tröster, 1999; Tröster et al., 1998). Early-stage and non-demented PD patients may be impaired on more demanding types of fluency, such as proper name fluency (Fine et al., 2011) or alternating fluency (Zec, 1999). In relation to semantic and phonemic fluency, alternating fluency has been reported to be most strongly affected in non-demented PD (Zec, 1999). Although verbal fluency tasks are often used as executive measures, fluency performances are most likely also influenced by other cognitive functions such as memory and psychomotor speed. At mild stages of PD, fluency performances have been shown to be influenced mainly by psychomotor speed, while reductions in both psychomotor speed and cognitive flexibility seem to influence performances at moderate disease stages (Koerts et al., 2013).

Both semantic fluency and phonemic fluency are dependent on widespread cortical and subcortical networks, but most significantly the left inferior frontal cortex (Costafreda et al., 2006; Hirshorn & Thompson-Schill, 2006). Semantic and phonemic

fluency are believed to rely on partially different neural circuits, with semantic fluency depending on temporal areas and phonemic fluency on more frontal regions (Henry & Crawford, 2004a). A reversible impairment in phonemic fluency, but not semantic fluency, has been demonstrated in non-demented, dopamine deprived PD patients (Herrera et al., 2012), supporting the idea that semantic and phonemic fluency rely on distinct neural connections. However, not all studies have found similar effects of dopaminergic medication (Hanna-Pladdy et al., 2013). Structural imaging studies in healthy individuals also suggest a role of the caudate in verbal fluency tasks, which is more pronounced for phonemic than for semantic fluency (Grogan, Green, Ali, Crinion, & Price, 2009). Alternating verbal fluency (switching between semantic categories or letters) has been found to be subserved by the left inferior frontal gyrus (Hirshorn & Thompson-Schill, 2006) and more widespread regions in the posterior parietal cortex (Gurd, 2002), bilateral premotor areas, superior parietal cortex, ventral occipito-temporal cortex, posterior cingulate areas (Birn et al., 2010), and subcortical structures including the putamen (Thames et al., 2012).

1.2 Examining cognition in early PD: An integrative neurocognitive approach

The heterogenous spectrum of cognitive impairment in PD constitutes a challenge for the quantification and description of disease-related neurocognitive changes. An integrative approach may be necessary to understand the relationships between impaired function and corresponding damaged neural substrates. As memory and verbal fluency impairments are undoubtedly present throughout the course of PD, and they have been demonstrated to be associated also with more severe cognitive impairment at later disease stages (Emre et al., 2007; Hanna-Pladdy et al., 2013; Williams-Gray et al., 2009), a closer study of these functions and their neural correlates in early disease stages is warranted. In the early stages when impairments are subtle, the detection of impairment may require refinement and new approaches to established conventional testing procedures. Detailed neuropsychological information can be complemented with information from corresponding functional and structural imaging techniques such as the electroencephalogram (EEG) and magnetic resonance imaging (MRI).

In order for information to be retrieved from memory, it first has to be successfully encoded and stored. One approach to examine the memory deficits in PD is therefore to study different aspects of encoding. Encoding processes are difficult to register behaviorally and thus functional correlates such as the simultaneous ongoing EEG

can shed light on neural mechanisms related to memory encoding. Another approach to study memory is to examine how the intentionality of encoding possibly affects retrieval as measured by free recall. Encoding-related intentionality can be studied behaviorally by varying task instructions. Recent recommendations on memory assessment (Pause et al., 2013) state that episodic memory should also be assessed by non-intentional tasks. In the following sections, functional and behavioral approaches to the study of memory encoding and retrieval are described.

1.2.1 Encoding and retrieval - Electroencephalography (EEG)

Electroencephalography (EEG) is one of the oldest methods for studying brain function. It has been proposed as a promising tool for the detection of cognitive decline in neurodegenerative disorders including PD (Caviness et al., 2007; Uhlhaas & Singer, 2006). The ongoing EEG reflects post-synaptic potentials in the brain, and due the excellent time resolution (millisecond level), neural events can be studied nearly in 'real-time'. The EEG signal is measured via scalp electrodes, and the digital signal can be decomposed into waveform (oscillatory) components of a certain frequency and amplitude (Pfurtscheller & Lopes da Silva, 1999). The EEG can be utilized in resting state situations as an indicator of spontaneous neural background activity as well in relation to specific cognitive tasks as an indicator of specific brain-behavior relationships.

Resting state oscillatory activity in PD. In resting state recordings, PD patients typically exhibit both diffuse and localized slowing of oscillatory activity (Bosboom et al., 2006; Moazami-Goudarzi, Sarnthein, Michels, Moukhtieva, & Jeanmonod, 2008). The risk of developing dementia has been estimated 13 times higher in PD patients exhibiting slow resting state EEG background activity in comparison with patients showing high resting state activity (Klassen et al., 2011). Studies utilizing magnetoencephalography (MEG) have shown that even in the earliest clinical stages, PD patients exhibit abnormal background oscillatory activity when compared to age-matched controls. A specific resting state feature seems to be a widespread increase in theta (4–8 Hz) activity, which is present already in de novo patients (Stoffers et al., 2007), and which further increases over time, along with a decrease in the lower (8–10 Hz) and upper alpha (10–13 Hz) frequency ranges (Olde Dubbelink et al., 2013). Relative theta increase has been identified as a predictor of PDD incidence (Klassen et al., 2011). In PDD, the background activity is further characterized by abnormal slow delta (0.5–4 Hz) activity and reduction of alpha activity including reduced reactivity to eye opening (Bosboom et al., 2006). In a longitudinal study, cognitive decline in

initially non-demented patients was associated with increases in delta and theta power, and decreases in alpha power and gamma power after four years. Increasing motor impairment was associated with increased theta power only (Olde Dubbelink et al., 2013). Notably, the changes observed in PD patients' quantitative resting state EEG do not seem to be explained by motor impairment, disease severity or dopaminergic medication (Klassen et al., 2011), suggesting that non-dopaminergic pathways are involved in abnormal EEG patterns (Stoffers et al., 2007).

Oscillatory activity in relation to cognitive processing. Oscillatory activity can also be studied during cognitive processing. Different frequencies are believed to originate from different parts of the brain, and they may also vary in their synchronous oscillatory patterns in response to different stimuli or cognitive tasks. The *theta* rhythm (~4–8 Hz), which is prominently observed in the hippocampus, is associated with working memory and episodic memory processes (Klimesch, Doppelmayr, Schimke, & Ripper, 1997; Osipova et al., 2006; Sederberg, Kahana, Howard, Donner, & Madsen, 2003). The *alpha* rhythm (~6–13 Hz) is believed to be generated in cortico-cortical and thalamo-cortical networks (Steriade, Gloor, Llinás, Lopes de Silva, & Mesulam, 1990), and has been related to both memory processing and attention (Klimesch, Doppelmayr, Schimke, et al., 1997). Particularly, modulations of the upper alpha (~10–12 Hz) seem to reflect semantic memory processes and to distinguish between good and bad memory performers (Klimesch, Doppelmayr, Pachinger, & Ripper, 1997). The *beta* rhythm (~20 Hz) has been found to reflect motor cortices activity, including planning and execution of movement (Neuper & Pfurtscheller, 2001). The beta frequency has also been associated with memory processing (Pesonen, Björnberg, Hämäläinen, & Krause, 2006), showing modulations dependent on memory load (Pesonen, Hämäläinen, & Krause, 2007).

Many early EEG studies related to PD cognition have utilized the Event-related potential (ERP) method. Most have focused on the N2 and P3 responses, which generally show prolonged latencies and diminished amplitudes in inhibition (Go/NoGo) paradigms (Bokura, Yamaguchi, & Kobayashi, 2005; Tachibana, Aragane, Miyata, & Sugita, 1997). Such results have been interpreted as electrophysiological signs of cognitive slowing (Robertson & Empson, 1999) with respect to stimulus classification and attentional processing (Tachibana et al., 1997). In the ERP method, however, responses are averaged across frequencies, and thus the functional significance of different frequency bands is lost.

Event-related desynchronization and synchronization (ERD/ERS). One technique to quantify the ongoing EEG in relation to cognitive processes is the event-related

desynchronization/synchronization (ERD/ERS) method (Pfurtscheller & Aranibar, 1977). ERD/ERS is quantified by comparing two different experimental conditions, and dynamic modulations are expressed as relative power decrease (ERD) or increase (ERS) in a given frequency band (Pfurtscheller & Lopes da Silva, 1999). The method is especially suitable for studying memory processing, as the technique allows for studying the distinct modulations of ongoing oscillatory activity during both encoding and retrieval.

ERD/ERS in the auditory modality has been extensively studied by Krause and co-workers They have repeatedly shown that in opposite to visual stimulation, which typically elicits alpha ERD responses in occipito-parietal regions, auditory stimulus encoding elicits widespread alpha ERS, whereas retrieval or recognition elicits alpha ERD (Krause, 2006). Using different modifications of a Sternberg recognition memory paradigm (Sternberg, 1966) and working memory n-back tasks, they have shown that in the alpha frequency range, ERD/ERS responses reflect cognitive task demands, not merely primary sensory processes. Additionally, also the theta (~4 Hz) and the beta (~20 Hz) frequencies seem to be modulated as a function of memory condition, memory load and stimulus type (Krause, 2006). In the modified auditory Sternberg working memory/recognition task, memory encoding elicits both alpha and theta ERS in healthy individuals, while recognition elicits alpha ERD and theta ERS (Karrasch, Laine, Rapinoja, & Krause, 2004; Krause, Lang, Laine, Kuusisto, & Pörn, 1996). ERD/ERS responses in applied clinical studies of the same research group have suggested that theta, alpha, and beta responses are affected during memory retrieval in normal aging (Karrasch et al., 2004), and that mild cognitive impairment (MCI) patients have abnormal (~7–17 Hz) ERD responses during word encoding, while patients with mild probable Alzheimer's disease (AD) show particularly deviant ERD responses during retrieval (Karrasch et al., 2006).

In PD populations, the ERD/ERS technique has mostly been applied in relation to voluntary movement, with the most consistent finding being delayed onset of the contralateral mu ERD (Leocani & Comi, 2006) which has been related to delayed motor programming (Defebvre et al., 1994) The ERD/ERS technique has also been utilized in relation to auditory discrimination tasks, in which PD patients exhibit deviant responses in both delta, theta and alpha frequencies when compared to healthy controls (Dushanova, Philipova, & Nikolova, 2009). In visual working memory tasks, PD patients have been shown to exhibit diminished theta ERS and upper alpha ERD responses during encoding, possibly reflecting alterations in higher-order visual processes (Schmiedt, Meistrowitz, Schwendemann, Herrmann, & Basar-Eroglu, 2005).

1.2.2 Incidental memory

Memory encoding can occur as a conscious event, involving an intention to memorize information that can later be retrieved and used for purposeful behavior. An important aspect of episodic memory is, however, that information on what has happened, where it happened and when it happened can also be encoded without an intention. In everyday-life situations, most spatial and temporal contexts are encoded without an intention, and it has recently been recommended, that episodic memory should be assessed also using incidental tasks (Pause et al., 2013).

As most clinical memory assessment tools are intentional, i.e. the subject is explicitly asked to memorize content or context, not much is known about the mechanisms of incidental memory. Whilst intentional memory is closely related to medial temporal lobe functioning (Squire, Stark, & Clark, 2004) and a frontotemporal network, different forms of unintentional memory have been proposed to be mediated by other, separate brain regions (Vingerhoets, Vermeule, & Santens, 2005). The neural correlates of incidental memory have, however, been sparsely studied. Findings from lesion studies in rodents have indicated a hippocampal-dependent basis also for incidental memory (Zhou, Hohmann, & Crystal, 2012). Experimental imaging studies in humans have focused mostly on intentionality effects related to memory retrieval, thus covering the concept of implicit memory, which in the literature has been defined as nonconscious retrieval which is facilitated by past experience (Schacter, 1997), and therefore not directly addressing different aspects of encoding. Positron emission tomography (PET) findings have shown increased hippocampal activation for both incidental (implicit) and intentional recall task conditions. The hippocampal activation, however, appears greater when items have been deeply encoded as compared to shallow encoding conditions (Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997). Intentional recall also more strongly activates the right dorsolateral prefrontal cortex and bilateral parietal areas than does incidental retrieval, which has been interpreted as reflecting strategic components of retrieval (Hall, Gjedde, & Kupers, 2008; Rugg et al., 1997).

Only a few behavioral studies have applied an incidental memory approach in PD samples. The results have been mixed. In the verbal memory domain, impairments on incidental wordlist learning tasks have been found in older, non-demented PD patients (Ivory, Knight, Longmore, & Caradoc-Davies, 1999). PD patients performed worse than controls after having rated wordlist items in terms of liking or disliking, but they performed equal to controls on the intentional Rey Auditory Verbal Learning Test (RAVLT). The authors related the impairment in incidental, but not in

the intentional memory task to the fact that the orienting instructions, which were present in the intentional memory task may have assisted the recruitment and direction of attentional resources necessary for successful encoding. In the visual memory domain, non-demented PD patients have been found to be impaired on incidental context recognition, as well as showing ineffective use of encoding strategies, which may also have deleterious effects on object recognition (dos Santos et al., 2010). Others have found impaired verbal and visual intentional memory performances, but spared incidental memory for context (Vingerhoets et al., 2005). More pronounced impairment on intentional than on incidental object recall in PD has not been found to be dependent on disease stage (Cooper & Sagar, 1993).

In comparison to AD patients, PD patients have been found to perform significantly better on an incidental adaptation of the WAIS-R Digit symbol test, and the incidental memory task correctly classified 76 % of the patients. The incidental measure was also strongly related to other memory measures (Demakis et al., 2001). In conclusion, PD patients seem to exhibit both spared and impaired incidental recall, depending on the task used.

1.2.3 Brain structure and cognition – Magnetic resonance imaging (MRI)

Brain magnetic resonance imaging (MRI) is an effective non-invasive method of studying brain structure. It is a widely used clinical diagnostic tool in neurological conditions such as traumatic brain injuries, vascular events and neurodegenerative diseases. Recent findings demonstrating widespread cortical and hippocampal atrophy in cognitively impaired PD patients, have suggested that structural MRI changes may be potential biomarkers for PDD (Weintraub et al., 2011). The imaging method is based on magnetic fields and radiofrequency pulses (RF), which produce signals of different properties depending on the reactive tissue. The signals are then turned into spatial representations, or digital images consisting of voxels (volume elements). The images provide good differentiation between gray matter, white matter and cerebrospinal fluid, as well as contrasts between healthy and damaged tissue such as tumors or infarctions (Kennedy, Makris, Herbert, Takahashi, & Caviness, 2002).

A number of MRI studies have demonstrated that PDD is associated with changes in limbic areas and widespread cortical atrophy in temporal, prefrontal, occipital and parietal areas (Song et al., 2011; Summerfield et al., 2005; Weintraub et al., 2011). Findings in non-demented patients have been mixed, but patterns of temporal,

parietal and occipital cortical involvement seems to be associated with PD-MCI (Nishio et al., 2010; Pagonabarraga et al., 2013). In relation to specific cognitive tasks, the most consistent finding in both demented and non-demented PD patients has been an association between hippocampal atrophy and impaired memory functioning (Brück, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Ibarretxe-Bilbao et al., 2008; Jokinen et al., 2009; Weintraub et al., 2011). Recent evidence suggests that in non-demented PD patients, worse memory performance is associated with volume loss in several temporal lobe structures, including the entorhinal cortex (Filoteo, Reed, Litvan, & Harrington, 2013). Entorhinal cortex atrophy has been shown to differentiate demented and cognitively intact patients (Goldman et al., 2012)

Few studies have addressed brain gray matter volume in relation to specific cognitive tasks in early-stage PD. Voxel-based morphometry (VBM) studies with untreated patients have mainly yielded no significant regional gray matter atrophy or correlations with cognitive tasks (Dalaker et al., 2010; Martin, Wieler, Gee, & Camicioli, 2009). A lack of structural-behavioral correlations has been suggested to result from the use of collapsed behavioral test scores, instead of targeting tests in single cognitive domains (Tinaz, Courtney, & Stern, 2011), such as memory. One study (Beyer et al., 2013) using radial distance mapping found significant associations between hippocampal volume and both short and long delay free recall at initial stages of PD. Another study (Pagonabarraga et al., 2013) using a surface-based approach reported right posterior cortical thinning in relation to a verbal immediate free recall task in PD-MCI patients, but no associations with free recall tasks in cognitively intact patients. In PDD patients, cortical thinning in right parahippocampal gyrus, bilateral anteromedial temporal cortex, and left lingual gyrus was related to a delayed recall task. As very few studies have reported structural correlates of specific free recall memory tasks in early PD, and few have included both verbal and visual memory tasks, it remains to be elucidated whether visual and verbal memory are differently reflected in cortical volume in PD.

Cerebral structural correlates of verbal fluency in PD have been sparsely investigated using VBM. One previous study (Pereira, Junqué, Martí, Ramirez-Ruiz, Bartrés-Faz, et al., 2009) with non-demented PD patients found that impaired semantic fluency was related to temporal, frontal, and cerebellar gray matter (GM) reduction. Impaired phonemic fluency scores were not related to gray matter volumes. A recent study (Pagonabarraga et al., 2013) assessing cortical thickness found an association between reduced alternating verbal fluency and cortical thinning in right parahippocampal gyrus, left lingual gyrus and left precuneus. This association was present in PDD patients, but not in cognitively normal or PD-MCI patients. Both of the above

mentioned studies included older (> 65 years) non-demented PD patients with disease durations up to ten years. To date, no structural neuroimaging studies comparing different types of verbal fluency in younger PD patients with shorter disease duration have been conducted.

2 AIMS

The general aim of the thesis was to investigate neural correlates of cognitive functioning in early-stage, non-demented PD. The neural basis of cognitive dysfunction in PD is not well understood, and information on neurocognitive changes at initial disease stages has been nearly non-existent. All four studies included early-stage (disease duration ≤ 3 years), non-demented, medicated PD patients and healthy controls. The first experimental study was followed by three clinical studies. Brain-behavior relationships were studied using cognitive tasks in combination with functional (EEG) and structural (MRI) neuroimaging. In the present work, the main focus was on memory functions and verbal fluency. Electrophysiological correlates of short-term recognition memory, behavioral aspects of incidental and intentional episodic memory, and brain volumetric correlates of episodic memory and verbal fluency, were studied. The specific aims and methods of the four studies were the following:

Study I
To explore 'on-line' working memory/recognition memory processing expressed as the modulation of ERD/ERS responses during the encoding and retrieval phases of an auditory-verbal recognition memory task. ERD/ERS responses in the 1-25 Hz frequency bands were studied using wavelet transforms. No previous EEG studies have been conducted using the Sternberg memory paradigm in early PD.

Study II
To examine if intentionality during memory encoding is reflected in the ability to recall previously named visual material. Intentionality was controlled by task instructions. Previous research has shown that a majority of PD patients are impaired on intentional memory tasks, but findings regarding incidental memory have been mixed. It was expected that the PD patients would perform worse that controls in the intentional encoding condition, but that they would perform as well as controls in the incidental encoding condition. A secondary aim was to study whether possible deficits in incidental or intentional recall are related to deficits in attentive/executive performance and/or subjective memory complaints.

Study III
To study brain gray matter volume in relation to visual and verbal memory tasks (both intentional and incidental tasks) using VBM. It has been established that many PD patients have memory problems, and that demented PD patients in addition

exhibit hippocampal and widespread cortical atrophy. Very few studies have examined volumetric relationships with single memory measures in early-stage PD patients, and there are no previous volumetric correlative studies on incidental memory in PD. As intentional tests are known to measure temporal lobe functions, it was expected that reduced intentional memory performances would be reflected in temporal gray matter volume.

Study IV

To examine brain gray matter correlates of semantic, phonemic, and alternating verbal fluency. Semantic and phonemic word fluency tasks are widely used simple and time-efficient clinical measures of frontal-temporal cortical functioning. Alternating fluency tasks provide additional frontal-executive cognitive demands, as they require both switching between two sematic categories and inhibiting category-unrelated responses. In PD, impaired semantic fluency has been related to an increased risk of dementia (Evans et al., 2011). It is, however, not known if different fluency tasks are reflected differently in brain gray matter at initial disease stages.

In summary:

- **I.** To explore ERD/ERS responses during the encoding and retrieval phases of an auditory-verbal recognition memory task.
- **II.** To examine whether the intentionality of memory encoding is reflected in memory recall.
- **III.** To examine brain gray matter volume in relation to visual and verbal memory tasks, including a measure of incidental memory.
- **IV.** To examine brain gray matter correlates of semantic, phonemic, and alternating verbal fluency.

3 PARTICIPANTS AND PROCEDURES

A summary of participant demographic characteristics and main interest variables are shown in Table 1. Early-stage PD patients (disease duration ≤ 3 years) and healthy controls were invited to participate. The study protocols were accepted by the local ethics committee, and written informed consent was obtained from all participants according to the Declaration of Helsinki.

Neuropsychological assessments were performed at the Centre for Cognitive Neuroscience at the University of Turku, at the Finnish Parkinson Association (PD Rehabilitation Center Suvituuli) in Turku (Study I), and at the Department of Psychology and Logopedics at Abo Akademi University (Studies II–IV). EEG recordings were performed at the Centre for Cognitive Neuroscience at the University of Turku (Study I) and brain MRI scans were carried out at the Turku PET Centre. In studies II–IV, motor functioning (UPDRS-III) (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003) and disease stage (Hoehn & Yahr, 1967) were evaluated prior to the MRI brain scan by medical doctors with expertise in movement disorders at the Turku PET Centre. The MRI scans were clinically rated by an experienced neuroradiologist.

The PD patients were recruited in collaboration with the Finnish Parkinson Association through PD rehabilitation courses (Study I), the newsletter of the Finnish Parkinson Association (Studies I–IV), an Internet survey on subjective cognition in PD, and from two outpatient neurology clinics (Studies II–IV). All participants were native Finnish speakers, and none of them had been diagnosed with neurological disease (except for PD in the PD group), major depression or other psychiatric disorders, vascular events, or had a history of traumatic brain injury. The healthy control participants were recruited from the PD forums described above, through city employee mailing lists of the City of Turku, and from friends and spouses of the PD patients. Controls (Studies II–IV) reporting subjective cognitive complaints in combination with near familial burden of neurological disease or multiple risk factors for vascular disease (hypertension and hypercholesterolemia) were excluded. Out of 59 initially volunteering controls, 29 fulfilled inclusion criteria and had representative education levels when compared to the PD group. None of the participants received monetary compensation, but they were provided written clinical feedback based on individual neuropsychological performance and the MRI scan (Studies II–IV). Patients in study I received a clinical summary of their resting state EEG recordings, which were visually evaluated by an experienced clinical neurophysiologist.

Table 1. Summary of participant characteristics, methods, and main interest variables.

Study	**Participants**	**N**	**Sex** M/F	**Age** *M (SD)*	**Education years** *M (SD)*	**Method**	**Interest variables**
Study I	PD patients Controls	7 10	4/3 1/9	59.7 (3.0) 61.8 (2.2)	Various levels Matched	EEG, ERD/ERS	1–25 Hz ERD/ERS responses, auditory-verbal working memory/recognition
Study II	PD patients Controls	29 29	14/15 15/14	60.0 (8.2) 60.8 (7.6)	13.7 (3.4) 14.7 (3.1)	Neuropsychological assessment, self-report questionnaires	Incidental and intentional memory, attentive/executive functioning, subjective memory complaints
Studies III & IV	PD patients Controls	28 28	14/14 15/13	60.3 (8.1) 61.3 (7.2)	13.8 (3.5) 14.8 (3.2)	MRI, Voxel-based morphometry	Brain gray matter volume, visual-, verbal-, and incidental memory, verbal fluency

3.1 Study I

The volunteering PD group consisted of 13 patients. Inclusion criteria were confirmed through the patients' medical records and a semi-structured interview. The final number of PD patients after exclusion (6 patients, due to comorbid diagnoses or low quality EEG data) was 7 (3 females and 4 males). They had been diagnosed with PD approximately 18 months prior to the study, and they were stable on their medication, which consisted of different combinations of antiparkinsonian drugs: L-dopa (n = 7), dopamine agonists (n = 3) and MAO-B inhibitors (n = 3). In order to reduce pharmacological variability, only patients receiving L-dopa were included. None of the patients received anticholinergic drugs. The control group consisted of 10 healthy volunteers (4 were excluded due to handedness or low quality EEG data) who were selected according to the age and education levels of the PD patients (primary school n = 3; secondary school/high school n = 2; academic n = 2). All participants were right-handed native Finnish speakers, and none of them reported appreciable or uncorrected deficits in hearing or vision. Both groups were screened for depressive symptoms using the Beck Depression Inventory (Beck, 1961). The groups did not differ regarding age, educational levels or BDI score.

To exclude significant cognitive impairment in the PD group, and to ensure normal cognitive functioning in controls, all participants underwent neuropsychological assessment prior to EEG recordings. The assessment included the Digit span, Block design, Digit symbol, and the Similarities subtests of the WAIS-R (Wechsler, 1992), the full Wechsler Memory Scale (WMS-R) (Wechsler, 1996), Trail Making Test (TMT) part A and B, Stroop Test (Lezak, Howieson, Bigler, & Tranel, 2012), Boston Naming Test (Laine, Koivuselkä-Sallinen, Hänninen, & Niemi, 1997), Benton Visual Retention Test, and verbal fluency (animals and words beginning with the letter *S*) (Lezak et al., 2012). Based on the neuropsychological assessment, none of the individual patients had significant cognitive impairment, and the two groups did not significantly differ on any of the neuropsychological measures.

3.2 Studies II–IV

A summary of the clinical characteristics of the two groups is presented in Table 2. The initial study group consisted of 31 PD patients and 29 healthy control subjects. Prior to neuropsychological assessments, a semi-structured interview covering health history, medication, subjectively experienced motor, cognitive and neuropsychiatric

symptoms, as well as medical records verified correct inclusion criteria. All participants underwent MRI scans, which were first visually rated to further ensure correct inclusion criteria. In study II, two PD patients were excluded due to a history of traumatic brain injury and minor vascular events, and the final sample consisted of 29 PD patients and 29 controls. This sample will be described in detail below. Further exclusion was performed in studies III and IV. A follow-up diagnostic questionnaire sent to the participants 1 year after participation revealed that one PD patient had received comorbid diagnoses (cervical dystonia, multiple system atrophy). The patient was therefore excluded from studies III and IV. As one control declined MRI imaging, the final study sample in studies III and IV consisted of 28 PD patients and 28 controls.

PD patients. In study II, the PD group consisted of 14 men and 15 women. The mean age of the patients was 60.0 (*SD* = 8.2, range 45–77) years, and they were diagnosed with PD (criteria according to the UK Parkinson's disease Brainbank) (Hughes et al., 1992) approximately 19 months before study enrolment. None showed structural brain MRI findings inconsistent with the PD diagnosis, and visually rated MRI scans included within normal range age-related changes. All patients were on their regular medication consisting of different combinations of L-dopa preparations. 14 patients were taking L-dopa, 28 patients were taking dopamine agonists, and 24 were taking MAO-B inhibitors. The mean daily L-dopa equivalent dose was 396.6 mg (*SD* = 227.5). None of the patients were taking anticholinergic preparations. Two patients were regularly taking benzodiazepine at small dosage levels and one patient was using a selective serotonin re-uptake inhibitor (SSRI). Neuropsychological assessments were performed in optimal medicated state (approximately one hour after intake). The testing situation lasted from 2.5 to 3 hours. The severity of the motor symptoms was rated using the UPDRS-III. The mean UPDRS score was 26.2 (*SD* = 7.5, range 12–40). The mean Hoehn and Yahr stage was 2.5 (*SD* = 0.3) indicating mild to moderate disease, and mean age at disease onset was 58.5 (*SD* = 7.9).

Healthy controls. The group of healthy controls consisted of 15 men and 14 women. The mean age was 60.8 (*SD* = 7.6, range 43 – 77). Visual neuroradiological evaluations revealed that one control had an asymptomatic meningeoma, and the control was thus excluded from the VBM analyses in Studies III and IV. The remaining MRI findings in the control group included within normal range age-related changes. One control was taking SSRI at minimum dosage.

Possible dementia was screened according to the recommendations of the MDS Task Force on Dementia (Emre et al., 2007), including the Mini Mental State Examination

(MMSE) (Folstein et al., 1975). Although six patients scored below the recommended cut-off score (< 26) for PD patients (Dubois et al., 2007), none of them reported cognitive deficits severe enough to impair daily life. Based on the neuropsychological assessment and clinical impression, none of the individual patients were clinically demented. Depression was screened using the Geriatric Depression Scale (GDS-15, short form) (Sheikh & Yesavage, 1986), which has been found to be an excellent screening tool in PD populations (Weintraub, Oehlberg, Katz & Stern, 2006). The groups did not differ regarding age, $p = .703$, education, $p = .245$, or MMSE scores, $p = .945$. There was a significant, $p = .002$, group difference in GDS-15 score. This was due to the fact that the mean score (2.5, *SD* = 2.0, *range* = 0–8) for the patients was higher than the mean score (1.0, *SD* = 1.0, *range* = 0–3) for controls.

Table 2. Clinical characteristics of the two groups.

	PD patients (*n* = 29) *M (SD)*	**Controls** (*n* = 29) *M (SD)*
MMSE score	28.1 (2.0)	28.1 (1.8)
GDS-15 score	2.5 (2.0)	1.0 (1.0)*
UPDRS-III motor score	26.2 (7.5)	1.7 (2.0)
Hoehn and Yahr stage	2.5 (0.3)	–
Disease duration (months)	19.1 (10.7)	–
Age at disease onset	58.5 (7.9)	–
Levodopa equivalent dose (mg/day)	396.6 (227.5)	–
Total intracranial volume (TIV)(ml)[a]	1515.1 (155.8)	1482.3 (160.8)

Note. Between-group difference * $p < .05$; [a]*n* = PD 28, Control 27 (studies III and IV).

Formal neuropsychological testing for background information was performed using three cognitive screening batteries and standard clinical neuropsychological tests. These included the CERAD (Hänninen et al., 2010; Welsh et al., 1994), The Parkinson neuropsychometric dementia assessment (PANDA) (Kalbe et al., 2008), The Frontal assessment battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000), similarities, block design, digit symbol and symbol recognition of the WAIS-III

(Wechsler, 1997a), the mental control subtest of WMS-III (Wechsler, 1997b), the Bourdon-Wiersma dot cancellation test, the TMT, and the Stroop test (Lezak et al., 2012). In the present work, performances on these tests were used as extended clinical background information to ensure correct exclusion of demented participants and outliers, and for preliminary explorative analyses. The neuropsychological background data is therefore not discussed in further detail. The TMT and the Stroop test were used as control variables in study II. The TMT, the Stroop test, the verbal and visual spans of the WAIS-III, WAIS-III Block design and CERAD Figure copying subtests were used as control variables in study III.

METHODS

4.1 EEG (Study I)

4.1.1 The experimental memory task

ERD/ERS responses during auditory encoding and retrieval (recognition) were studied using a modified auditory version of the Sternberg's memory search paradigm (Krause et al., 1996; Sternberg, 1966). Trials comprised a memory set including four spoken Finnish words, followed by and a fifth target word. The task was to decide whether the fifth word had been presented in the previous list of four words. Out of a total of 24 different Finnish verbs, 192 memory sets were constructed. Words occurred with equal frequency across sets and no word appeared more than once in any memory set. The matching target stimulus was present in 50% of the memory sets and absent in the remaining 50%. The average length of the stimuli was 6.7 letters (SD = 0.9) and the mean duration of each word was 764ms (SD = 81.7).

Each trial had a length of 16.7 seconds (not including the participant's response time), beginning with a 3500ms inter-trial interval (ITI). The 2000-3500ms time window of the ITI was used as an intra-experimental reference interval (non-stimulus condition). After this, a red warning signal appeared on the screen for 100ms, and after a pause of 1500ms the memory set was presented to the subject. The duration of the memory set was 7000ms. A pause of 2000ms preceded the presentation of the probe. After 1500ms a green signal appeared on the screen, indicating that the subject should respond (yes or no) by pressing a response pad. The total registration time was approximately 60 minutes.

4.1.2 EEG data acquisition and processing

Raw EEG signals were recorded using the Neuroscan 386 Scan 3.0 data acquisition system with a Braintronics CNV/ISO-1032 amplifier[2]. The frequency band of the amplifier was 0.3–70 Hz and the sampling rate used for recording was 200 Hz. 20 Ag/AgCl electrodes were placed in line with the international 10/20 electrode placement system. Two electrodes were fixed next to the eyes to register eye movement. All electrodes were referred to linked mastoids, which also served as

[2] A Synamps 5083 amplifier was used for the recording of one control at a sampling rate of 250 Hz. The data was downsampled to 200 Hz using Matlab.

ground electrodes. After electrode impedance adjustment, the presence of an adequate EEG signal was determined by visual inspection throughout recordings. Participants were asked not to perform any unnecessary movements during testing and the behavior of the subject was monitored by a video camera during the entire testing session.

The digital EEG data was processed in a MATLAB 6.1 environment (Math Works Inc., 1999), using 4-D Toolbox modifications (Jensen, 2002). The analyses resulted in time-frequency representations (TFRs), which display the power of a continuous EEG signal as a function of time and frequency, in the same matrix (Auranen, 2002). The EEG-data file was first epoched using a 2000 ms time-window (–400 to 1600 ms from stimulus onset). Epochs including artifacts (eye movement channel power exceeded 100 μV) were rejected from further analysis.

Absolute power changes. To display the frequency content of the EEG signal during the presentation of the stimuli and the non-stimulus reference interval (2000 to 3500 ms time window within the inter-trial interval, ITI), TFRs (time-frequency representations) for each subject were calculated using mathematical functions (Morlet wavelets, width 8). The calculations were performed for each EEG channel separately. This resulted in TFRs displaying the absolute power changes as a function of frequency and time (1–25 Hz, –400 to 1600 ms from stimulus onset) in the EEG signal for the different stimulus conditions (the four stimuli in the memory set and the target) for each subject separately.

Absolute power changes averaging. The TFRs for each of the four stimuli in each memory set were then averaged separately for each individual, and then the TFRs for all four stimuli in the memory sets were averaged, resulting in one TFR for the memory set (encoding). Similarly, mean power values were calculated for the presentation of the target (retrieval) and the reference interval (non-stimulus condition) for each individual. This procedure resulted in average TFRs displaying absolute power modulations for each subject during the presentation of the memory set (encoding) and the target (retrieval). Bad channels were excluded by visual inspection of the absolute power value TFRs (the C3, Pz and O2 electrodes from one control, the Fz from one control, and the Fp2 from one patient).

Relative power changes: ERD/ERS. The relative difference in the power between the reference interval and the two memory conditions (encoding and retrieval) was calculated as a function of time and frequency, resulting in ERD/ERS TFRs. The relative difference in power during the presentation of the stimuli (encoding and

retrieval) and the reference interval was expressed as a percentage. Negative values indicate a relative power decrease (ERD) and positive values indicate a relative power increase (ERS). Finally, the ERD/ERS TFRs were averaged within each of the two groups (PD patients and controls). Grand average ERD/ERS matrices were displayed as ERD/ERS TFRs for five electrode locations (frontal, left temporo-central, right temporo-central, parietal, and occipital). The ERD/ERS values were displayed as a function of time (–400 to 1400 ms) and frequency (1–25 Hz). As the TFR calculations result in some inaccuracy in border points due to the wavelet analysis method, inaccurate points were omitted by selecting time windows of –200 to 1400ms for plotting the final results.

4.2 Incidental and intentional memory tasks (Studies II and III)

Incidental memory was assessed using a novel memory modification (Memo-BNT) (Karrasch et al., 2010) of the Finnish version of the Boston Naming Test (BNT) (Laine et al., 1997). The memory extension assesses the ability to recall named BNT items. An incidental encoding context is created by task instructions, which do not include a warning of later recall. In order to avoid interference from other tasks and to reduce the possibility of participants activating spontaneous mnemonic strategies, the incidental Memo-BNT task was always the first test presented within the formal neuropsychological assessment, followed by the 20 Objects test.

The Memo-BNT provides measures of immediate free recall, recognition of content, and recognition of temporal order. After picture naming (BNT items 30–60), *free recall* is measured by asking the subject to recall as many of the previously named BNT items as possible (maximum score 31). Free recall is followed by a *recognition* task (recognition of content) consisting of 16 items (pictures) of which 50% origin from the BNT naming task (targets), and 50% are distracters. The *temporal ordering* task consists of pair-wise presented items from the naming task. The participant is asked to recall which one of the two items was originally presented before the other (recall of temporal order). There are 22 item pairs in total. Within the temporal order condition, task difficulty is varied by differences in the temporal distance of the item-pairs. In the first condition, the original temporal presentation (BNT naming) distance between the items is the largest (one item from the beginning of the naming task and the other item from the end of the task). In the second condition the temporal difference is smaller (both items are originally among the first presented). In the third condition, the items are originally presented among the last in the naming task.

Intentional memory was studied using the 20 Objects test (Portin et. al, 1995). The task consists of the naming of 20 common physical objects (e.g. a coin, a pencil, a pair of scissors), which are displayed to the subject in a single exposure. A time limit of 75 seconds is set for rapid naming and encoding. Correct names are given if necessary. Object naming is followed by immediate free recall. A warning of object recall is included in the task instructions preceding object naming, thus an intentional learning context is created. The 20 Objects test also includes a measure of delayed recall, but as the Memo-BNT currently lacks the corresponding measure, delayed recall was not addressed here.

Memo-BNT immediate free recall is also referred to as the *incidental memory task* in the present work. The 20 Objects test immediate free recall is also referred to as the *intentional memory task* in the present work.

4.2.1 Attentive/executive control measures and awareness of memory failures

In order to control for possible effects of attentive and executive impairment on incidental and intentional memory performances, attentive/executive measures were calculated from the participants' test performances on the TMT and the Stroop task. Proportion scores, taking into account individual baseline speed differences, were calculated by subtracting the performance time for the easy condition from the more demanding condition and dividing the difference score by the easy condition (Stuss, Floden, Alexander, Levine, & Katz, 2001). The proportion scores indicate the relative slowing due to increased task demands. Hence, higher values indicate more attentive/executive deficits. A set-shifting proportion score was calculated as (TMTB – TMTA) / TMTA x 100. The corresponding inhibition proportion score was calculated as (Stroop interference naming – Stroop color naming) / Stroop color naming x 100.

Subjectively experienced failures in cognitive functioning and their possible relationship with memory performances were examined using the Cognitive Failures Questionnaire (CFQ) (Broadbent et al., 1982). The CFQ consists of 25 short statements related to common cognitive slips occurring in everyday life. Self-ratings are performed on a five-point scale (0 = *never*, 4 = *very often*). In addition to the total score (max 100), a memory-specific variable, CFQ Forgetting, was created by adding together the scores of memory-related items (16, 17, and 23) of the CFQ.

4.3 Conventional intentional memory tasks of the CERAD (Study III)

In addition to the incidental and intentional memory tasks described in study II (Memo-BNT free recall and the 20 Objects test), conventional intentional verbal memory tasks were used in study III. Immediate and delayed free recall was assessed using the wordlist learning (sum of three trials), delayed recall and relative saving percentage (savings%) of the CERAD (Hänninen et al., 2010; Welsh et al., 1994). Savings% expresses the percentage of words learned by the third trial that are retained at delayed recall. Possible effects of executive impairment on memory performances were studied using a sum score calculated as (TMTB – A) + (Stroop interference naming – color naming). Possible effects of working memory impairment on memory performances were examined using a sum score of the verbal and visual backward spans (sum of entities) of the Wechsler Memory Scale-III.

4.4 Verbal fluency tasks (Study IV)

Three different fluency tasks, with performance times of 60 seconds each, were used. Semantic fluency was assessed by the generation of animal names, phonemic fluency by the generation of words beginning with the letter S, and alternating fluency by alternating between two semantic categories, animals and furniture. The alternating fluency task was administered and scored according to the Parkinson neuropsychometric dementia assessment (PANDA) (Kalbe et al., 2008). The total correct raw scores were used for all analyses.

4.5 MRI imaging (Studies III and IV)

4.5.1 Voxel-based morphometry (VBM)

MRI images are well suited for computerized quantitative morphometric group analyses. Voxel-based morphometry (VBM) is a fully automated, straightforward whole brain analysis method, which can detect regionally specific differences in brain tissue composition, including gray matter. In the VBM procedure, images from all study subjects are first normalized into the same stereotactic space, then gray matter is extracted and smoothed from the normalized images, and finally, voxel-wise parametric statistical tests are performed on the gray matter segments to compare study groups (Ashburner & Friston, 2000).

In the present study, MRI data was acquired using a 1.5 T scanner (Philips Gyroscan Intera 1.5T CV Novo Dual) equipped with a SENSE head coil. For VBM analyses, T1-weighed three-dimensional fast field echo images were obtained in transverse planes with contiguous 1x1x1 mm voxels, 25 ms echo time, 30° flip angle, and field-of-view 256x256 mm yielding at least 160 contiguous slices. T2-weighted, diffusion and FLAIR sequences were obtained for visual evaluation.

Preprocessing of T1-weighted images was performed using the VBM8 toolbox for SPM. Voxel-wise analyses of gray matter segments were conducted using SPM8 running in Matlab R2011a (MathWorks, Natick, MA). Total intracranial volumes (TIVs) were obtained from native-space images. The images were normalized to Montreal National Institute (MNI) space using the high-dimensional DARTEL normalization procedure (Ashburner, 2007), and the images were partitioned into gray matter, white matter and cerebrospinal fluid images (Ashburner & Friston, 2005). The analyses were conducted using modulated images (1.5x1.5x1.5 mm voxels) (Ashburner & Friston, 2000), which were smoothed with a 10 mm full width half maximum Gaussian kernel to improve signal-to-noise ratio. The images were thresholded with voxel value 0.1 to include the whole brain and restrict the analyses only to the gray matter.

4.6 Statistical analyses

In **Study I**, independent samples T-tests were used to study behavioral differences in neuropsychological overall performance between PD patients and controls. Multiple comparisons were Bonferroni-corrected resulting in an alpha level of $p < .0016$.

As the distributions of the EEG data did not allow for parametric testing, nonparametric analyses were used for the ERD/ERS responses. Within-subjects effects were analyzed using the Quade test (Quade, 1979), which compensates for dependencies between preceding and following points in the time-frequency space within one channel. Between-group differences ($p < .05$) were analyzed using the independent samples Mann-Whitney U test. In order to minimize the risk of accepting false positives due to multiple testing, only those results in the between-groups probability matrices in which the temporal duration of the significant difference exceeded 100 ms were reported and discussed. The analyses were performed in a MATLAB 6.1 environment (The MathWorks Inc, 1999) using modifications of the Statistics Toolbox (Jensen, 2002a). Differences in response

accuracy between the two groups in the memory task were analyzed with the independent samples T-test.

In study II, multivariate analysis of variance (MANCOVA) was used to study overall group differences across the Memo-BNT subtests (BNT naming, Memo-BNT free recall, Memo-BNT free recall items 30 – 45, Memo-BNT free recall items 46 – 60, Memo-BNT recognition of temporal order total score), and the 20 Objects test free recall. Age was used as covariate. Follow-up univariate analyses of covariance (ANCOVA) were conducted for the individual test scores. A Bonferroni-corrected significance level was set to $p < .008$ for univariate analyses. Significant results were further examined by correlation analyses and mixed model ANOVAs. Potential associations with medication, motor symptoms, disease stage, attentive/executive measures, and subjective cognitive complaints were examined in relation to the significant results. Non-parametric tests (Mann-Whitney *U* test and Spearman correlation) were used when distributions did not allow for parametric testing. For data presentation, effect sizes (Cohen's *d*) for the parametric and non-parametric analyses were calculated according to the formula $d = M_1 - M_2 / \sigma_{pooled,}$ where $\sigma_{pooled} = \sigma_{full\ sample\ (n = 58)}$. A value of .20 corresponds to a small effect, .50 to a medium effect, and .80 to a large effect (Cohen, 1992).

The five examined Memo-BNT variables described above were included based on preliminary exploratory and correlational analyses. The Memo-BNT recognition of content subtest was excluded due to a ceiling effect (nearly all participants correctly recognized 100 % of the targets). To reduce the number of examined variables, none of the separate temporal ordering tasks were included in the MANCOVA (for details, see Publication II). As age, education and depression are known to affect cognition, correlation analyses were conducted between the background variables (age, education, GDS-15, MMSE) and the dependent variables. Age was significantly correlated with the Memo-BNT and 20 Objects test scores over the whole sample and was therefore used as a covariate in further analyses.

In study III, group differences on the demographic and clinical background variables were analyzed using the independent samples T-test, the Pearson chi-square test and the Mann-Whitney *U* test. Group differences on the memory measures (intentional memory task, incidental memory task, wordlist learning, wordlist delayed recall and savings%) were assessed using univariate ANOVAs and ANCOVAs. Non-parametric correlational analyses were conducted to examine possible relationships between the memory variables, executive functioning and working memory. Correction for multiple comparisons was performed resulting in a significance level of $.05 / 7 = p <$

.007. Post-hoc group comparisons (ANOVA) and correlative analyses with visual control tasks (Figure copy task of the CERAD, Block Design of WAIS-III) were performed for the intentional and incidental memory tasks. Effect sizes (Cohen's *d*) were expressed according to the formula $d = M_1 - M_2 / \sigma_{pooled}$, where $\sigma_{pooled} = [(\sigma_1 + \sigma_2) / 2]$ (also in study IV).

MRI images were analyzed using the general linear model (GLM) in SPM8. Potential confounding factors (gender, age, handedness, education and TIV in the whole sample; and UPDRS score in PD patients) were first analyzed using single variable regression. Factors associated with local gray matter were then added as nuisance covariates to subsequent multiple regression analyses. Of the tested variables, sex, age, and TIV were associated with local gray matter volumes. As sex and TIV were strongly correlated, only TIV was included as a covariate in further analyses. The raw scores of the memory variables (intentional memory task, incidental memory task, wordlist learning, wordlist delayed recall and wordlist savings%) were analyzed using multiple regression analysis. The analyses were performed at height threshold of uncorrected $p < 0.005$, and family-wise error corrected (FWE) cluster-level $p_{fwe} < 0.05$ was considered significant.

In **Study IV**, group differences on the verbal fluency measures were assessed using univariate ANOVAs and ANCOVAs using SPSS 21. Associations between verbal fluency, clinical and demographic background variables were examined using parametric correlations. The total correct raw scores of the three fluency tasks were then examined in relation to brain gray matter volume using VBM. The VBM procedures were identical to the analyses in study III, with the exception that the cerebellum was included in the whole brain analysis mask.

5 RESULTS

5.1 ERD/ERS responses during memory encoding and retrieval (Study I)

Both patients and controls performed well on the Sternberg memory task. The mean percentage of correct answers was 92.1 (*SD* = 2.8) for the control subjects and 92.0 (*SD* = 2.2) for the PD patients.

Memory encoding elicited statistically significant ERS in the *theta* frequency range (~3–8 Hz) in both PD patients and controls. Within the control group, significant synchronization in the *alph*a frequency range (~10–15 Hz) in posterior electrodes was also present. Between-group differences in the ERD/ERS TFR matrices were statistically significant at frequencies ~10–15 Hz at –200 to 1400 ms in posterior electrodes. These differences were due to the fact that in the PD group, encoding did not elicit ERS. ERD/ERS modulations within the two groups during memory encoding as well as significant between-group differences are shown in Figure 1.

Memory retrieval elicited statistically significant ERD in the *alpha* and *beta* frequency ranges (~6–25 Hz) in both groups. Within the control group, also significant *theta* (~3–6 Hz) synchronization was elicited in the ~50–700 ms time window in left temporal, central and parieto-occipital electrodes. Few statistically significant between-group differences in ERD/ERS responses were present. However, significant group differences were present in the ~600–900 ms time-window at anterior electrode locations. This was most likely due to the fact that stronger ERD was elicited in the PD group than in the control group during memory retrieval. Statistically significant differences between the groups were also observed in the 10–15 Hz *alpha* frequency range in the –200 to 100 ms time window in occipital and right temporal electrodes. This was related to the fact that the responses of the control group were characterized by weak synchronization whereas weak desynchronization was observed in the PD patients. ERD/ERS modulations within the two groups during memory retrieval as well as statistically significant between-group differences are shown in Figure 2.

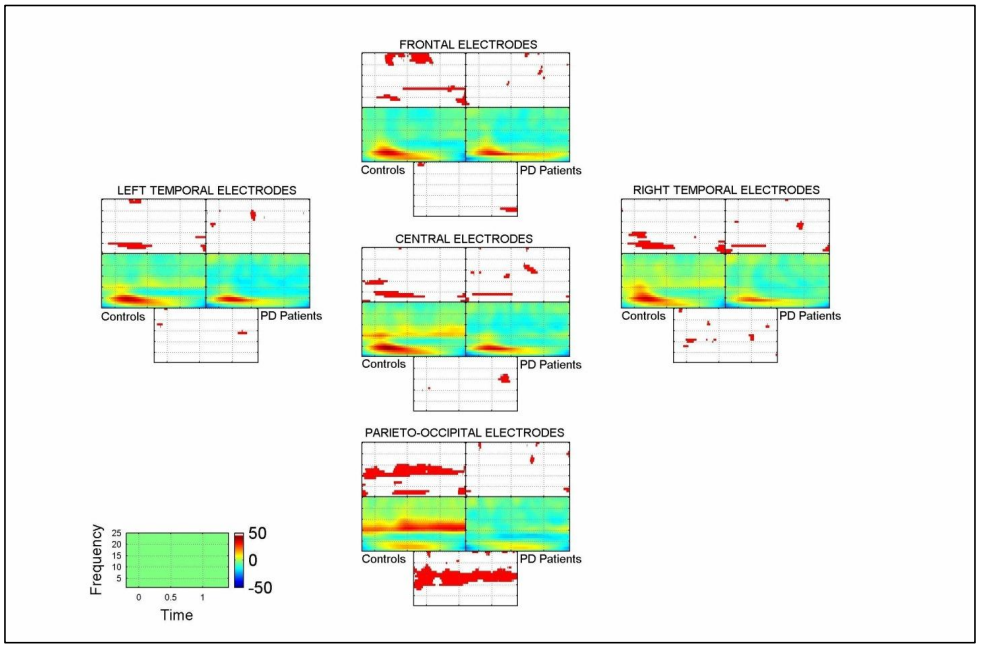

Figure 1. Grand average ERD/ERS TFRs and probability TFRs for the control group and the PD patients during the presentation of the memory set. In the grand average TFRs, red denotes ERS and blue denotes ERD. The *x*-axis depicts time (–200 to 1400 ms from stimulus onset), the *y*-axis depicts frequency (1–25 Hz). The probability matrix above each grand average ERD/ERS matrix displays the statistical significance of within-groups ERD/ERS responses ($p < .01$). The probability matrix below the grand average ERD/ERS matrices shows the significance of between-group differences in the ERD/ERS responses ($p < .05$)

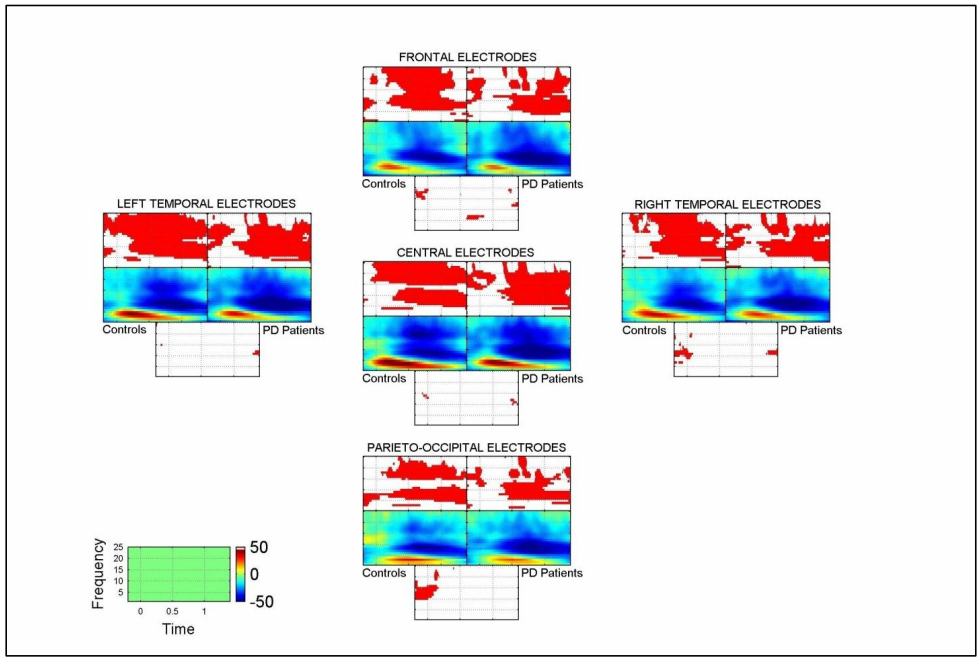

Figure 2. Grand average ERD/ERS TFRs and probability TFRs for the control group and the PD patients during the presentation of the probe. In the grand average TFRs, red denotes ERS and blue denotes ERD. The *x*-axis depicts time (–200 to 1400 ms from stimulus onset), the *y*-axis depicts frequency (1–25 Hz). The probability matrix above each grand average ERD/ERS matrix displays the statistical significance of within-groups ERD/ERS responses ($p < .01$). The probability matrix below the grand average ERD/ERS matrices depicts the significance of between-group differences in the ERD/ERS responses ($p < .05$).

5.2 Incidental and intentional memory performance (Study II)

Performances on the Memo-BNT subtest and the 20 Objects test. When the groups were first examined for overall differences across the Memo-BNT subtests and the 20 Objects test using MANCOVA, a significant main effect for group, but not for age, was found. Subsequent ANCOVAs showed that out of the six incidental Memo-BNT subtests, PD patients performed worse than controls only on Memo-BNT immediate free recall. There was a trend towards significance on Memo-BNT free recall items 30–45, but there were no significant group differences on BNT naming, free recall of items 46–60, or recognition of temporal order total score. PD patients performed significantly worse than controls on the intentional 20 Objects test free recall. Means

and standard deviations for the performance of the two groups on the individual measures as well as group comparison effect sizes (Cohen's *d*) are shown in Table 3.

Table 3. Neuropsychological performances and subjective cognitive complaints (CFQ) in the two groups.

	PD patients (*n* = 29) *M (SD)*	**Controls** (*n* = 29) *M (SD)*	*d*
Memo-BNT			
Naming (max.31)	26.7 (3.0)	27.8 (3.0)	-.36
Free recall (Incidental memory)	8.4 (3.1)	10.7 (2.9)	-.71**
Items 30-45	3.5 (2.1)	4.8 (1.9)	-.62
Items 46-60	4.9 (2.0)	5.9 (2.1)	-.48
Recognition of temporal order (%)	72.1 (10.0)	75.8 (10.3)	-.36
20 Objects test naming score	19.6 (0.8)	19.7 (0.5)	-.14
20 Objects test free recall (Intentional memory)	12.6 (2.5)	14.4 (1.6)	-.79**
Trail Making Test A (time)	37.7 (8.9)	32.2 (9.2)	.59*
Trail Making Test B (time)	83.5 (33.8)	72.0 (16.8)	.42
Trail set shifting score (%)	131 (107)	137 (71)	-.07
Stroop color naming score (time)	81.0 (21.8)	71.2 (11.0)	.55*
Stroop interference naming score (time)	137.2 (42.1)	116.5 (22.8)	.59*
Stroop inhibition score (%)	70 (31)	65 (33)	.16
CFQ Total score	38.1 (12.4)	29.3 (6.5)	.82*
CFQ Forgetting score	4.4 (2.0)	3.3 (1.4)	.60*

Note. ** $p < .008$, * $p < .05$.

Free recall after incidental and intentional encoding. In order to determine whether free recall would be differently affected in the incidental and the intentional encoding conditions, a mixed model ANOVA was performed. Significant main effects of group and encoding condition indicated that the PD patients performed worse than the controls on both tasks, and that all scores were higher on the intentional memory task. The higher scores on the intentional task were due to the fact that the two tasks were different regarding to the number of items (31 in the incidental task versus 20 in the intentional task). A non-significant interaction term indicated that the differences between the groups were similar in both task conditions. The performance scores on the incidental and intentional task in the two groups are presented in Figure 3.

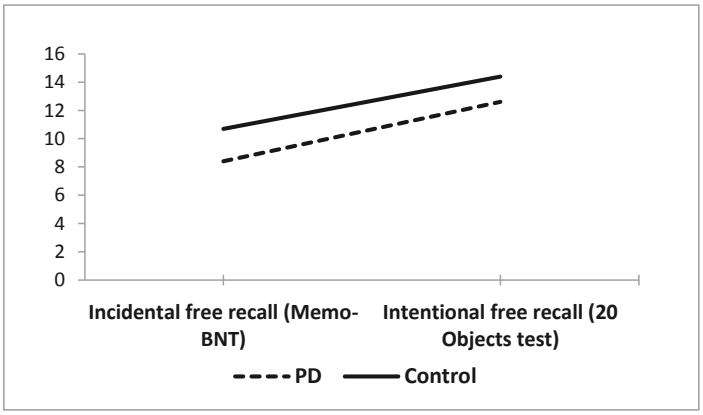

Figure 3. Free recall raw scores for the Memo-BNT and 20 Objects test.

A correlation analysis revealed a strong association between incidental and intentional task recall scores in the PD group (Figure 4). The corresponding association was absent in controls, indicating that the tasks were different in nature. Partial correlations showed that either age, GDS-15 score or naming scores on the two memory tasks influenced the observed associations between the two memory tasks in the PD group. The incidental and intentional task performances were not significantly related to PD medication, severity of motor symptoms, or disease stage.

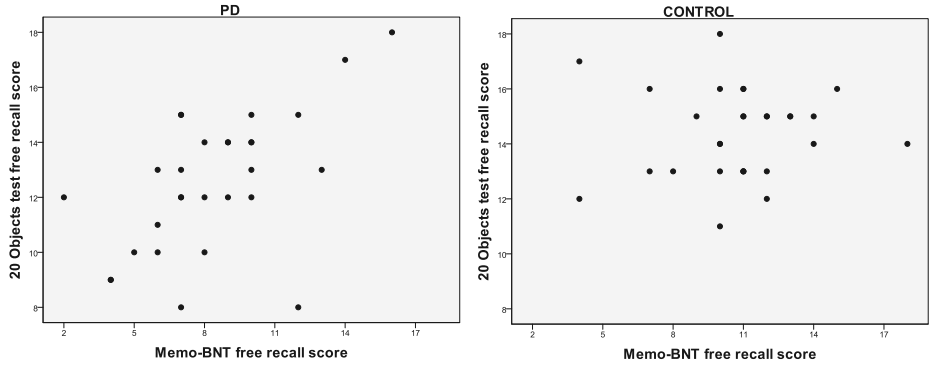

Figure 4. The relationships between the incidental and intentional recall raw scores for the two groups.

Free recall in relation to attentive/executive performance. In order to examine possible effects of attentive/executive functioning on memory recall, the set-shifting and inhibition proportion scores were examined in relation to Memo-BNT free recall and the 20 Objects test free recall. As the proportion scores of the two attentive/executive measures did neither differentiate the two groups, nor were they significantly correlated with either the incidental or the intentional free recall task, the raw scores of TMTA, TMTB, Stroop color naming, and Stroop interference naming were examined using correlation analyses for both groups separately.

In the PD group, Memo-BNT free recall was significantly associated with Stroop color naming, but not to Stroop interference naming, indicating that worse incidental performance was more likely associated with general slowing than to inhibition problems in PD patients. Strong associations between the 20 Objects test free recall and both Stroop conditions were also present, suggesting that worse intentional memory was related both to slowing and to impaired inhibition ability in PD patients. None of the memory tasks were associated with the more motor-dependent TMT visual tracking performances in the PD group. In the control group, none of the individual attentive/executive measures correlated with either of the two free recall tasks, indicating that the memory and attentive/executive variables were measures of separate cognitive functions.

Subjective memory complaints and memory test performances. Univariate ANOVAs showed that the PD patients reported significantly more cognitive slips in everyday situations than controls, as measured by the CFQ total score. The patients also reported significantly more memory-related problems, as measured by the CFQ Forgetting variable. However, a correlation analysis showed that subjective forgetting was not related to objective memory impairment (Memo-BNT free recall and the 20 Objects test) in either PD patients or controls.

5.3 Brain gray matter volume in relation to visual and verbal memory tasks (Study III)

Univariate ANOVAs showed that PD patients were significantly impaired on the two visual memory tasks (incidental and intentional free recall memory tasks). They were also significantly impaired on wordlist learning, but not on the delayed verbal measures (wordlist delayed recall and wordlist savings%). Age and education did not explain the impairment in memory performances. Nonparametric testing showed that the PD patients performed equal to controls on both of the executive and

working memory control tasks. Means and standard deviations on neuropsychological performances as well as between-group comparison effect sizes are presented in Table 4.

Table 4. Neuropsychological performances of the two groups.

	PD patients (n = 28) *M (SD)*	**Controls** (n = 28) *M (SD)*	*d*
Memory tasks			
Incidental free recall (Memo-BNT)	8.3 (3.1)	10.6 (2.9)	–.77*
Intentional free recall (20 Objects test)	12.5 (2.5)	14.4 (1.6)	–.91*
Wordlist learning (CERAD)	20.4 (3.3)	22.9 (3.1)	–.78*
Wordlist delayed recall (CERAD)	6.2 (2.2)	7.1 (1.9)	–.44
Wordlist savings% (CERAD)	79.4 (23.4)	81.4 (19.2)	–.09
Executive control tasks			
Executive cost sum score	97.9 (46.9)	84.8 (28.7)	.34
Working memory sum score	10.1 (1.8)	10.2 (1.4)	–.06
Visuospatial control tasks (Post-hoc analyses)			
Cerad Figure copy total score	9.9 (1.3)	10.8 (0.6)	–.87*
WAIS-III Block design total score	34.2 (9.8)	43.1(10.4)	–.88*

Note. $^{*}p < .01$

Within the PD group, worse delayed recall of the wordlist was significantly related to both worse executive and worse working memory performance. Worse wordlist savings% was related to worse working memory in PD patients. Wordlist learning was not significantly associated with either executive or working memory functioning in the PD group. None of the memory tasks or executive tasks was related to PD medication or motor impairment. In controls, wordlist learning was related to the executive control measure, but none of the memory tasks were associated with working memory performances. The visual intentional and incidental free recall tasks were not related to executive or working memory performance in either of the two groups.

The VBM analysis revealed no statistically significant difference between PD patients and controls in local gray matter volumes. The largest non-significant cluster with reduced gray matter volume in PD patients was observed in the right parietal cortex. When the memory performances were first analyzed in relation to gray matter volume over the whole group, lower score on the incidental memory task was associated with smaller local gray matter volume in the right parietal cortex (Figure 5A). Subsequent analyses revealed that lower incidental memory scores were associated with smaller right parietal gray matter volume in PD patients, but not in controls. The associated cortical regions were the right postcentral gyrus and the inferior parietal lobule (Brodmann areas 2 and 40) (Figure 5B). There were no other associations between local gray matter volumes and any of the other memory variables.

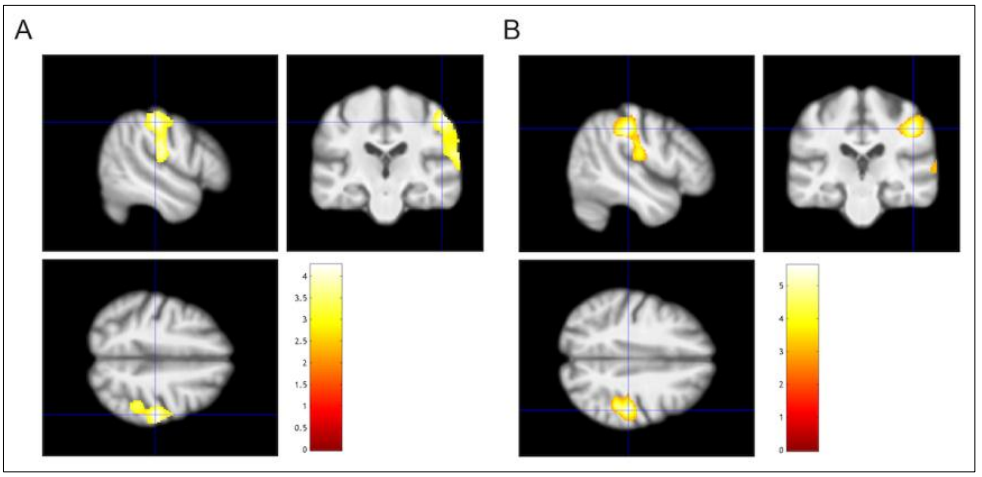

Figure 5. Association between right parietal gray matter volume and incidental memory (A) in the whole study group and (B) in PD patients, overlaid on the average, normalized within MNI space, T1-weighted image of the study subjects. The color bar represents T-values.

Due to the association between right parietal volume reduction and the incidental memory task in the PD group, post-hoc analyses were conducted for the two visual memory tasks in order to clarify their possible association with visuospatial functioning. Although univariate ANOVAs showed that the PD patients performed significantly worse than controls on both a simple figure copying task (CERAD) and the complex block design task of WAIS-III (see Table 4), a partial correlation analysis

accounting for age and education did not yield significant associations between visuospatial performance and performance on the two visual memory tasks. This suggests that the correlation between right parietal volume reduction and incidental memory performance in the PD group was most likely not due to or modulated by visuospatial processing deficits.

5.4 Brain gray matter correlates of verbal fluency (Study IV)

The PD patients performed significantly worse than controls on the alternating fluency task, but they performed equal to controls on the semantic and phonemic fluency tasks. Age and education did not explain the group differences, but they were differently related to fluency performances in the two groups. Means and standard deviations for the fluency performances of the two groups on the individual measures as well as group comparison effect sizes (Cohen's *d*) are shown in Table 5. Within the PD group, worse alternating fluency score was significantly associated with older age and lower MMSE score. Worse semantic fluency and lower MMSE score were associated only on a trend level. None of the verbal fluency measures were associated with education or motor impairment in the PD group. In healthy controls, worse phonemic and alternating fluency performance was associated with less education, whereas none of the verbal fluency tasks were related to age or MMSE scores.

Table 5. Verbal fluency performances of PD patients and controls.

	PD patients	**Controls**	
	M (SD)	*M (SD)*	*d*
Verbal fluency performances during 1 minute			
Semantic (animals)	24.8 (6.3)	26.6 (5.3)	-.31
Phonemic (letter S)	14.5 (5.8)	16.4 (5.0)	-.35
Alternating (animals, furniture)	15.3 (3.9)	17.3 (2.8)	-.59*

Note. $^{*}p < .05$

On the neuroanatomical level, lower phonemic fluency scores were associated with smaller volumes of the striatum in the PD group (Figure 6). The significantly associated regions were the right caudate nucleus, with the largest cluster size in regions of the head of the caudate, extending to the caudate body. Near-significant

associations were also found in the left hemisphere, involving the putamen and the left caudate head. The corresponding associations were absent in controls.

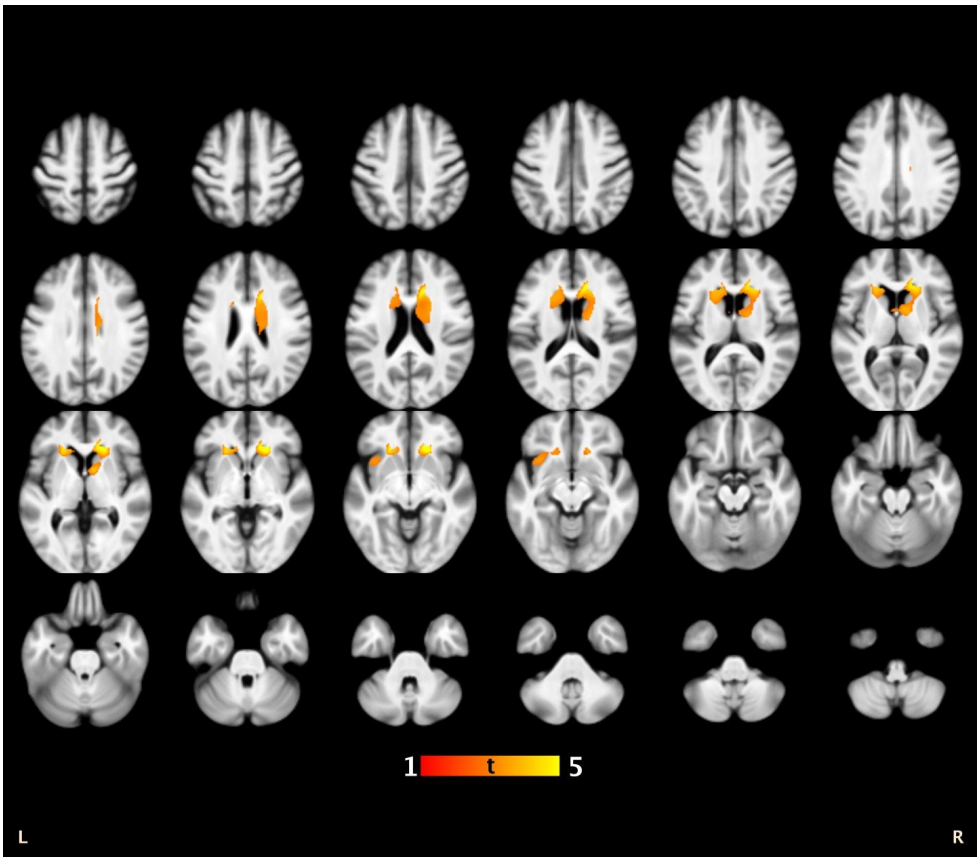

Figure 6. Associations between phonemic fluency and brain gray matter volume in PD patients. The results are shown at height threshold T = 2.80, $p < 0.005$ overlaid on the average normalized (MNI space) T1-weighted image of the whole study group. Only (near) significant clusters are shown.

Over the whole study group, lower semantic fluency scores were associated with smaller local gray matter volume in the left parietal cortex (Figure 7). The main associated region was the left precuneus (Brodmann area 7). A trend-level association was also found between worse semantic fluency and smaller bilateral cerebellar

volume over the whole study group. There were no associations between local gray matter volumes and the alternating fluency task.

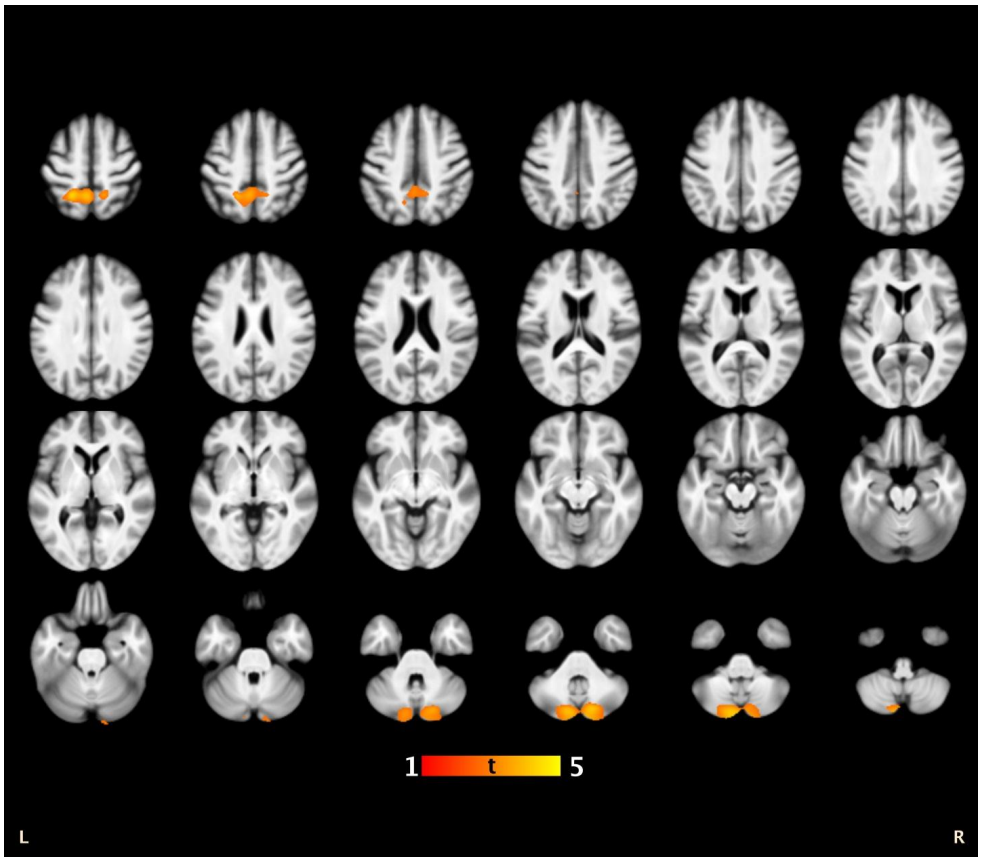

Figure 7. Associations between semantic fluency and brain gray matter volume in the whole study group. The results are shown at height threshold T = 2.68, $p < 0.005$ overlaid on the average normalized (MNI space) T1-weighted image of the whole study group. Only (near) significant clusters are shown.

6 DISCUSSION

The present work aimed at studying cognitive functions and their neural basis in early-stage, non-demented, medicated PD patients. Specific cognitive tasks were examined in combination with electrophysiological (EEG) and structural brain imaging (MRI) methods. Brain-behavior relationships of different aspects of memory and verbal functioning were the main focus.

6.1 ERD/ERS modulations during the encoding and retrieval phases of a working memory/ recognition task (Study I)

The neural background of memory encoding and retrieval processes has not been extensively studied in PD, and conclusive findings from early PD samples are lacking. It has been established that PD dementia is related to brain electric oscillatory activity slowing in resting state, but not much is known about the possible abnormalities in memory-related ERD/ERS responses in PD patients. The aim of study I was to explore the ERD/ERS modulations related to memory encoding and retrieval/recognition processes in PD patients who were at an early disease stage. In this study, a well-established Sternberg auditory working memory/short-term recognition paradigm was used.

ERD/ERS modulations in the control group during both encoding and retrieval were similar to those reported in previous studies for healthy adults during auditory information processing (Karrasch et al., 2004; Krause et al., 1996; Krause, Åström, Karrasch, Laine, & Sillanmäki, 1999). As expected, theta frequency ERS was elicited both during encoding and retrieval. Theta synchronization has repeatedly been demonstrated in relation to successful memory encoding and retrieval (Klimesch, Doppelmayr, Schimke, et al., 1997; Klimesch et al., 2001). In the alpha frequency range, encoding elicited ERS and retrieval elicited ERD. Alpha frequency ERS during encoding have been proposed to reflect active working memory maintenance and attentional processes (Jensen, 2002b; Klimesch, 1997; Pesonen et al., 2006). Alpha frequency ERD during retrieval has been proposed to reflect memory search processes and lexical-semantic activation (Klimesch, 1997). During both encoding and retrieval, alpha ERS was elicited in the control group also before the presentation of the stimuli. A possible explanation could be that the pre-stimulus alpha frequency ERS might be related to attentional direction processes and the fact that the subjects were expecting the stimuli. Alpha ERS has previously been found in conditions

where subjects control or withhold a response, thus it has been proposed that alpha ERS reflects inhibitory control and timing processes (Klimesch, Sauseng, & Hanslmayr, 2007). In context of the inhibitory control theory, alpha ERD has again been suggested to reflect the gradual release of inhibition. A third explanation is that the pre-stimulus response possibly reflects processes related to memory retention during the inter-stimulus-intervals.

Although both the PD patients and the controls performed equally well on the neuropsychological background measures and the experimental memory task, the ERD/ERS responses differed in the two groups. The most pronounced difference was observed during memory encoding. The posterior ERS in the alpha frequency range (~10-15 Hz) was absent in the PD patients. In similar experimental paradigms, alpha frequency ERS has been suggested to reflect active memory maintenance (Pesonen et al., 2006), thus the absence of alpha frequency ERS could possibly reflect a covert memory maintenance impairment in PD. The pre-stimulus alpha ERS, which was observed in the controls both before the presentation of the memory set and the probe, was also absent in the PD group. This finding is interesting but more difficult to explain. It is possible that the lack of pre-stimulus alpha ERS reflects changes in the maintenance of auditory information in working memory and memory retention in the inter-stimulus-intervals. Another possible explanation is that the absent pre-stimulus alpha ERS in PD patients may be a neural manifestation of altered inhibitory control processes and altered evoked responses, which are related to oscillatory phase resetting (Klimesch et al., 2007). There were few differences between the groups during retrieval, suggesting that auditory memory encoding might be more affected than short-term retrieval/recognition memory in early-stage PD.

ERD/ERS responses in auditory working memory tasks have to the author's knowledge not previously been studied in PD patients. Findings from one study (Schmiedt et al., 2005) utilizing a visual working memory paradigm suggest that both theta and alpha frequency modulations differentiate between PD patients and controls. Reduced posterior theta ERS in the PD patients was proposed to reflect disturbances in the integration of information in a visual-mnemonic network, while a reduction of upper alpha ERD in frontal locations was suggested to reflect an absence in the use of spontaneous encoding strategies, which are relying on fronto-striatal circuits (Schmiedt et al., 2005). Although the present study yielded no significant differences between the two groups in the theta frequency range during encoding, it is interesting to note that especially the upper alpha frequency appears to be sensitive to information processing alterations in PD patients in both auditory and visual working memory tasks.

Furthermore, it is intriguing to note, that the ERD/ERS responses during encoding and retrieval in auditory working memory tasks seem to differ in clinical populations of different neurodegenerative diseases. Findings in Alzheimer's disease patients have shown that ERD/ERS responses are altered specifically during memory retrieval, which has been suggested to reflect alterations in lexical-semantic memory processing (Karrasch et al., 2006). The current results and those reported by Karrasch et al. (2006) suggest that memory related ERD/ERS responses may reflect the different underlying neuropathological and cognitive changes in neurodegenerative diseases such as PD and AD. It is, however, important to acknowledge that the current understanding of the electrophysiological changes related to cognitive processing in clinical populations is limited. There are most likely multiple possible physiological explanations for EEG changes that correlate with cognitive status and cognitive performance in PD, and the precise circuitry defects underlying those changes are largely unknown (Caviness, Lue, Adler, & Walker, 2011).

In summary, the encoding of auditory information in a working memory task did not elicit an expected occipital alpha ERS in the PD group. A pre-stimulus alpha ERS seen in the controls was also absent in the PD group. The absence of such responses could be hypothesized to be an early neural manifestation of covert memory encoding deficits, possibly comprising abnormal inhibitory control and timing of cortical processing in early PD.

6.2 Incidental and intentional memory are equally affected in PD (Study II)

Study II aimed at examining incidental and intentional memory performances in early-stage PD patients. The main question was whether the encoding condition (incidental and intentional) is reflected in the ability to recall visual stimuli, and whether possible deficits in incidental or intentional recall are related to deficits in attentive/executive performance and/or subjective memory complaints. Based on previous research, PD patients were expected to perform worse than controls in the intentional encoding condition, and equal to controls in the incidental encoding condition. The main finding was that the PD group was equally impaired on both incidental and intentional free recall when compared to healthy controls. The expectation of a selective impairment in recall of intentionally encoded material was thus not supported. The fact that the PD patients were impaired on the intentional free recall memory task is in line with numerous studies (Elgh et al., 2009; Stebbins, Gabrieli, Masciari, Monti, & Goetz, 1999). Free recall of incidentally encoded items

has been scarcely studied in PD, and results have been mixed. Most studies seem to report impaired intentional, but intact incidental memory (Azuma et al., 2000; Cooper & Sagar, 1993; Vingerhoets et al., 2005). Ivory et al. (1999), however, found that non-demented PD patients were impaired on incidental recall of verbal material, but not on intentional recall. Conflicting findings have been suggested to relate to age-dependent factors such as chronological age at disease onset and differences in disease duration (Vingerhoets et al., 2005). Azuma et al. (2000) found that only demented PD patients were impaired on an incidental task, whereas non-demented patients performed equal to controls. However, in that study, PD patients using anticholinergic drugs were included with the most frequent use in the group classified as demented. Possible differences in results on incidental memory could also be related to the tasks used. If the incidental recall task is performed within the context of an intentional memory task (e.g. rating items on some contextual aspect that has not been the primary target of encoding), the task most likely activates encoding strategies, thus also facilitating incidental contextual encoding. As the Memo-BNT naming task instruction used in the present work includes no warning of items to be remembered, the incidental aspect of encoding most likely is minimally affected by intentional encoding strategies.

An interesting finding was that free recall in both types of encoding conditions were highly correlated in the PD group, while no such correlation was present in controls, indicating that the two memory tasks tap qualitatively different types of memory processes in healthy subjects. The strong positive correlation between the two recall performances in the PD group could indicate either that their memory encoding was deficient irrespective of whether they used intentional memory strategies or not. Another possibility is that the correlation was due to a general recall deficit.

Although it has been suggested that free recall problems may be secondary to fronto-striatal executive dysfunction (a consequence of disrupted connection between the caudate and the dorsolateral prefrontal cortex) (Higginson et al., 2003), no associations between memory performance and attentive/executive performance when using a combined measure of set-shifting and inhibition ability, were found. Instead, when examining the raw scores of each task, free recall after incidental encoding was significantly associated with Stroop color naming, but not to Stroop interference naming, indicating that worse incidental performance was more likely associated with general slowing than to inhibition problems in PD patients. Strong associations between the intentional memory task and both Stroop conditions were also present, suggesting that worse intentional memory was related both to slowing and to impaired inhibition ability in PD patients. The pattern of associations suggest

that the incidental task was more dependent on processing speed than the intentional task, which is supported by previous studies on the influence of psychomotor speed on free recall in non-demented PD patients (Stebbins et al., 1999). However, the influence of processing speed seemed to be task specific and perhaps pronounced in tasks demanding oral output, as none of the memory tasks were associated with the more motor-dependent TMT visual tracking task performances in the PD group. In the control group, none of the individual attentive/executive measures correlated with either of the two free recall tasks, indicating that the memory and attentive/executive variables were measures of separate cognitive functions.

An expected finding in study II was that PD patients reported more subjective cognitive and memory complaints than healthy controls. Relatively few studies have assessed subjective memory complaints in relation to objective performance in PD samples. Non-demented PD patients have been reported to be relatively aware of having memory problems, however, with poorer ability to identify the specific memory impairments (Ivory et al., 1999; Sitek, Sołtan, Wieczorek, Robowski, & Sławek, 2011). Objective cognitive decline has been found to be more frequent in PD patients with subjective complaints, but complaints alone have been found to poorly discriminate between demented patients and non-demented PD patients (Dujardin et al., 2010). In the present study, the subjective complaints were not related to memory performance in either the PD group or the control group. One possible explanation could be that the subjective memory complaints of the PD patients stem from a variety of cognitive deficits rather than from a specific memory impairment. Interestingly, similar discrepancies between subjective ratings of executive functioning and objective performance have been obtained in a study by Koerts et al. (2012). PD patients reported significantly more problems than controls in daily life executive functioning, but the complaints did not correspond with neuropsychological test performance. Discrepancies between subjective ratings and objective findings may be related to the ecological validity of neuropsychological testing. Structured testing situations and specific tasks mostly have a clear, predetermined goal and a limited set of available strategies is needed to reach the goal. Everyday situations, on the other hand, are unstructured, requiring self-generated setting of goals as well as initiating strategies to reach them. It can nevertheless be ascertained that the PD patients in the present work reported more subjective memory complaints and performed worse than controls on immediate memory recall. Most importantly, the finding indicates that subjective memory complaints exist among PD patients at an early stage of the disease, and that they can be interpreted at least to some extent, as an unspecific indicator of cognitive impairment.

In summary, the results of study II indicate that PD patients are impaired on immediate free recall of visual material regardless of encoding condition. In the PD group, the recall performances were mainly related to cognitive/psychomotor slowing, and not to attentive/executive task demands. Subjective memory complaints in PD patients were not related to impaired immediate free recall memory performance, thus they may reflect metacognitive awareness of general impairment stemming from mild deficits in several cognitive domains.

6.3 Brain gray matter volume is related to incidental memory in PD (Study III)

The aim of study III was to examine brain gray matter volume in relation to different aspects of visual and verbal memory tasks. Four conventional memory tasks and one incidental memory task were used. These included two visual, immediate free recall tasks that were introduced in study II (one incidental and one intentional). Additionally, three verbal memory measures were obtained from the CERAD verbal learning task; immediate and delayed recall, as well as memory consolidation. The main finding was a significant association between worse incidental task performance and reduced right parietal gray matter volume in PD patients. None of the other memory measures were associated with gray matter volumes. Statistically significant group differences in regional gray matter volumes were not observed, but there was a non-significant trend in right parietal gray matter volume, with PD patients having smaller volumes.

The association between right parietal gray matter volume reduction and worse performance on the incidental memory task only was unexpected. In comparison with the other memory tasks, the most distinct feature of the incidental task was the absence of an explicit instruction to memorize items. PD patients are known to perform worse on memory tasks when they have to self-initiate remembering strategies, but in the literature this has mostly been related to the disruption of the fronto-striatal circuit (Dujardin & Laurent, 2003). Another distinct feature of the incidental task was related to task difficulty in terms of memory load. The incidental memory task contained somewhat more items than the other, highly similar visual free recall task, and the verbal learning task. However, memory load alone may not fully explain the specific incidental memory correlation with brain volume in PD patients, as study II demonstrated that the two visual tasks were highly correlated in the PD patients.

The lateralization to right parietal regions was also unexpected. Interestingly, right hemisphere cortical thinning in parietal regions has previously been found in both cognitively intact (Pagonabarraga et al., 2013) and non-demented PD patients (Pereira et al., 2012). In PD patients with longer disease durations, gray matter reductions in bilateral parietal areas have been found to correspond with performance on visual form discrimination (Pereira, Junqué, Martí, Ramirez-Ruiz, Bargalló, et al., 2009). The right hemisphere is dominant for aspects of attention (Corbetta & Shulman, 2002), and the right parietal cortex has been related to interactions between different attentional processes (Cabeza & Nyberg, 2000). Parietal regions are believed to track the intention to remember by directing attention to memory contents (Corbetta & Shulman, 2002), as well as maintaining qualitative content, such as mental images (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). It is interesting to note, that the parietal lobe is one of the most frequently activated areas also during episodic memory retrieval (Wagner, Shannon, Kahn, & Buckner, 2005), and that dorsal and ventral parietal cortex seem to have distinct functions within episodic memory, as well as overlapping activity for memory and perception (Cabeza et al., 2011; Cabeza, Ciaramelli, & Moscovitch, 2012). One fMRI study (Christensen et al., 2012) using a verbal incidental memory task in healthy individuals, found that activity in the right inferior parietal and prefrontal networks was modulated by the level of attention during initial encoding.

Although many questions regarding the functional role of the parietal cortex remain (Levy, 2012; Singh-Curry & Husain, 2009), it is possible that the incidental memory task put more demand on retrieval after spontaneous 'on-line processing' and thus tapped parietal-driven attentive and mnemonic functions. There is functional imaging evidence of right lateralization effects for visual items (Nagel, Herting, Maxwell, Bruno, & Fair, 2013), thus the visual nature of the task items in the present study could also explain some of the right hemispheric lateralization. Within working-memory paradigms, right inferior parietal activity has been associated with memory for object location (Rottschy et al., 2012) and visuo-spatial imagery strategies to maintain information in short-term memory (Salmon et al., 1996). Although none of the visual free recall measures were directly associated with working memory performance, the visual content in the incidental memory task may have required subjects to rely more on visual imagery strategies instead of lexical-semantic search in order to access content from memory during free recall. Visuoperceptual aspects of the incidental memory task could contribute to the present parietal finding in PD patients. However, this seems less likely as the other very similar visual memory task was not related to gray matter volume. Also, post-hoc analyses of the neuropsychological measures indicated that that the right parietal volume reduction

associated with the incidental task in PD patients was not likely to be related visuospatial functioning.

Due to the fixed setting used in the study, it is not possible to definitively untangle whether the observed gray matter association was related to encoding or to retrieval. However, the fact that gray matter volume in PD patients was associated only with free recall following incidental encoding suggests that the finding was related to differences in the encoding conditions, and that different memory tasks may be differently reflected in gray matter volume. The lack of association between hippocampal gray matter volume and any of the other memory measures also suggests a non-dominant role of the hippocampal circuit in the free recall deficit seen in early PD.

The volumetric results are in agreement with previous studies, which generally have demonstrated significant regional gray matter atrophy in more advanced PD patients with cognitive impairment, but not in early-stage patients. In the earliest disease stages and in cognitively intact patients, others have found either no global or regional gray matter volume loss (Dalaker et al., 2010; Melzer et al., 2012) or they reported minimal changes (Agosta et al., 2012; Pereira et al., 2012). In relation to memory tasks, VBM findings have been absent in untreated patients (Dalaker et al., 2010; Martin et al., 2009) and restricted to the hippocampus when reported in non-demented or cognitively intact PD patients (Weintraub et al., 2011). The absence of volumetric changes and the intact memory consolidation performances in the present PD sample is consistent with the fact that the patients were at early stage of the disease with no significant cognitive impairment. The fact that the PD patients performed worse than controls on the verbal learning task, but they were not impaired on delayed recall or memory consolidation, is also consistent with findings drug-naïve patients (Brønnick et al., 2011). In the present study, verbal learning, delayed recall and memory consolidation were associated with executive and working memory functioning predominantly in the PD group, which is also in line with previous findings in PD (Higginson et al., 2003). None of the two visual free recall memory tasks were related to executive functioning or working memory in either of the groups, suggesting that verbal memory may rely more strongly on executive functioning than does visual memory.

In conclusion, smaller right parietal gray matter volume in early-stage PD was related to worse free recall on an incidental visual memory task, but there were no associations between gray matter volume and conventional visual and verbal memory tasks.

6.4 Phonemic fluency is related to striatal volume in PD (Study IV)

The aim of study IV was to examine brain gray matter correlates of semantic, phonemic, and alternating verbal fluency. Despite substantial evidence on verbal fluency deficits at different stages of PD (Henry & Crawford, 2004b), information on underlying neural substrates has been lacking. Whilst reduced semantic fluency has been related to an increased risk of PDD (Evans et al., 2011) which is also associated with widespread cortical atrophy (Duncan, Firbank, O'Brien, & Burn, 2013), it is not known if different fluency tasks are reflected differently in brain gray matter at initial disease stages. The main finding was a significant association between worse phonemic fluency performance and smaller gray matter volume of the right caudate in PD patients. The corresponding association was absent in controls. Additionally, across the whole sample, worse semantic fluency performance was associated with smaller, dominantly left hemisphere parietal gray matter volume. A trend-level association between worse semantic fluency and smaller bilateral cerebellar GM volume was also found across the whole sample, but not in the separate groups. Alternating fluency was not associated with local gray matter volume in any of the two groups or across whole sample.

In non-demented PD patients, associations between worse semantic fluency and reduced temporal, frontal and cerebellar volumes have previously been reported in one study (Pereira, Junqué, Martí, Ramirez-Ruiz, Bartrés-Faz, et al., 2009). Thus, the present association between phonemic fluency, but not semantic fluency, and local gray matter is in contrast with previous findings. This contrast may be related to fact that the patients in the present study were younger (age < 65 years) and were at an earlier disease stage (disease duration < 3 years) than the PD patients in the previous study (age > 70, disease duration > 10 years). In the present work, a more conservative statistical threshold was also applied, which may partly explain some of the differences between previous and present findings. The present results suggest that phonemic processing in early PD is related to striatal volume, mainly the caudate head, in the absence of significant behavioral decline or significant local GM atrophy.

The phonemic fluency and GM volume correlation in the PD group was significant in the right caudate, whereas the association with the left caudate showed only a trend toward significance at corrected threshold levels. Whilst activation studies mainly report language-related tasks in left hemisphere locations (Birn et al., 2010), right volumetric caudate dominance for phonemic fluency has been reported in healthy individuals (Grogan et al., 2009). Both right (Apostolova et al., 2010; Burton, McKeith,

Burn, Williams, & O'Brien, 2004) and bilateral (Nagano-Saito et al., 2005) caudate atrophy has been reported in PDD patients, but it remains unclear if structural caudate volume loss contributes to cognitive decline in PD. One study (Pitcher et al., 2012) reported diminished caudate volumes in cognitively normal PD, PD-MCI, and PDD patients, but the degree of atrophy was not related to cognitive status. However, neuroanatomical correlates of single cognitive measures such as verbal fluency were not reported.

There were no significant associations between semantic fluency and gray matter volumes in either the PD patients or in controls. However, across the whole group, worse semantic fluency scores were associated with smaller, dominantly left hemisphere parietal gray matter volume, including parts of the precuneus. The functions of this posteromedial cortical area are not well understood, but it has been associated with a variety of highly integrated tasks, such as visual imagery and episodic memory retrieval (Cavanna & Trimble, 2006). At trend level, worse semantic fluency was also associated with smaller cerebellar volumes. The cerebellum has repeatedly been associated with verbal fluency tasks in functional imaging studies (Gauthier, Duyme, Zanca, & Capron, 2009; Weiss et al., 2003), and greater cerebellar engagement has been demonstrated in easy relative to more demanding fluency task conditions (Senhorini et al., 2011).

Out of the three fluency tasks, only alternating fluency was significantly impaired in PD patients. The task required switching between two semantic categories, thus both semantic search and switching mechanisms were needed to perform well. The fact that the PD patients performed worse than controls on this theoretically most demanding "frontal" task is in line with previous studies reporting larger deficits in alternating semantic fluency than on standard semantic fluency tasks in PD (Henry & Crawford, 2004b; Pagonabarraga et al., 2008; Zec, 1999). As the alternating fluency task was not related to gray matter volume, it seems likely that alternating fluency deficits in early-stage, non-demented PD are related to functional, rather than structural, disruptions of the fronto-striatal circuitry, and may best be captured using functional imaging approaches. Associations between attentional set-shifting, dopamine levels and fronto-parietal networks (Williams-Gray, Hampshire, Barker, & Owen, 2008) as well as hypometabolism in the dorsolateral prefrontal cortex (Sawada et al., 2012) have previously been reported in PD. Interestingly, in PDD patients with longer disease duration, alternating fluency has also been associated with cortical thinning of the parahippocampal gyrus, lingual gyrus, and precuneus (Pagonabarraga et al., 2013). In contrast to the findings of Pereira et al (2009), no

associations between any of the verbal fluency performances and motor impairment were found in the PD group.

Most studies have examined only phonemic and semantic fluency in PD, and they generally reported more pronounced semantic than phonemic fluency deficits (Henry & Crawford, 2004b). Based on the present findings, these differences may be less pronounced at early disease stage and in cognitively preserved patients. Only the alternating fluency task was difficult enough to differentiate between cognitively preserved, early-stage PD patients and controls, supporting previous suggestions that alternating fluency tasks are useful in early diagnostic settings (Pagonabarraga et al., 2008).

In summary, phonemic fluency, but not semantic or alternating fluency, was related to brain gray matter volume in PD patients. The associated neuroanatomical region was located in the right caudate. Worse semantic fluency was related to smaller left parietal and at trend level bilateral cerebellar, gray matter volume over the whole group. On the behavioral level, PD patients performed worse than controls only on the alternating fluency task. The results indicate that different verbal fluency tasks are related to different neural substrates, and that alternating fluency is more impaired than semantic and phonemic fluency in early-stage, non-demented PD.

6.5 Methodological considerations and future directions

As a general remark, it is important to note that the results of the present study are based on relative small convenience samples. Small samples often result in low statistical power, increasing the risk for type II errors, i.e. not detecting significant results when they are present. Selection bias related to the present PD sample may have resulted in better functioning PD participants, while patients with more impairment might have declined. Previous studies have indicated, that younger PD patients tend to be more active participants (Muslimović, Post, Speelman, De Haan, & Schmand, 2009), and that longitudinal participant attrition is greater for those who have greater disease severity at baseline (Broeders et al., 2013). Thus, the true extent of impairment might have gone undetected in the present sample. It is possible, that the opposite selection bias is true for controls, resulting in false healthy volunteers performing below their premorbid level. However, the latter is less likely in the present work, as the controls especially in studies II-IV were very extensively screened prior to inclusion. All groups used in the study were also thoroughly

matched for age and education on the group level, thus further diminishing the possibility of additional age- and education related confounders.

Another general issue concerns the principles of conducting and interpreting statistical testing in the present work. First, as a general rule, non-significant neuropsychological results were not discussed. Second, correction for multiple comparisons was performed using rather strict criteria. Third, some of the data was not normally distributed in the PD group. As a consequence of this fact, non-parametric testing was performed, which is a less powerful way of detecting differences between groups. All the before mentioned choices were made to reduce the risk of conducting type I-errors, i.e. reporting false positive results. However, some of the criteria may have been too strict to reveal subtle trends in the data. Considering the relatively small sample and the large symptom variability in PD (both inter- and intra-individual variability in terms of cognitive profile coherence), the group differences reported here most likely represent robust findings. In order to demonstrate the magnitude of the observed findings, effect sizes were presented along with neuropsychological performances within the results section.

In study I, several methodological issues should be pointed out. First, the sample was very small, thus the findings need to be further validated in larger samples. As a result of both efforts to reduce the heterogeneity of the PD study group, as well as high criteria regarding the quality of the EEG-data, several PD patients had to be excluded due to either not using L-dopa or due to insufficient EEG task trial data as a consequence of movement induced artifacts. Standard clinical ratings of motor functioning (UPDRS-III) or disease stage (H&Y) were also not available. While the small sample most likely was compensated by repeated trials in the experimental task, the small sample size reduced the number of conclusions that could be drawn from the neuropsychological background data. Unexpectedly, there were no significant differences between the groups on the neuropsychological background measures. This was likely due to a few high performing PD individuals and strict correction for multiple testing. However, PD patients did show a trend towards impairment on associative wordlist learning as well as on a visual memory task, which is consistent with de novo and early-stage PD samples (Brønnick et al., 2011; Elgh et al., 2009)

Additionally, The ERD/ERS responses in study I most probably reflect both induced and evoked EEG activity. Thus, in the future phase-locked components could be studied. The early initiated responses occurring after the presentation of both the stimuli and the probe are most likely influenced by phase locked components related

to acoustic stimulus perception, i.e. the N1 in the ERPs (event-related potentials). By means of the EEG signal analysis technique used in the present study (wavelet analysis) it was not possible to discriminate between phase-locked and non-phase locked oscillatory responses. The presence of pre-stimulus alpha ERS responses as well as the simultaneously appearing ERPs is, however an important issue for future studies investigations. In light of the accumulating data from quantitative resting state EEG-studies showing clear associations between a shift towards lower frequencies and PD cognitive impairment, it would be interesting to further investigate the ERD/ERS correlates in relation to memory processing in patients who are at different disease stages. However, if repeated measures are performed within the same individuals (e.g. longitudinal settings), test-retest consistency effects need to be acknowledged. Within a 9-day time interval, the highest consistency (measured during a memory task) in healthy individuals has been found in the theta frequency (4–6 and 6–8 Hz), with poorer consistency in the 8–10 Hz range, and the poorest consistency in the 10–12 Hz frequency range (Krause, Sillanmäki, Häggqvist, & Heino, 2001).

In study II, the main methodological issue was related to the incidental and the intentional tasks that were used. Although both of the two free recall tasks were similar with regard to the visuo-verbal qualities of the tasks, they were not identical regarding the number of items, time of exposure to items, sequence of exposure to items, or item difficulty. Future studies need to address intentionality in counterbalanced experimental settings. This would require a larger set of similar incidental and intentional task items, as an incidental exposure cannot be repeated. Repeated measurements induce task expectations, which in turn activate conscious encoding strategies and semantic networks, and thus the incidental aspect of episodic memory is lost (Pause et al., 2013). Another issue that should be emphasized is that incidental memory in the present work refers to the *explicit retrieval* of information acquired in the context of an unexpected task in the absence of any instructions at *encoding*. The concept of incidental memory is thus not directly comparable to the concept of implicit memory, which in the literature has been defined as the *unconscious retrieval* of past events (Dew & Cabeza, 2011). The concepts of incidental and implicit memory are, however related in the sense that they both refer to unintended aspects of memory. It is therefore tempting to speculate that incidental and implicit memory may in fact be different sides of the same coin, possibly engaging common neural networks, which in turn arises interesting questions for future investigations on episodic memory in PD.

The ecological validity of incidental memory tasks should also be acknowledged, as they may provide valuable insights to the everyday functioning of PD patients. The Memo-BNT is a novel, simple and time efficient extension of an existing, widely used valid naming test. Free recall has been shown to reliably differentiate between mild AD and healthy old controls (Karrasch et al., 2010). The current Memo-BNT, however, has some limitations, including a lack of a delayed recall measure and a clear ceiling effect in the recognition task. Possible effects of delay should indeed be studied in the future, and delayed recall can easily be added to the original test protocol when used in a clinical assessment setting. Future studies including larger samples and patients at more advanced stages of PD should be conducted in order to further address the possible diagnostic properties of the Memo-BNT in identifying PDD. Further, incidental testing paradigms using different types of stimulus modalities could provide useful and ecologically valid information on episodic memory in PD.

Regarding the findings in study III and IV, it is important to note that these studies addressed neuroanatomical, structural changes in relation to separate cognitive task performances. The findings can thus not directly be compared to results obtained using functional brain imaging techniques, such as fMRI, which measure neural events as they occur during the performance of specific cognitive tasks. The present findings, however contribute to the understanding of structural changes in early-stage PD. When relating the results from study III to previous correlative structural imaging studies in PD, it is also important to note, that most have used verbal memory tasks such as the California Verbal Learning test or Rey Auditory Verbal Learning test. In these tasks, an explicit instruction to memorize is given, which automatically creates an intentional condition. Thus most currently available information on structural correlates of memory in PD comprises intentional verbal memory, which may rely more on semantic memory systems, instead of engaging episodic memory (Pause et al., 2013).

It is also noteworthy that possible early stage functional disruptions of the hippocampus cannot be excluded by structural imaging, and that VBM might not be an optimal method for analyzing small subcortical structures like the hippocampus. It has been suggested, that surface-based neuroanatomical approaches such as cortical folding and cortical thickness may be more sensitive methods than VBM to identify subtle changes (Pereira et al., 2012). As both cortical and subcortical neural networks are thought to be involved in both intentional and incidental memory in healthy individuals, further studies are needed to establish the role of brain volumetric degeneration in free recall deficits in early PD. Functional brain imaging studies on

free recall could contribute to the understanding of memory in PD from early stages and prior to overt symptoms of hippocampal atrophy.

Regarding the neuroanatomical correlates of verbal fluency performances in PD, it is worth to note that in healthy elderly, age has been found to have a greater impact on semantic fluency than on phonemic fluency (Mathuranath et al., 2003; Stokholm, Jørgensen, & Vogel, 2013). This suggests that age is an important factor to consider when comparing verbal fluency findings across studies. It is possible that some of the variability in semantic fluency tasks previously reported in PD may be moderated by the effect of age, as most have studied older (> 65 years) PD patients. Different types of fluency also seem to be differently related to education, as in the present sample, worse phonemic and alternating fluency were related to less education in controls, but not in PD patients. Pereira et al. (2009) also found that phonemic, but not semantic fluency was related to education in PD patients, but the mean performances and mean education levels of the PD patients in that study were clearly lower than the performance scores and education levels of the PD patients in the present study.

When interpreting the results from the present work, it should be noted that subgrouping of PD patients according to cognitive status was not performed. Instead, the sample was restricted to early stage, short disease duration PD already at the inclusion phase of the study. A majority of studies reporting anatomical correlates of cognitive tasks in PD have included older (≥ 65 years) PD patients with longer disease durations (≥ 5 years) (Beyer et al., 2013; Filoteo et al., 2013; Nishio et al., 2010; Pagonabarraga et al., 2013; Weintraub et al., 2011). Future studies including younger patients at initial disease stages could therefore improve the understanding of the neural changes associated with cognitive impairment at different stages of PD. However, as cross-sectional cohort studies may yield varying results depending on variability in patient selection and cognitive subtyping across studies, longitudinal settings will be necessary for a better understanding of the full neurocognitive trajectory in PD.

A final important question regarding all studies in the present work concerns possible influences of motor impairment and effects of PD medication. It's noteworthy, that in the present work, none of the examined neuropsychological variables were related to the degree of motor symptoms as measured by the UPDRS-III or daily intake of PD medication as measured by LEDD. This suggests either that medication has little impact on cognitive performance, or that all the PD patients were in optimal medicated state. All patients in the present study reported to be stable on their medication, and patients receiving anticholinergic drugs were

excluded. There is currently insufficient evidence-based information on the cognitive effects of PD medication (for a review, see Poletti & Bonuccelli, 2013). Clinical studies have shown that the effects of dopaminergic medications may vary depending on the stage of the disease and motor status of patients (Pagonabarraga & Kulisevsky, 2012). In the earliest stages, medication-induced improvement has been found in learning, memory, visuospatial, and frontal tasks, but the effects are not sustained over time (Kulisevsky et al., 2000). Other studies have found modest positive effects on tasks involving flexibility and working memory, while amnestic features such as visual recognition memory, associative learning and verbal memory seem unaffected (Kehagia et al., 2010). Contradictory effects have been explained by the spatiotemporal progression of dopamine depletion in the striatum (Poletti & Bonuccelli, 2013). Adverse cognitive effects such as impaired learning- and decision making have been related to the overdosing of the ventral striatum, while improving functions that rely on the dorsal striatum (Kehagia et al., 2010). Comparisons between on/off state in L-dopa treated PD patients have shown only slight modulations on resting state EEG spectral power, namely decrease in right frontal theta, left occipital beta and left temporal gamma as well as increase in right parietal gamma frequency after intake (Stoffers et al., 2007). Based on the before mentioned findings, it is plausible to assume that PD medication probably diminished behavioral and electrophysiological differences between the controls and the early-stage PD patients in the present study.

As longitudinal studies have found that the most disabling long-term problems of PD relate to symptoms which are not improved by L-dopa (Hely, Morris, Reid, & Trafficante, 2005), it is of uttermost importance that future studies on PD continue to investigate the spectrum of non-motor symptoms, including cognitive impairment and dementia, and their underlying neural manifestations. The results from the present study demonstrate that neurocognitive changes may be present in PD already prior to the stages when formal criteria of mild cognitive impairment or dementia are fulfilled, thus bringing to light the importance of including early-stage PD patients in future studies. A better understanding of the different cognitive trajectories in PD may support the targeting of future therapeutic interventions and improve quality of life for PD patients.

SUMMARY AND CONCLUSIONS

The present work addressed neurocognitive changes in early-stage, non-demented, and medicated PD. Electrophysiological, neuropsychological and structural brain imaging methods were used, with particular focus on aspects of short-term memory and verbal functioning. The findings revealed subtle neural manifestations of overt and covert dysfunctions within the domains of memory and verbal functioning.

Study I
Encoding of auditory information in a working memory/recognition task did not elicit occipital alpha ERS in the PD group. A pre-stimulus alpha ERS seen in the control group was also absent in the PD group. Absent responses in PD patients may be a neural manifestation of covert memory encoding impairment, possibly comprising components of abnormal inhibitory control and timing of cortical processing.

Study II
PD patients were impaired on immediate free recall of visual items regardless of the intentionality of the encoding condition. Recall performances were associated with cognitive/psychomotor slowing, and not to attentive/executive task demands. PD patients also had more subjective memory complaints than controls. Complaints were not related to memory performances, thus memory complaints may reflect metacognitive awareness of general impairment stemming from mild deficits in several cognitive domains.

Study III
Worse free recall on an incidental visual memory task was related to smaller right parietal gray matter volume PD in patients. No associations between gray matter volume and conventional visual and verbal memory tasks were present. Whilst both cortical and subcortical neural networks are believed to be involved in both intentional and incidental memory in healthy humans, further studies are needed to establish the role of brain volumetric degeneration in free recall deficits in early PD.

Study IV
Worse phonemic fluency, but not semantic or alternating fluency, was related to smaller brain gray matter volume in PD patients. The associated striatal regions were located in the right caudate. Worse semantic fluency was related to smaller left parietal and at trend level bilateral cerebellar, gray matter volume across groups. On

the behavioral level, PD patients performed worse than controls only on the alternating fluency task. The results suggest that different verbal fluency tasks are related to different neural substrates, and that alternating fluency is more impaired than semantic and phonemic fluency in early PD.

General conclusion

The present work revealed manifestations of subtle, but behaviorally measurable dysfunctions in memory and verbal functioning as well as evidence of more covert changes in the neural networks subserving these functions in early-stage, non-demented, medicated PD patients. The findings demonstrate that neurocognitive changes may be present in PD already prior to the stages when formal criteria of mild cognitive impairment or dementia are fulfilled. In order to expand the knowledge of the different cognitive trajectories in PD, patients at an early disease stage should be included in future studies on cognitive functioning. The findings also have clinical implications. Identifying cognitive deficits through neuropsychological assessment, even if mild, may help PD patients increase their awareness of cognitive strengths and weaknesses, and to develop compensatory strategies for coping in everyday life.

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