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Executive functioning in early stage Parkinson's disease

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Executive functioning in early stage Parkinson's disease

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Summary

Background: Cognitive decline is commonly reported in Parkinson's disease (PD), with some deficits evident even at the onset of PD. Executive functions (EF) are extensively studied in PD and emerge as the domain involving the most profound deficits. Nevertheless, there are some inconsistencies in the literature with regard to the exact pattern of executive deficits and their impact on everyday life in PD. The aim of the literature review presented in this thesis was to synthesise and clarify existing research evidence on EF in early stage PD, and to explore what are the possible factors affecting the consistency of research findings. The empirical studies had three distinct aims: to clarify the pattern of EF deficits in PD; to determine how accurately PwPD appraise potential EF-related difficulties; and to identify how executive deficits impact on people with PD (PwPD) and their families.

Method: Studies of EF in PD were systematically reviewed and the findings were synthesised in a series of meta-analyses. Three empirical studies drew on cross-sectional data collected from PwPD and their caregivers, and from healthy older controls. Sixty-five PwPD in mild to moderate stages of PD completed an assessment of EF, awareness, quality of life, and health status, and 43 healthy older controls completed assessment of EF and awareness. Fifty caregivers of PwPD rated the EF of the PwPD and their own burden associated with caring for a PwPD. A sub-group of 34 PwPD, identified as having potential EF deficits, completed a more extensive neuropsychological assessment of executive abilities.

Results: The systematic review included 33 studies of EF in early stage PD, and meta-analysis of data from 5 commonly-used tests of EF revealed consistent evidence for executive deficits. The review suggested that the consistency of the research evidence may

be improved by more precision in defining EF and more careful selection and interpretation of EF measures. A data-driven analysis examining the pattern of EF impairment distinguished differences between two groups of standard tests of EF, with attentional control tests more frequently compromised than abstract thinking in early stage PD. PwPD were found to be accurate when making general evaluative judgments about their own functioning, but in specific tasks PwPD with executive deficits overestimated their performance in comparison to PwPD without EF deficits and healthy controls. EF-related behavioural difficulties were shown to impact on subjective quality of life in PwPD and on burden in their caregivers.

Conclusions: The results of this thesis suggest that EF-related difficulties are frequently present in early stage PD, with attentional control aspects of EF particularly affected, that it may be difficult for PwPD to accurately appraise their own ability to carry out specific activities, and that EF-related difficulties have a significant impact on quality of life in PwPD and their families. A thorough understanding of executive deficits in PD is important in the provision of adequate person-centred care for PwPD and their family members, and could help to inform the development of PD-specific rehabilitative interventions aimed at reducing activity limitation and restrictions on social participation and supporting PwPD in living well with the condition.

Chapter 1

Introduction

1.1 Introduction

Parkinson's disease (PD) not only affects movement, but is also associated with numerous non-motor symptoms, including cognitive decline. Extensive research into cognition in PD demonstrates that deficits in the executive function (EF) domain are common even at the earliest stages of the disease. However, there are certain limitations in the existing literature. The reported prevalence rates and characteristics of executive deficits differ substantially between studies. There is limited understanding of how people diagnosed with PD (PwPD) perceive their executive functioning and how accurate they are in acknowledging potential EF-related difficulties. Finally, we know surprisingly little about the impact of EF deficits on the quality of life of PwPD and their families.

Thorough understanding of the nature of EF deficits and their impact on PwPD is crucial for providing adequate person-centred care for PwPD, as it may facilitate development of targeted medication and may provide a basis for developing non-pharmacological treatments (Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006; Wurtman, 2012). While it might not be possible to address underlying executive impairment directly, it might be possible to improve self-management of the deficits and reduce activity limitation (functional disability) and restrictions on social participation (handicap) through a rehabilitative approach (Clare, 2008; World Health Organisation, 1998). For example, cognition-focused interventions can help to reduce the secondary consequences of cognitive impairment, such as loss of confidence or restriction of activities (Reifler & Larson, 1990).

This thesis aims to address the above-mentioned limitations, extend our understanding of executive deficits in PD, and assist development of adequate person-centred support for people with PD.

The following sections will introduce background information relevant for the studies presented in this thesis. First, prevalence, neuropathology and symptoms of Parkinson's disease (PD) will be briefly summarised. Then, definitions of executive functions (EF), the neuronal basis of EF, and methods for assessing EF will be described. Finally, research on EF in PD will be discussed, and research questions and methodology for this thesis will be introduced.

Following the introductory chapter, one chapter outlines a systematic review and meta-analysis and three chapters report findings from an empirical study. In the final chapter the results from the empirical chapters are summarised and discussed in the context of existing evidence.

1.2 Prevalence, neuropathology and symptoms of Parkinson's disease

Parkinson's disease (PD) is, after Alzheimer's disease, the second most common neurodegenerative disease, with the prevalence rate in Europe estimated as 108 to 257 per 100,000 people. The prevalence of PD is higher in older age, with a prevalence rate of 1280 to 1500 per 100,000 in people over 60 (von Campenhausen et al., 2005). It is estimated that in 2005 there were around 4.5 million PwPD in the five most populous nations of Western Europe and the world's ten most populous nations, and this number is expected to double by 2030 (Dorsey et al., 2007).

The central pathological feature of PD is loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to dopaminergic deficiency in the striatum and subsequently affects other brain regions (Dauer & Przedborski, 2003). The cell loss occurs in various brain areas, including non-dopaminergic structures, for example the nucleus basalis of Meynert (acetylcholine) and the raphe nucleus (serotonin). There are numerous processes leading to cell death in PD, some of which are also observed in other age-related neurodegenerative conditions as well as in normal aging. These processes include the presence of intraneuronal proteinacious cytoplasmic inclusions (Lewy Bodies) in brain tissue, protein misfolding and aggregation related to ubiquitin-proteasomal system dysfunction. Other pathologies are associated with mitochondrial dysfunction, impaired lysosome- and chaperone-mediated autophagy, as well as glutamate-related excitotoxicity and oxidative stress (Hindle, 2010). In contrast to relatively well-described pathological changes, the causes of PD are less clear. There is evidence for genetic factors in some cases, classed as familial, as opposed to sporadic, PD. It has also been observed that the neurodegenerative process may be provoked by the exposure to environmental (e.g. pesticides and herbicides) or endogenous neurotoxins(Dauer & Przedborski, 2003). However, the exact causes of PD are unknown.

The clinical presentation of PD is multifaceted and clinically heterogeneous, with numerous symptoms affecting various aspects of functioning. There are four cardinal motor symptoms of PD: resting tremor, bradykinesia, rigidity, and impaired postural reflexes (Jankovic, 2008). Resting tremor in PD is described as supination–pronation tremors with 4-6 Hz frequency most commonly starting in one hand and later affecting the other hand, or another part of body, for example legs or jaw. Bradykinesia means slowness of movement,

and refers to difficulties in planning, initiating and executing movement. It manifests in longer reaction time, slowness in task performance and loss of spontaneous movements, for example blinking, arm swing while walking, and facial expression. Rigidity means increased resistance in a muscle, typically associated with jerky movements when the muscle is passively stretched (cogwheel rigidity). Postural instability refers to impaired postural reflexes and is associated with a higher risk of falls. Other motor features of PD include abnormal axial postures (stooped posture), and freezing of gait, which is a sudden and transient inability to move.

The above mentioned cardinal motor symptoms are accompanied by a plethora of non-motor disturbances and there are various approaches to categorising PD, for example, PD can be characterised with regard to age at onset, side of onset, and rate of progression or aetiology. On the basis of clinical presentation related to the cardinal motor symptoms, three subtypes of PD have been identified: tremor dominant, postural instability gait disorder (PIGD) and akinetic-rigid.

Non-motor symptoms in PD include neuropsychiatric problems (e.g. cognitive deficits, depression and apathy), sleep disturbances, gastrointestinal problems, and bladder dysfunction (Chaudhuri, Yates, & Martinez-Martin, 2005; Poewe, 2008). These have a major impact on the overall quality of life of PwPD and their caregivers, and increase the risk of early institutionalisation. However, they tend to be under-recognised and under-treated in routine healthcare, as treatment concentrates on alleviating motor symptoms (Chaudhuri, Healy, & Schapira, 2006).

Cognitive deficits are frequent in PD, even at the onset of the disease, with increasing rates of cognitive impairment and dementia in later stages of PD (Perez et al.,

2012). Hely, Morris, Reid, and Trafficante (2005) reported that among those surviving 15 years from PD onset, 84% had some cognitive impairment, and 48% of them met diagnostic criteria for dementia. Impairments are detected in various cognitive domains, including memory, language, attention, visuospatial and visuoconstructive abilities, and executive functions (Zgaljardic, Borod, Foldi, & Mattis, 2003). Severity ranges from mild single-domain difficulties, sometimes referred to as Mild Cognitive Impairment (PD-MCI, Litvan et al., 2012), to dementia (Mindham & Hughes, 2000; Owen, 2004; Zgaljardic et al., 2003). Dysfunction in the area of EF is particularly common and is described as possibly contributing to deficits observed in other cognitive domains (McKinlay, Grace, Dalrymple-Alford, & Roger, 2009; Muslimovic, Post, Speelman, & Schmand, 2005). PwPD with certain types of cognitive impairment may be at greater risk for more rapid progression to dementia (Janvin, Larsen, Aarsland, & Hugdahl, 2006; Williams-Gray et al., 2009; Woods & Tröster, 2003), and there is growing evidence that executive deficits may have predictive value in identifying those at risk of dementia (Janvin et al., 2006; Woods & Tröster, 2003). Varying prevalence rates for cognitive impairment are reported in the literature, and this variability may reflect methodological differences. It has been demonstrated that with different criteria for diagnosing PD-MCI the prevalence rates change from 9.9% to 92.1% in the same group of PwPD (Liepelt-Scarfone et al., 2011). Most studies report that around 25% of PwPD have some cognitive deficits, classified as mild cognitive impairment (Aarsland et al., 2010; Jellinger, 2013) and 24 to 31% of PwPD meet diagnostic criteria for dementia (Aarsland, Zaccai, & Brayne, 2005).

1.3 Executive functions (EF)

1.3.1 Definitions and historical background of executive functions

The term 'executive functions' (EF) serves as an umbrella term to describe a number of attentional control processes and higher level cognitive processes, which play an overarching role in regulating thoughts, emotions and actions in order to enable successful goal-oriented behaviour. The role of EF is particularly prominent when a person is faced with novel situations requiring non-automatic actions (Burgess & Alderman, 2004; Lezak, 2004; Strauss, Sherman, & Spreen, 2006). The use of the term *executive function* in its singular form suggests that there might be a core executive ability, and indeed EF is often investigated as a homogenous ability. However, most researchers acknowledge the heterogeneity of the concept and distinguish various abilities that may contribute to overall executive control (Baddeley, 1998; Jurado & Rosselli, 2007; Miyake et al., 2000). There are numerous definitions of EF that list various EF-related abilities (Jurado & Rosselli, 2007). The well-known conceptualisation of Lezak (2004) distinguishes four EF components: volition, planning, purposive action, and effective performance. Another frequently cited classification by Smith and Jonides (1999) proposes five components of EF: i) attention and inhibition, which refers to focusing attention on the most relevant task and inhibiting less relevant responses; ii) task management, including switching attention between tasks; iii) planning; iv) monitoring; and v) coding. Attention-inhibition and task management were considered by the authors as highly interrelated and elementary for executive control. Stuss and Alexander (2000) suggested that although the great majority of recent studies seem to concentrate on 'cognitive' aspects of behavioural control (e.g. attention, set-shifting, inhibition, and task management), there are also other concepts at least equally important for successful goal-oriented behaviour, such as personality, emotions, motivation, and

awareness. It has been suggested that EF may be characterised by unity as well as internal diversity. Miyake et al. (2000) suggested that EF refers to abilities that are "separable but moderately correlated" (p. 87) and hypothesized that while particular components may be clearly separated, other processes (e.g. maintaining task-relevant information in working memory, or inhibitory processes) may constitute the underlying unitary EF factor. Salthouse (2005) found that EF-related abilities are strongly related to reasoning and perceptual speed.

Executive functions were first described following observations of the consequences of frontal lobe damage. The case of Phineas Gage, whose personality and behaviour was dramatically changed following severe damage to the frontal lobe, is frequently mentioned as a ground-breaking case for understanding the contribution of the frontal lobe to human functioning (Wilgus & Wilgus, 2009). The accident revealed that anterior parts of the brain may influence those aspects of behaviour, including morality, social appropriateness, will, judgment and abstraction, that are crucial for achieving relevant personal goals in a socially appropriate manner (Ardila, 2008; Lezak, 2004). Alexander Luria examined a number of brain-injured soldiers, and on the basis of his studies identified the anterior part of the brain as playing a crucial role in programming and regulating mental activity and behaviour, abilities now seen as synonymous with EF (Luria, 1973). In recent decades the abilities related to frontal lobe functioning have been extensively studied and a number of EF conceptualisations have emerged. The Supervisory Attentional System (SAS) proposed by Norman and Shallice (1986) is one of the most influential models linked to the concept of EF. It distinguishes two aspects of cognitive functioning: routine activity and a non-routine, executive multicomponent system (the Supervisory System). Another influential model

comes from the context of working memory, specifically the multi-component model of working memory introduced by Baddeley and Hitch (1974). They described three components of working memory: the visuospatial sketchpad, the phonological loop and a central executive that controls attention and enables manipulation of information (Baddeley & Hitch, 1994). In a subsequent reformulation, the authors distinguished the episodic buffer as a function that enables communication between the other three components of working memory and long term memory (Baddeley, 2000). A concept closely related to the central executive and the SAS is attention, which refers to efficient distribution of cognitive resources and may be seen as an ability crucial for managing behaviour (Krpan, Levine, Stuss, & Dawson, 2007). Stuss and colleagues (1995) described seven aspects of attention that are related to frontal lobe function: sustaining, concentrating, sharing, suppressing, switching, preparing and setting of attention. Further observations of the consequences of frontal lesions led the authors to postulate that EF is only one category of frontal functions. They defined EF as 'a collection of anatomically and functionally independent but interrelated attentional control processes' (Krpan et al., 2007, p. 901), and distinguished three main processes contributing to this frontal attentional control: energization, task setting and monitoring.

In summary, there are numerous definitions and conceptualisations of abilities responsible for successful purposive behaviour, referred to as executive functions. Some models refer to relatively specific attentional control abilities, while other definitions include highly complex phenomena of human behaviour, such as will, motivation, and insight. Theories of EF are constantly evolving in the light of growing evidence from clinical,

experimental and neuroimaging studies, and to date no definition or conceptualisation has been agreed upon to serve as a point of reference for various studies of EF.

1.3.2 Neuronal basis of executive functions

Results of neuroimaging studies suggest that there is no direct overlap between cognitive abilities regarded as executive and abilities known to be related to frontal lobe functioning (Alvarez & Emory, 2006). However, it is now well documented that the prefrontal cortex (PFC) plays a crucial role in behaviour regulation. The prefrontal cortex (PFC) is typically divided into two regions: anterior PFC, also referred to as the frontopolar or rostrolateral prefrontal cortex, and posterior PFC, further divided into the dorsolateral, ventral, medial, and orbitofrontal regions (Alexander, DeLong, & Strick, 1986; Christoff & Gabrieli, 2000). The activity of the PFC is modulated by multiple neurotransmitters, with extensive interconnections with sensory and motor cortical systems and subcortical structures (Alvarez & Emory, 2006; Tekin & Cummings, 2002). As described by Alexander, DeLong, and Strick (1986), specific aspects of motor, cognitive and behavioural control are mediated by five frontostriatal circuits that interconnect specific areas of the prefrontal cortex with separate, well-defined areas of the striatum (Dubois & Pillon, 1997). The disruption of circuits involving the PFC may result in particular cognitive, emotional and motivational deficits. More specifically, disruption of the orbitofrontal circuit is reported to cause disinhibited behaviour and other personality changes, while disruption of the anterior cingulate circuit is frequently associated with apathy, and disruption of the dorsolateral prefrontal circuit seems to be central for executive deficits (Tekin & Cummings, 2002).

1.3.3 Measuring executive functions

There are a number of measures commonly employed to assess frontal-type abilities; however, there is no gold standard for measure selection to ensure a comprehensive assessment of various aspects of EF (Chan, Shum, Toulopoulou, & Chen, 2008; Strauss et al., 2006). Well-known tests of executive abilities include verbal fluency tasks (Strauss et al., 2006), Stroop tests (Jensen & Rohwer Jr, 1966), and the Wisconsin Card Sorting test (Jensen & Rohwer Jr, 1966), and variations on these (Lezak, 2004). Some of these tests were designed to capture specific aspects of executive control, such as the Stroop test assessing ability to inhibit unwanted automatic reactions (Delis, Kaplan, & Kramer, 2001). Other tests aim to assess EF in a more general sense, for example the Brixton test (Burgess & Shallice, 1997). Assessment of EF is complicated because of the uncertainty surrounding the concept (Manchester, Priestley, & Jackson, 2004). As there is no agreement with regard to what ability or abilities constitute EF, it is not clear what precisely should be measured as EF. For example, Lezak's conceptualisation of EF (2004) does not include concept formation or reasoning, although these abilities are included in other classifications of EF (Delis et al., 2001; Lafleche & Albert, 1995). Furthermore, performance on a single test of EF may involve various executive processes as well as lower level cognitive functions (e.g. visuospatial abilities, memory, and language), and to draw conclusions about a particular aspect of EF the assessment needs to be detailed and well-structured. Having a well-defined structure, however, might mean that a test places fewer demands on abilities regarded as central for EF, for example problem solving, coping with novelty, and decision making.

Another problem with EF assessment is the limited correspondence between test results and how people with frontal-type impairment function in everyday life. Low ecological validity may be related to the limitations of the measures themselves, or may

reflect issues in defining EF. For example, in the assessment of EF, only specific aspects of attentional control are typically assessed (e.g. switching, inhibition), without including a broader range of abilities relevant for successful goal-oriented behaviour (Ardila, 2008). Some of these limitations may be overcome by including questionnaires developed specifically to capture EF-related behavioural difficulties experienced by those with frontal lesions in everyday life. The Behavior Rating Inventory of Executive Function (BRIEF; Roth, Isquith, & Gioia, 2005) provides two parallel versions, a self-rating form for an individual with suspected EF deficits and an informant rating form for a person that knows that individual very well. Inclusion of an informant rating is useful in controlling for potential limitations in the accuracy of self-appraisal, frequently observed in individuals with brain injuries (Ownsworth, Clare, & Morris, 2006), and offers a more clinically comprehensive picture of executive functioning in everyday life.

1.4 Executive functions in Parkinson's disease

1.4.1 Mechanisms and characteristics of executive deficits in EF

Executive functions have been extensively studied in PD, but the evidence is equivocal. For example, many studies report that PwPD perform worse than healthy controls on verbal fluency tasks (Euteneuer et al., 2009; Muslimovic et al., 2005; Price, 2010; Zgaljardic et al., 2006), while other studies report no significant differences between PwPD and controls (Colman et al., 2009; Cools, Barker, Sahakian, & Robbins, 2001; Kehagia, Cools, Barker, & Robbins, 2009; Saltzman, Strauss, Hunter, & Archibald, 2000). Similar inconsistencies are observed in other tests used to assess EF in PD. For example, there are reports of impaired performance in PwPD on the Wisconsin Card Sorting Test (WCST) and the Stroop test (Colman et al., 2009; Euteneuer et al., 2009; Price, 2010; R. Tomer, Fisher, Giladi, & Aharon-

Peretz, 2002; Witt et al., 2006), while other studies report no differences between PwPD and controls on these tests (Dujardin, Defebvre, Grunberg, Becquet, & Destee, 2001; Kliegel, Phillips, Lemke, & Kopp, 2005; Muslimovic et al., 2005; Price & Shin, 2009; Saltzman et al., 2000). Some EF deficits seem to be present even in people with early stage PD with normal general cognition (i.e. performing in the normal range on screening tests covering lower level cognitive functions), but it is not clear how common, severe or specific these deficits are. The differences between studies might to some extent result from the methodological challenges involved in studying EF. Alternatively, they may reflect the clinical heterogeneity of PD, as cognition might be differently affected by different neurodegenerative processes in the brain, in the same way that motor symptoms vary among people with PD (Dauer & Przedborski, 2003). Deficits seem to arise as a consequence of a general dopaminergic imbalance affecting the activity of frontostriatal circuitry (Dauer & Przedborski, 2003; Royall et al., 2002; Zgaljardic, Foldi, & Borod, 2004). The disruption may reflect PD-specific dopaminergic depletion in the striatum and cortical areas as well as the effects of dopaminergic medication. For example, dopaminergic drugs may 'overdose' brain regions with relatively preserved dopamine levels (Cools, Miyakawa, Sheridan, & D'Esposito, 2010). Executive deficits in PD may also be associated with deficient cholinergic projections to various cortical areas and to the hippocampus (Bohnen et al., 2006; Klein et al., 2010). It has been proposed that the striatum and the mesocortical dopaminergic projection may be crucially involved in goal-oriented behaviour by regulating the balance between responsiveness to changing circumstances and resistance to distraction, the executive processes underling appropriate updating of goal representation in PFC (E. K. Miller & Cohen, 2001; Seamans & Yang, 2004).

1.4.2 Impact of executive deficits on quality of life in Parkinson's disease

Quality of life (QoL) is a term referring to the subjective evaluation of one's current situation in the context of one's individual needs and expectations (WHOQOL group, 1998). With person-centredness becoming a priority in healthcare, measures of QoL are more frequently used in health-related research to incorporate the subjective perception of the overall impact of the illness. However, such measures tend to focus on physical health and as such they provide a rating of subjectively perceived health status rather than QoL (Den Oudsten, Van Heck, & De Vries, 2007a). Non-motor symptoms are reported to have a significant impact on everyday life in PD (Hely et al., 2005), but their mechanisms are not well understood, and they are less likely than motor symptoms to be diagnosed and treated. To adequately support PwPD, we need to have a full understanding of various factors that impact on their subjective quality of life. Only then might it be possible to specifically target those aspects of PD that are most important to PwPD and most likely to result in positive changes if addressed effectively.

People with PD complain about forgetfulness, slowness of thinking and difficulty in maintaining concentration (Brod, Mendelsohn, & Roberts, 1998; Poliakoff & Smith-Spark, 2008), and the presence of attention or memory complaints has been associated with poorer quality of life (Barone et al., 2009). Several studies have reported that executive deficits might be associated with problems in everyday functioning (Bronnick et al., 2006; Cahn et al., 1998; Hobson, Holden, & Meara, 1999; Schrag, Jahanshahi, & Quinn, 2000), but the evidence is not consistent (Muslimovic, Post, Speelman, Schmand, & de Haan, 2008). One limitation of the existing literature is that many studies that refer to quality of life in PD in fact assess subjective perception of the severity of physical symptoms rather than a broader concept of quality of life (Den Oudsten et al., 2007a). The second limitation is that

cognitive assessment typically includes only a brief screening tool to evaluate general cognition, which is not sensitive to mild cognitive deficits and executive dysfunction (Lee, Walker, Hildreth, & Prentice, 2006; Schestatsky et al., 2006).

When considering the impact of PD on a person's life, it is important to acknowledge the role of family members and close friends. Their role increases as the disease progresses, and is likely to have a crucial impact on the quality of life of PwPD. The availability of informal caregiving has serious economic implications for healthcare, as it is the care provided by family members that enables PwPD to continue living at home in the more advanced stages of PD. In this thesis the terms caregiver, carer and informant are used interchangeably, as all tend to be used in the literature to refer to a person that supports and cares for PwPD, and may provide additional information about the health and functioning of PwPD to the clinicians or in research project. Caring for PwPD may be associated with significant physical and emotional strains (Martínez-Martín et al., 2007; Roland, Jenkins, & Johnson, 2010) and it is crucial to support them in their caregiving work (A'Campo, Wekking, Spliethoff-Kamminga, Le Cessie, & Roos, 2010; Secker & Brown, 2005). Better understanding of the factors affecting caregivers in PD may help improve existing interventions and contribute to development of new approaches. The burden associated with caring for PwPD may be influenced by the severity of motor symptoms (Cifu et al., 2006; Happe & Berger, 2002; Martínez-Martín et al., 2007) as well as various non-motor difficulties, for example depression and sleep disturbances (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999; Martinez-Martin et al., 2005; E. Miller, Berrios, & Politynska, 1996). The impact of EF deficits on caregiver burden is not clear, as EF-specific measures are rarely employed, and studies investigating the relationship between cognition and caregiver

burden produce mixed findings (D'Amelio et al., 2009; Leroi, Harbishettar, et al., 2012; Martinez-Martin et al., 2005; Peters, Fitzpatrick, Doll, Playford, & Jenkinson, 2011; Schrag et al., 2006).

1.4.3 Awareness of executive functioning in PD

Accuracy in appraising one's own functioning, sometimes referred to as awareness or insight, relies on various higher level meta-cognitive processes frequently included within the umbrella term of EF, such as judgment, comparison, and decision-making (Clare, 2002). Awareness may be compromised in conditions involving brain damage and cognitive impairment, particularly when the frontal lobe is affected (Leritz, Loftis, Crucian, Friedman, & Bowers, 2004; Northoff & Bermpohl, 2004; Ries et al., 2007). Inaccuracies in acknowledging one's own deficits are frequently observed in traumatic brain injury and dementia (Ownsworth et al., 2006), but the level of awareness found in PwPD has been less extensively studied. There are reports suggesting that PwPD may express adequate awareness in some areas of functioning, for example with regard to their deficits in facial expression (Mikos et al., 2009) and severity of dyskinesia (Sitek, Sołtan, et al., 2011), but there are also studies reporting that reduced awareness of limitations impacts negatively on driving abilities and medication compliance in PD (Devos et al., 2007; Grosset, Bone, Reid, & Grosset, 2006; Kulkarni et al., 2008; Rizzo, Uc, Dawson, Anderson, & Rodnitzky, 2010; Uc et al., 2007). There are a few studies of awareness of cognitive functioning in PD, with ambiguous findings (Ivory, Knight, Longmore, & Caradoc-Davies, 1999; Seltzer, Vasterling, Mathias, & Brennan, 2001; Sitek, Soltan, Wieczorek, Robowski, & Slawek, 2011).

Reduced awareness might have implications for treatment outcomes in PwPD and for overall functioning. Poor response to medication could be associated with forgetting to

take medication, but if a person does not acknowledge the problem, it would not be reported to the clinician and no action would be taken to enhance treatment compliance (Koerts et al., 2012). The view of cognitive functioning held by the PwPD might be discrepant from that held by the caregivers, resulting in particular stresses in the caregiving relationship. PwPD who are unaware of their executive difficulties might not adjust their behaviour by employing compensatory strategies or asking for assistance, or avoiding dangerous situations (e.g. driving), and might benefit less from available support. In particular, PwPD with reduced awareness of their own deficits would not seek advice on how to cope better, and might decline available help, creating a false impression about how well they are able to manage. While some difficulties might be observable by family members and clinicians, others, such as mild cognitive decline, might be less obvious. Reduced awareness of one's own limitations may therefore constitute a barrier to more efficient treatment, and might have implications for quality of life. This area certainly needs to be better understood in order to provide appropriate support.

1.5 Aims of the thesis and research questions

The aim of this thesis is to extend our understanding of EF in PD by clarifying the pattern of executive impairment in early stage PD, assessing the impact of executive deficits on quality of life in PwPD and their families, and investigating the accuracy of PwPD in recognising potential EF-related difficulties.

The following research questions (RQ) are addressed in this thesis:

RQ 1. What pattern of executive impairment can be identified from the research literature on EF in people with early stage PD without dementia, and what are the critical issues for improving consistency in this field?

RQ 2. Which areas of EF are particularly problematic in early stage PD?

RQ 3. How do EF deficits affect quality of life and health status for the PwPD, and the caregiver stress associated with caring for PwPD?

RQ 4. How accurate are PwPD in assessing their overall executive functioning and their performance in a given task?

The following methods are used to address each of the research questions posed in this thesis:

RQ 1 is addressed by conducting a meta-analysis (Chapter 3).

RQ 2 is addressed with quantitative analyses based on cross-sectional data from a subgroup of PwPD identified as having EF deficits (Chapter 4).

RQ 3 is addressed with quantitative analyses based on cross-sectional data from PwPD and their caregivers (Chapter 5).

RQ 4 is addressed with quantitative analyses based on cross-sectional data from PwPD and their caregivers, and data from healthy controls in similar age (Chapter 6).

Research methodology employed for conducting a systematic literature review and a meta-analysis (RQ 1) and the empirical studies (RQ 2, RQ 3, and RQ 4), including the design,

procedures relating to recruitment and assessment study participants, and to data analyses, is presented in Chapter 2 *Method*. Further details are presented in the method sections of the subsequent chapters (chapters 3 – 6).

1.6 Structure of the thesis

The thesis consists of seven chapters: the general introduction, method, a systematic review and meta-analysis, three empirical chapters, and the final discussion of the results. The systematic review and empirical chapters are presented in the format of journal articles; in each case, these articles have been published or accepted for publication in peer-reviewed academic journals (see below). The following is a summary of the content of each chapter:

Chapter 2 – Research methodology

Chapter 2 presents an extended description of methodology employed in the empirical studies presented in chapters 4, 5, and 6. As the empirical chapters are based on data from the same study and presented in the format of journal articles, there will be some repetition in the method sections where the study groups and measures are described.

Chapter 3 – Executive functions in Parkinson's disease: Systematic review and meta-analysis

Chapter 3 presents the results of a systematic literature review and meta-analysis of studies examining EF in people who have early stage PD without dementia. The review provides a structured overview of the current state of research in this area, identifies some gaps and inconsistencies in the literature, and suggests critical issues for improving consistency in the field. The meta-analysis synthesises data from five commonly used tests of EF drawn from 18 studies, and reveals consistent evidence for deficits in the EF domain.

Chapter 4 – Pattern of executive impairment in early stage Parkinson's disease

Chapter 4 examines the relationships among different executive abilities in early stage PD. The study employs a comprehensive set of standard EF measures, and focuses exclusively on people with mild to moderate PD, without dementia, but with frontal-type deficits indicated by screening using the Frontal Assessment Battery. A data-driven approach reveals a possible dissociation in executive functioning in early stage PD, with the attentional control aspect of EF being affected to a greater extent than the abstract reasoning aspect of EF.

Chapter 5 – Quality of life, health status and caregiver burden in Parkinson's disease: Relationship to executive functioning

Chapter 5 examines how EF deficits contribute to quality of life and health status for the PwPD, and to burden for the caregiver. The study suggests that EF-related behavioural problems may contribute to quality of life and health status in PwPD, and affect caregiver burden. The findings support the view that the concepts of subjective QoL and self-assessed health status are only partially related and that assessing the two concepts separately is relevant to understanding what factors impact on QoL in PD.

Chapter 6 – Awareness of executive deficits in people with Parkinson's disease

Chapter 6 presents findings from an evaluation of awareness of executive functioning in PwPD with and without EF deficits, and in healthy controls. The results suggest that while PwPD may accurately acknowledge their deficits at a general level, they are less accurate in appraising their performance on specific tasks.

Chapter 7 – General discussion

The final chapter summarises the results from the systematic review and empirical studies and discusses the findings in the context of the existing literature.

1.7 Dissemination of findings

Chapters 3 – 6 have all been submitted for publication in peer-reviewed academic journals.

Chapter 3 has been published in *Movement Disorders*:

Kudlicka, A., Clare, L., & Hindle, J. V. (2011). Executive functions in Parkinson's disease: Systematic review and meta-analysis. *Movement Disorders*, *26*(13), 2305-2315. doi: 10.1002/mds.23868

Chapter 4 has been accepted for publication in *Dementia and Geriatric Cognitive Disorders*:

Kudlicka, A., Clare, L., & Hindle, J. V. (in press). Pattern of executive impairment in mild to moderate Parkinson's disease. *Dementia and Geriatric Cognitive Disorders*.

Chapter 5 has been published in the International Journal of Geriatric Psychiatry:

Kudlicka, A., Clare, L., & Hindle, J. V. (2013). Quality of life, health status and caregiver burden in Parkinson's disease: Relationship to executive functioning. *International Journal of Geriatric Psychiatry.* Advance online publication. doi:10.1002/gps.3970

Chapter 6 has been published in the *Journal of the International Neuropsychological Society*:

Kudlicka, A., Clare, L., & Hindle, J. V. (2013). Awareness of executive deficits in people with Parkinson's disease. *Journal of the International Neuropsychological Society, 19*(5), 559–570. doi:10.1017/S1355617713000064

Several conference presentations have been made to date based on findings from this thesis:

Kudlicka, A., Clare, L., & Hindle, J. V. (2012, November). *Quality of life, health status and caregiver burden in Parkinson's disease: Relationship to executive functioning.* Paper presented at The NEURODEM Cymru Annual Conference, Cardiff.

Kudlicka, A., Clare, L., & Hindle, J. V. (2011, March). *Executive functions in Parkinson's disease: Systematic review and meta-analysis.* Poster presented at The Welsh Branch of the British Geriatric Society Spring Meeting, St Asaph.

Kudlicka, A., Clare, L., & Hindle, J. V. (2010, December). *Executive functions in Parkinson's disease: Systematic review and meta-analysis.* Poster presented at The 7th International Congress on Mental Dysfunctions and Other Non-Motor Features in PD, Barcelona.

Kudlicka, A., Clare, L., & Hindle, J. V. (2010, October). *Executive functions in Parkinson's disease: Systematic review and meta-analysis.* Poster presented at The NEURODEM Cymru Annual Conference, Cardiff

Kudlicka, A., Clare, L., & Hindle, J. V. (2010, July). *Executive functions in Parkinson's disease: Systematic review and meta-analysis.* Poster presented at The International Neuropsychological Society Midyear Meeting, Kraków.

1.8 Conclusions

Despite considerable evidence of impaired performance on neuropsychological tests among people with PD, there is no agreement about the exact prevalence of particular executive

deficits, or about whether there is any pattern in what abilities are impaired and what abilities are preserved. Only limited information is available about how people with PD appraise their own executive functioning and how executive deficits influence their everyday lives. Addressing these questions is important in order to provide adequate support for PwPD and their families. The aim of this thesis is to extend our understanding of EF in early stage PD and provide information to assist in the development of adequate person-centred support for people diagnosed with PD and their family members. While it might not be possible to address underlying cognitive impairment directly, it may nonetheless be possible to reduce activity limitation (functional disability) and restrictions on social participation (handicap) through a rehabilitative approach.

Chapter 2

Method

This chapter describes the methodology employed in the systematic literature review and in the empirical studies. It summarises and complements information reported in the method sections of chapters 3, 4, 5, and 6.

I Systematic literature review and meta-analysis

The first research question posed in this thesis aimed to clarify what pattern of executive impairment emerges from the existing literature (see section 1.5 *Aims of the thesis, research questions, and research methodology* in Chapter 1). The extensive body of research on executive functions (EF) in Parkinson's disease (PD) is complex and combines a variety of disciplines and research methods. For example, cognitive change is investigated in the context of the neuronal and neurochemical basis of PD (Lewis, Dove, Robbins, Barker, & Owen, 2003; Monchi, Petrides, Mejia-Constain, & Strafella, 2007), effects of medication and medical treatments (Cools, Barker, Sahakian, & Robbins, 2003; Jahanshahi et al., 2000), genetic predisposition (Williams-Gray, Hampshire, Robbins, Owen, & Barker, 2007), economic impact on society (Huse et al., 2005), and relevance for well-being of PwPD (Klepac, Trkulja, Relja, & Babic, 2008). A range of research methods are employed, such as brain imaging, experimental paradigms, neuropsychological assessment, animal models or questionnaire surveys. It was decided that to allow a meaningfully synthesis of this complex literature the review should focus on a clearly defined aspect of the research into EF in PD. The neuropsychological perspective was chosen as it is closely linked to the everyday functioning of PwPD and seems most appropriate in the context of the research questions posed in this thesis.

It is recommended that systematic reviews base literature searches on MeSH terms. However, at the time of the literature search, the term ‘executive’ was not included as a MeSH term. The term ‘executive’ was added as a MeSH term in 2010 and suggests the following entry terms: ‘Executive Functions’, ‘Function, Executive’, ‘Functions, Executive’, ‘Executive Control’, ‘Executive Controls’. The scope note acknowledges the modular nature of EF, but lists only some examples of EF-related abilities, without formally providing narrower terms for literature searches. Some of the included EF-related abilities are not listed as MeSH terms and the abilities that are listed as MESH terms are indexed in the MeSH hierarchies without being linked to the term ‘executive’ (e.g. inhibition is indexed in ‘behavior’, ‘learning’, and 'psychoanalytic theory’). There is no widely accepted and sufficiently detailed definition of EF and EF-related abilities that could guide selection of the search terms (see section *Definitions and historical background of executive functions* in Chapter 1).

In the review presented in this thesis the following two-stage strategy was implemented to capture studies investigating a broad range of EF-related abilities. In the first stage the following broad EF-related terms were used: ‘cognitive impairment’, ‘dysexecutive’ or ‘executive’. Based on the initial analysis of the articles retrieved in the first search 11 subcomponent functions were identified as commonly investigated in relation to or as a part of EF. These terms, used in the second stage search, were: ‘frontal’, ‘working’, ‘set-shifting’, ‘switching’, ‘fluency’, ‘inhibition’, ‘decision making’, ‘planning’, ‘flexib*’, ‘processing speed’, ‘cognitive speed’. Terms used in both searches were combined with the term ‘Parkinson’s disease’.

Studies on cognition and EF in PD report varying prevalence rates and severity of cognitive deficits (Costa, Peppe, Caltagirone, & Carlesimo, 2008; Foltynie, Brayne, Robbins, & Barker, 2004; McKinlay et al., 2009; Muslimovic et al., 2005), and several PD characteristics have been identified as impacting on cognition in PD and possibly contributing to the observed differences (Colman et al., 2009; Cools et al., 2010; Kobayakawa, Koyama, Mimura, & Kawamura, 2008; Leh, Petrides, & Strafella, 2010). To improve clarity in synthesising the existing evidence, the review focused on the studies with PwPD groups that were similar in terms of the PD stage (H&Y stage I-III), depression level (no significant depression) and general cognition (no dementia). In addition a number of sample characteristics, such as age, PD duration, side of PD onset, medication, and whether participants were tested 'on' or 'off' medication, were monitored in the reviewed papers (see a structured form to summarise articles in Appendix F). A list of the selection criteria applied in the review is presented in Table 3.1 in Chapter 3.

A systematic literature search was performed in the following databases: PsycInfo (CSA), MEDLINE (Web of Knowledge), PubMed, CINAHL, and the Cochrane Library. This yielded 3,264 unique hits. Following the screening of titles and abstracts, 393 articles were retrieved for more detailed inspection. This included 22 articles that were received either following requests sent to authors (8 articles) or ordered via inter-library loan (14 articles). There were 189 articles that unambiguously failed to meet the eligibility criteria and were excluded at this stage. The key reasons for excluding papers at this stage were as follows:

1. Cognition, EF or a relevant executive ability was mentioned in the abstract, but not investigated in the study (e.g. Nobukatsu Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002).

2. The study focused on cognition in a clinical group other than PD (e.g. Hanes, Andrewes, & Pantelis, 1995).
3. EF was investigated from the neurochemical or neuroanatomical perspective (e.g. Beste, Dziobek, Hielscher, Willemssen, & Falkenstein, 2009).

The full text of the remaining 204 articles were examined, and 134 articles were excluded. The main reasons for excluding the studies at this stage were as follows:

1. The article retrieved was a theoretical study or a literature review (e.g. Leh et al., 2010).
2. The cognitive abilities studied were not from the EF spectrum (Taylor, Saint-Cyr, & Lang, 1990).
3. Cognition was assessed in a general manner without distinguishing EF (Ryder et al., 2002).
4. The study specified that the sample included PwPD with dementia or people in the more advanced stages of PD (H&Y > III) (e.g. O'Brien et al., 2009).

The remaining 70 studies were carefully analyzed using a structured form (see Appendix F), and summarized in a table (see Appendix G). Thirty-seven studies were excluded at this stage; the reason for the exclusion of each article is specified in Appendix G. The main reasons for exclusions at this stage were:

1. No depression, dementia, and/or H&Y PD severity rating was provided.
2. No control data were provided.
3. EF was assessed with an experimental paradigm and not with standardized measures.

The remaining 33 studies were included in the review (see Appendix G and Table 3.2 in Chapter 3).

A meta-analytic approach (Borenstein, Hedges, Higgins, & Rothstein, 2009) was employed to quantitatively synthesize the results of studies identified in the literature review. The results were compared using a random-effects model, which provides a statistical parameter representing the inter-study variation and allows for better control of heterogeneity. Further details of the literature search and meta-analysis are presented in the method section of Chapter 3.

II Empirical studies

2.1 Design

The empirical studies presented in chapters 4, 5, and 6 present the results of quantitative analyses based on cross-sectional data from a sample of PwPD and their caregivers, and from healthy controls of a similar age:

I. Chapter 4 presents analyses based on cross-sectional data from a subgroup of the sample of PwPD who were identified as having EF deficits.
II. Chapter 5 presents analyses based on cross-sectional data from PwPD and their caregivers.
III. Chapter 6 presents analyses based on cross-sectional data from PwPD, their caregivers, and healthy controls.

Ethical approval was obtained from the Research Ethics Committee of the School of Psychology, Bangor University, and from the National Health Service (NHS) North Wales (West) Research Ethics Committee (Appendix A). All participants provided written informed consent (see Participant Information Sheets and Consent Forms in appendices B – D).

2.1.1 Participants

To address the research questions posed in this thesis (see section 1.5 *Aims of the thesis, research questions, and research methodology* in Chapter 1) data were collected from a group of PwPD and their caregivers, and healthy older people.

Potential participants for the PwPD group were identified from Movement Disorders clinics in North-West Wales by the consultant physician Dr John Hindle, and invited to participate in the study by the author or by staff members of the National Institute for Social Care and Health Research Clinical Research Collaboration (NISCHR CRC); these are NHS staff with a specific remit to support identification and recruitment of research participants. In addition, some participants were invited to take part upon completion of their involvement in another research project.

People with Parkinson's disease

The eligibility criteria for the PwPD group were chosen to control a number of factors that may impact on performance in EF tests (Colman et al., 2009; Cools et al., 2010; Kobayakawa et al., 2008; Leh et al., 2010). It was expected that collecting data from a well-defined group of PwPD, similar in terms of PD stage, depression level and general cognition will facilitate better clarity in the performed analyses.

Inclusion criteria for the PwPD group were mild to moderate PD (Hoehn and Yahr stage I-III; Hoehn & Yahr, 1967) diagnosed according to the UKPDS Brain Bank criteria (Daniel & Lees, 1993), stable antiparkinsonian medication, normal general cognition, as indicated by an Addenbrooke's Cognitive Examination – Revised (ACE-R) score ≥ 82 (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) and a MMSE score ≥ 24 (Folstein, Folstein, & McHugh, 1975), and no clinically significant depression, as indicated by a Hospital Anxiety

and Depression Scale (HADS) score ≤ 11 (Snaith & Zigmond, 1994). Exclusion criteria were presence of a serious neurological condition other than PD, severe hearing or eyesight loss, and lack of proficiency in English.

Over the 18 month recruitment period, 75 PwPD agreed to take part in the study. Sixty-five of them met the above-mentioned eligibility criteria and completed an assessment of EF, awareness, QoL, and subjective health status.

PwPD with probable executive deficits

The prevalence rates of executive deficits in PwPD without dementia vary, with some studies reporting the impairment as affecting less than 20% of PwPD (Muslimovic et al., 2005) and other studies reporting a 50% impairment rate (McKinlay et al., 2009). However, it is evident that executive impairment affects only some of PwPD, while a large proportion of PwPD seem to have intact EF. In order to determine what are the most problematic areas of EF in early stage PD (Chapter 4) it was therefore decided to identify a subgroup of PwPD with probable EF deficits. It was expected that excluding PwPD with no evidence of executive impairment would allow for the pattern of executive impairment to emerge more prominently in the analyses. EF were assessed with the Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000; see description of the FAB in section 2.4.1 Screening measures in this chapter) and the study adopted a cut-off score of 15 for probable frontal-type deficits, which is 2 SD below the mean reported for healthy controls (M = 17.3, SD = 0.8) (Dubois et al., 2000). Some studies report lower mean FAB scores for healthy older people (Appollonio et al., 2005), but in this study a less conservative cut-off score was adopted as higher sensitivity of the screening assessment (a correct classification of PwPD with EF deficits as 'impaired') was considered more relevant for the purpose of this study.

Forty (61.1%) of the 65 participants meeting the general inclusion criteria for the PwPD group had a FAB score ≤ 15, indicating possible frontal type cognitive deficits (Dubois et al., 2000), and were thus eligible for the in-depth EF assessment. Three of these participants did not complete the in-depth EF assessment due to elective withdrawal and three due to fatigue, leaving a sample of 34 who completed the assessment.

Caregivers of PwPD

To obtain a more comprehensive picture of how executive impairment may impact on PwPD (chapters 5 and 6), in each case people who support and know the PwPD very well (n = 50; referred to in this thesis as caregivers, carers or informants) provided information about the executive functioning of PwPD and their own perception of burden associated with supporting a PwPD. A proportion of PwPD lived alone and did not specify a suitable informant, and some family members who lived with PwPD and were invited to participate did not return the questionnaires. In one case the caregiver opted not to take part in the study.

Control group

To examine whether PwPD can accurately appraise their executive functioning (Chapter 6) it was necessary to compare ratings made by PwPD with ratings from a control group. Forty-three healthy older people were recruited and assessed by MSc students as part of their master's research. They were recruited from various community sources (e.g. over-50s clubs, University of the Third Age branches, church groups). Inclusion criteria for healthy older people were no dementia, as indicated by an ACE-R score ≥ 82 (Mioshi et al., 2006) and an MMSE score ≥ 24 (Folstein et al., 1975), and no significant depression, as indicated by a Geriatric Depression Scale (GDS-15) score ≤ 5 (Burke, Roccaforte, & Wengel, 1991;

Sheikh & Yesavage, 1986). The master's project included additional measures not presented in this thesis. I helped to devise the assessment for the master's project, and contributed to training and supervision of the students.

2.1.2 Sample size calculations

Sample size calculations were based on the analyses planned for exploring the relationship between executive functioning and other variables of interest in the subgroup of PwPD showing executive deficits (RQ 2, see section 1.*5 Aims of the thesis, research questions, and research methodology* in Chapter 1). To demonstrate that a correlation coefficient of 0.46, an average value reported in previous studies (Siegert, Weatherall, Taylor, & Abernethy, 2008), is different from zero in a test with 80% power for a 5% significance level, a sample of 34 PwPD is needed. McKinlay et al. (2009) reported that 50% of PwPD may have deficits specifically in the EF domain. Therefore, it was anticipated that approximately 70 PwPD would need to be assessed in order to identify the required sample of individuals with EF deficits for Research Question 2. The sample size of 70 was considered appropriate for the analyses planned for Research Questions 3 and 4.

2.2 Measures

In this section all measures used in the empirical studies will be introduced and the rationale for their selection will be presented. All measures were administered according to the procedures described in the relevant manuals and publications.

2.2.1 Screening measures

The following screening measures were used in the empirical studies to screen for cognitive and executive deficits and depression.

Screening for deficits in general cognition

There are a number of generic tools designed to screen for cognitive deficits and many of them, for example the Mini-Mental State Examination (MMSE; Folstein et al., 1975), the Mattis Dementia Rating Scale (MDRS; Mattis, 1988), the Addenbrooke's Cognitive Examination – Revised (ACE-R; Mioshi et al., 2006), and the Cambridge Cognitive Assessment (CAMCOG; Athey, Porter, & Walker, 2005) are validated for use in PD. There are also several PD-specific dementia screening tools, for example the Scales for Outcomes of Parkinson's disease—Cognition (SCOPA-COG; Marinus, Visser, Verwey, et al., 2003), the Parkinson's Disease—Cognitive Rating Scale (PD-CRS; Pagonabarraga et al., 2008), and the Mini-Mental Parkinson (MMP; Mahieux et al., 1995). These screening measures differ with regard to what cognitive abilities they assess and the extensiveness of their psychometric evaluation. There is also a trade-off between the feasibility of measure administration and the comprehensiveness of the assessment (Barone et al., 2011; Chou et al., 2010; Kulisevsky & Pagonabarraga, 2009).

In this thesis general cognition was assessed with the Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi et al., 2006), which is a well-established tool for screening cognitive abilities and which has been validated in PD studies (McColgan et al., 2012; Reyes et al., 2009; Rittman et al., 2013). The ACE-R takes longer to complete than some other screening measures, but it provides a relatively comprehensive assessment of the key cognitive domains: attention and orientation, memory, verbal fluency, language and visuospatial abilities. The ACE-R has been reported to have very good reliability ($\alpha = .80$), and the validity was demonstrated by significant correlation with the Clinical Dementia Scale ($r = -0.32$, $p < 0.001$) (Mioshi et al., 2006). The maximum total score of 100 indicates errorless performance and an MMSE score can also be calculated (Folstein et al., 1975).

Screening for executive deficits

The screening tools designed to capture overall cognitive decline aim to assess various cognitive domains, and do not focus specifically on EF (e.g. PD-CRS , SCOPA-COG); executive functioning may be assessed with a single item or not assessed at all (Folstein & Folstein, 2010). While these tools are useful in screening for global cognitive decline, they are less able when screening specifically for EF deficits as required for the purpose of this thesis. The Frontal Assessment Battery (FAB, Dubois et al., 2000) was used in the empirical studies as it appears to be the only screening tool developed specifically to capture frontal-type cognitive deficits. The FAB assesses six aspects of frontal-type abilities: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy, and includes some well-known tasks sensitive to frontal lobe damage (e.g. verbal fluency, Go/NoGo).

The psychometric properties are well-described and indicate strong concurrent validity (correlation with MDRS, r = .82, $p < .001$), and good internal consistency ($\alpha = .78$) and inter-rater reliability ($_K$ =.87, $p < .001$) (Dubois et al., 2000). The FAB is time-efficient and has been validated for use in conditions involving frontal-lobe dysfunction (Lima, Meireles, Fonseca, Castro, & Garrett, 2008).

Screening for depression

Depression is common in PwPD (Brown et al., 2011) and may impact on cognitive test performance (Stefanova et al., 2006; Uekermann et al., 2003). It was therefore decided to exclude PwPD who had significant depressive symptoms. The available depression screening tools were carefully considered as they often include a proportion of questions about somatic symptoms that overlap with PD symptoms and may inflate depression scores. For

example, in the Hamilton Depression Rating Scale (Ham-D, Hamilton, 1960) and the Beck Depression Inventory (BDI, Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) over 50% of the questions refer to symptoms that may be normally experienced by PwPD who are not depressed.

In the present study depression levels in PwPD were assessed with the Hospital Anxiety and Depression Scale (HADS; Snaith & Zigmond, 1994). The HADS is a self-rating questionnaire consisting of two 7-item subscales: HADS – Anxiety and HADS – Depression. Scores for each of the scales range from 0 to 21, with higher scores indicating higher levels of self-rated anxiety/depression. The HADS includes a limited number of questions about somatic symptoms and is recommended for use in PD (Schrag et al., 2007). It is reported to have good internal consistency (Cronbach $\alpha = .88$) and test-retest reliability ($r = .84$) in PwPD (Marinus, Leentjens, Visser, Stiggelbout, & van Hilten, 2002), and is widely used in PD studies (Schrag et al., 2007). The empirical studies adopted the cut-off of 11 suggested for depression screening purposes (Crawford, Henry, Crombie, & Taylor, 2001).

In healthy older people depression levels were assessed using the Geriatric Depression Scale (GDS-15; Sheikh & Yesavage, 1986) (Appendix J), which is a short and convenient screening tool with good psychometric characteristics that is widely used for assessing depression in older people. It consists of 15 yes-no questions, scored 1 or 0, with higher scores indicating higher levels of self-rated depression. The study adopted the cut-off of ≤ 5 recommended for depression screening (Burke et al., 1991).

2.2.2 Executive functions (EF)

The modular nature of the EF concept means that a single measure of EF does not suffice and to comprehensively assess executive abilities a set of measures needs to be employed.

However, as there is no clear definition of EF there is little guidance to inform measure selection for a comprehensive assessment of EF (Strauss et al., 2006).

There are numerous tests and procedures used to assess various EF-related abilities (Strauss et al., 2006) and choosing the appropriate test and version requires careful consideration. Some of the most popular tests of EF include the Stroop test (Jensen & Rohwer Jr, 1966), the Trail Making test (Reitan, 1971), the Tower of London (Shallice, 1982), the Wisconsin Card Sorting Test (WCST; Milner, 1963), and verbal fluency tasks (Bechtoldt, Benton, & Fogel, 1962). The Stroop test assesses the ability to inhibit unwanted automatic reactions; the Trail Making test evaluates the ability to switch between mental sets; the Tower of London test requires planning abilities; the WCST involves the ability to form abstract concepts; and the verbal fluency test is used to assess initiation and cognitive flexibility (see also Table 3.4 in Chapter 3).

The best-known tests of EF are often available in several versions based on the same paradigm (Strauss et al., 2006). For example, there are several commercially-available versions of the Stroop test: the Golden version (Golden, 1978), the Victoria version (Spreen & Strauss, 1998), and the Color-Word Interference test (Delis et al., 2001). There are also groups of EF tests that differ significantly in terms of administration procedures and materials, but are based on the same underlying paradigm. One example is provided by the Tower of London test (Shallice, 1982) and the Stockings of Cambridge test (Robbins et al., 1994); another is provided by the WCST (Milner, 1963), the Intra/Extradimensional Shift test (Robbins et al., 1994), the Rule Shift Cards Test (B. A. Wilson, Evans, Alderman, Burgess, & Emslie, 1997), and the Sorting test (Delis et al., 2001). Some of the best-known EF tests are part of large batteries of tests, such the Cambridge Neuropsychological Test Automated

Batteries (CANTAB; Robbins et al., 1994), which is a multi-domain battery of tests, or the Delis-Kaplan Executive Functions System (D-KEFS), which consists solely of EF tests.

Several tests of EF were derived from a non-clinical basis; for example the 20 Questions test (Delis et al., 2001) is based on a spoken game, and the Tower of London (Shallice, 1982) is based on a mathematical puzzle. There are also a number of EF tests and test batteries that were developed specifically as neuropsychological tools, such as the Behavioural Assessment of the Dysexecutive Syndrome (BADS; B. A. Wilson et al., 1997), and the Hayling and Brixton Tests (Burgess & Shallice, 1997).

When choosing tests of EF for this study a number of factors were considered. The key aim was to ensure that a broad range of executive abilities could be assessed, and that the chosen tests have good psychometric properties. Priority was given to measures offering reliable normative data, as the study objectives included classification of test performance in terms of impairment (Chapter 4). It was important that the tests should have minimal motor skills involvement or offer a way to control the impact that motor symptoms of PD might have on test performance. Finally, the assessment had to be time-efficient and portable to permit administration in participants' homes.

The Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) was chosen for the empirical studies as it meets the above criteria, and having normative data from the same large sample allows for a direct comparison of the scaled scores from different subtests (Homack, Lee, & Riccio, 2005). The D-KEFS includes nine standard tests of EF: Trail Making, Verbal Fluency, Design Fluency, Colour Word Interference, Sorting, 20 Questions, Word Context, Tower, and Proverb. Most of them are the variations of well-known tests of EF (e.g. Tower or Verbal fluency), but the D-KEFS versions address some of the limitations

reported for original versions; for example, the length of lines drawn to connect numbers and letters in various conditions of the Trail Making test is always the same.

All PwPD completed the Trail Making and Colour Word Interference tests, and PwPD who were identified as having probable EF deficits completed all nine tests. Healthy older people completed the Trail Making test. Detailed descriptions of the tests and interpretations of the relevant performance indices are given at the appropriate points in subsequent chapters (see section 4.3.4. Assessment of EF, and Table 4.1 in Chapter 4; section 5.3.3. Measures in Chapter 5; and section 6.3.3. Measures in Chapter 6).

2.2.3 EF-related behavioural problems

Executive deficits may be manifested in various ways, including inappropriate social behaviour, difficulties in planning and organising daily responsibilities, making unwise decisions and carelessness (Strauss et al., 2006). These aspects of EF are known to be poorly addressed in standard performance-based tests of EF. It is therefore important to complement standard tests of EF with behavioural ratings of everyday functioning (Manchester et al., 2004).

Several generic behaviour rating scales have been developed to assess behavioural disturbances in dementias and brain injury (Malloy & Grace, 2005), but there seems to be no PD-specific scales. The rating scales designed for people with dementia include the Neuropsychiatric Inventory (NPI; Cummings et al., 1994), and the Frontal Behavior Inventory (FBI; Kertesz, Davidson, & Fox, 1997), and the rating scales designed for people with brain injury include the Dysexecutive Questionnaire (DEX; B. A. Wilson et al., 1997), the Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001), the Iowa Rating Scales of Personality

Change (IRSPC; Barrash & Anderson, 1993), and the Behavior Rating Inventory of Executive Functions – adult version (BRIEF-A; Roth et al., 2005).

The rating scales listed above are designed to gather information about relevant behavioural difficulties, but the majority provide no standardized norms or offer norms that based only on a small sample (DEX, FBI, IRSPC, and NPI) (Malloy & Grace, 2005). Some of the ratings were considered inappropriate for the purpose of this thesis as they require a comparison of the behaviour before and after brain injury (FrSBe, IRSPC), and the ratings developed for people with dementia were considered less practical as they require an expert interviewer to administer the measure. Not all scales provide for parallel ratings as a means of assessing the accuracy of self-appraisal in PD (Chapter 6).

In this thesis EF-related behavioural disturbances were assessed with the Behavior Rating Inventory of Executive Functions-Adult (BRIEF-A; Roth et al., 2005), as it provides the two parallel versions (self-rating and informant-rating) needed for evaluation of awareness levels in PD (Chapter 6), and the interpretation of the results is supported by normative data from a large sample. Internal consistency is reported as high for the summary index (Global Executive Composite, GEC), with Cronbach α = .96 for the self-rating, and Cronbach α = .98 for the informant rating (Roth et al., 2005). The test–retest reliability was also reported as high, with correlation r = .94 in self-rating, and r = .96 in informant rating (Roth et al., 2005). The validity of the BRIEF-A was confirmed by demonstrating strong correlations of the GEC with other behavioural ratings of EF, the DEX and FrSBe. The BRIEF-A has been used in various clinical groups, including Alzheimer's, MCI and TBI (Roth et al., 2005; Waid-Ebbs, Wen, Heaton, Donovan, & Velozo, 2012), and has been reported as sensitive to subtle executive changes in MCI (Rabin et al., 2006).

The BRIEF-A assesses the ability to efficiently regulate behaviour and emotional responses, and to appropriately distribute attention to sustain task-completion efforts and systematically solve problems. The BRIEF-A provides a list of 75 behaviours to be rated on a 3-point scale (never, sometimes, often; scored 1, 2, 3 respectively). Participants and their informants indicate on two parallel versions which of the described behaviours has been a problem for the participant during the past month. A higher GEC summary score (range 70-210) indicates more EF-related difficulties in the everyday environment. The GEC scores are converted to age-scaled T scores (M = 50, SD = 10), which indicate whether the reported degree of difficulty suggests a clinically-significant level of EF-related behavioural problems (T ≥ 65, 1.5 SD above the mean).

2.2.4 Quality of life and subjective health status

The importance of acknowledging PwPD subjective perception of the illness is widely recognised, and there are several measures developed to examine the subjectively perceived impact of the illness on PwPD lives. The terms that are used in this context include quality of life, health-related quality of life, and subjective health status. It is argued that while these concepts might be related, the subjective perception of the severity or magnitude of symptoms (subjective health status) should not be treated as equivalent to how satisfied people feel with their health or life in general (quality of life) (Den Oudsten, Van Heck, & De Vries, 2007b; Hunt, 1997; Sprangers & Schwartz, 1999; The WHOQOL Group, 1995). This distinction is often missing in research studies, and in some cases the questionnaires reported as measures of QoL consist of questions about health status. In this study both subjective health status and QoL were investigated and in both cases a questionnaire developed specifically to capture that particular aspect of well-being was carefully selected. To identify relationships between EF deficits and QoL and health status

specific to PD, as well as to allow a meaningful comparison of the two concepts, it was considered more appropriate to use PD-specific measures for both concepts.

As far as could be determined, only one questionnaire has been developed specifically to assess QoL in movement disorders, the Questions on Life Satisfaction Scale (Henrich & Herschbach, 2000; Kuehler et al., 2003) (Appendix G), and it was chosen for this study. The scale has been validated for use in PD and includes PD-specific items (Henrich & Herschbach, 2000; Kuehler et al., 2003). The questionnaire examines subjective quality of life in three dimensions: general life satisfaction (QoL-Life, 8 items), satisfaction with health (QoL-Health, 8 items), and satisfaction with health in relation to movement disorders (QoL-MD, 12 items). On two separate 5-point scales participants indicate the subjective importance of specific areas of life and health (importance rating), and the degree of satisfaction in these areas (satisfaction rating). The two ratings for each item are converted into a weighted satisfaction score (WS) with a formula: WS = [importance rating - 1] x [(2 x satisfaction rating) - 5]. The WS scores are summed to provide global ratings for each of the three dimensions. For QoL-Life and QoL-Health the possible values range from -96 to 160, and for QoL-MD the possible values range from -144 to 240. Negative values indicate a predominance of “dissatisfaction”. Internal consistency is reported as high, with α = . 82 for QoL-Life, α = .89 for QoL-Health (Henrich & Herschbach, 2000), and α = .87 for QoL-MD (Kuehler et al., 2003). The test–retest reliability was satisfactory and the validity of the scale was confirmed by demonstrating adequate correlations with other ratings of well-being (Henrich & Herschbach, 2000; Kuehler et al., 2003).

There is a wide range of PD-specific questionnaires assessing subjective health status (Martinez-Martin et al., 2011), such as the Parkinson’s Disease Questionnaire (PDQ-39;

Jenkinson, Fitzpatrick, & Peto, 1998), Scales for Outcomes in Parkinson's Disease – Psychosocial (SCOPA-PS; Marinus, Visser, Martínez-Martín, van Hilten, & Stiggelbout, 2003), and Parkinson's Impact Scale (PIMS; Calne et al., 1996). They differe with regard to comprehensiveness of assessment, for example how many questions relate directly to physical health, and what aspects of health and well-being are considered.

In this thesis, subjective health status was assessed with the PDQ-39 (Jenkinson et al., 1998) (Appendix H), which consists of 39 questions about the subjectively-perceived severity of various PD symptoms that are of particular relevance to PwPD. The questionnaire covers a broad range of health-related topics and is widely used in PD studies (Martinez-Martin et al., 2011). It appears to be the only PD-specific health status questionnaire that includes items on social support and one of the few that includes questions about cognition (Den Oudsten et al., 2007b). It assesses the following eight dimensions: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. Participants indicate on a 5-point scale how often they have been affected by each of the 39 problems listed. The total score for each dimension is calculated on a scale from 0 to 100 using the following formula: [sum of scores in a dimension/(the maximum score per question x number of questions in dimension)] x 100, with higher scores indicating a higher level of problems. The mean value for all eight dimensions provides a summary index. The questionnaire has high internal consistency, with $\alpha = .84$ for the summary score (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997), and between $\alpha = .69$ (Social support) and $\alpha = .94$ (Mobility) for the individual scales (Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995). The test–retest reliability has been

reported as adequate to good, with correlation values between r = .68 (Social support) and r = .94 (Mobility)(Peto et al., 1995).

2.2.5 Caregiver Burden

A number of generic questionnaires have been developed to assess burden associated with providing informal care for a family member (Deeken, Taylor, Mangan, Yabroff, & Ingham, 2003; Vitaliano, Young, & Russo, 1991). These questionnaires differ with regard to the number of questions and comprehensiveness of assessment, as well as the extent to which their psychometric properties have been established (Deeken et al., 2003). For example, the Caregiving Stress Inventory (Pearlin, Mullan, Semple, & Skaff, 1990) provides a comprehensive assessment of burden in caregivers as it yields 15 different subscales, but the internal consistency of some of the scale is low (α = .48) and as there are 89 questions, administration is time-consuming. The Zarit Caregiver Burden Interview (Zarit, Reever, & Bach-Peterson, 1980) is relatively brief as it consists of 29 questions, but it provides only one summary score. It was originally validated in a group of 29 caregivers of people with dementia, and the analyses showed no correlations with other established measures. As far as can be determined, the only PD-specific questionnaire assessing specific needs of people caring for PwPD is the Belastungsfragebogen Parkinson Angehörigen questionnaire (Spliethoff-Kamminga, Zwinderman, Springer, & Roos, 2003). It was considered less appropriate for the purpose of this thesis, as it was developed to identify caregivers in need of additional support, rather than to provide a detailed picture of the overall impact of caregiving in PD, and it was validated only on a relatively small group of PwPD. A generic tool, the Caregiver Burden Inventory (CBI; Novak & Guest, 1989) (Appendix I) was chosen, as it provides a comprehensive evaluation of the caregiver's feelings and responses to the burden of care, while remaining relatively brief. It consists of 24 questions related to five

areas that might be affected by caregiving: flexibility with time, physical health, social relationships, emotional well-being, and life in general. Responses are rated on a 4-point scale, with the maximum score of 96 indicating the highest level of burden. Internal consistency was reported as good, with α = .85 for the flexibility with time subscale, α = .86 for the physical health subscale, α = .73 for the social relationships subscale, α = .77 for the emotional well-being subscale, and α = .85 for the life in general subscale. The CBI is a generic tool, but it has been used previously in PD studies (D'Amelio et al., 2009; Happe & Berger, 2002; Schrag et al., 2006).

2.3 Procedure and data collection

Sixty-five PwPD who met the inclusion criteria for the study completed the assessment of executive functions, awareness, QoL, and subjective health status. A sub-group of 34 PwPD identified as having possible EF deficits completed a more extensive neuropsychological assessment of executive abilities.

PwPD were assessed during their 'on' phase and the majority of them were visited at home. Six PwPD chose to meet at the University. The initial assessment (screening, EF, awareness, QoL, and health status) took between 1.5 and 3 hours, with some participants completing the assessment over two shorter visits and some opting to send the self-completion questionnaires by post. In-depth assessment of EF took another 4 to 6 hours over two to three visits, and included measures not reported in this thesis.

Fifty people who lived with PwPD and/or knew the participants very well (e.g. spouses or adult children) provided informant ratings of the executive functioning of PwPD and their own level of burden associated with caring for a PwPD. The majority of caregivers

completed the questionnaires during the home visit by the researcher and some opted to send the questionnaires by post.

Healthy older people completed the assessment of EF and awareness. The majority of them were visited at home, with nine choosing to meet at the University. The assessment took 1.5 to 2.5 hours and included measures not reported in this thesis.

2.4 Data handling and statistical analyses

2.4.1 Data entry and cleaning

Participants' responses were recorded on the relevant score sheets and summary indices were calculated according to the procedure outlined in the test manuals or relevant publications. The performance scores for the D-KEFS were calculated using the D-KEFS Scoring Assistant software, which has built-in minimum and maximum values, reducing the risk of erroneous data entry, and automatically calculates the summary scores, eliminating possible calculation errors. It also generates the scaled scores without the need for checking the complex normative data tables, again reducing the risk of inaccuracy in the final dataset. The Scoring Assistant produces test reports detailing the chosen performance indices (raw and scaled scores) for individual participants. These reports were printed out, cross-checked for accuracy with the scoring sheets, and used for entering data into SPSS.

The relevant performance indices from the D-KEFS and the other measures and questionnaires were entered into a study-specific spreadsheet in SPSS v.19.0 (IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). The study-specific spreadsheet for data entry contained all variables of interest, with built-in validity checks for each variable: pre-specified entry format, possible range of scores and coding (where

feasible), and codes for missing data. The accuracy of the final data set was checked visually and the descriptive statistics for individual variables were explored to identify unlikely values. For example, the summary scores were checked against the possible maximum values. Additionally, the total scores were recalculated in SPSS where feasible and cross-checked with the values calculated manually. Finally, the accuracy of data entry was validated by comparing data in the SPSS spread sheet against the actual questionnaires and scoring sheets from a random sample of 10 participants (15%).

One of the questionnaires, the BRIEF-A, provides an additional validity check. It has three validity scales (Negativity, Infrequency, and Inconsistency), which highlight abnormal patterns of responses (Roth et al., 2005, pp. 16-19). The validity scales were inspected for both self- and informant ratings for all participants and the recommended procedure for elevated scores was followed when necessary (see details in Table 6.3 in Chapter 6).

2.4.2 Dealing with missing data

Missing data were identified in the SPSS spreadsheet with an appropriate code (999, 9999 or 99999). For one of the questionnaires (BRIEF-A) the test manual specifies a detailed procedure for dealing with missing responses (Roth et al., 2005, p. 8), and the recommended procedure was observed in this study. In all other measures missing data were not imputed and cases were excluded pairwise in the analyses. The only exception related to the hierarchical cluster analysis examining associations between cases (participants) in EF test performance, where missing values were excluded listwise (see Figure 4.3 in Chapter 4). See also Table 2.1 below for information about the completeness of the data set and descriptive statistics for the study measures.

Table 2.1. Completeness of the data set and descriptive statistics for the study measures.

Measures administered to the full sample of PwPD	**N**	**M (SD)**	**Range**	**Min. and Max.**
ACE-R	65	93.83 (4.41)	82 – 100	0 – 100
HADS-Depression	65	4.43 (2.51)	0 – 10	0 – 21
HADS-Anxiety	65	5.42 (3.52)	1 – 16	0 – 21
FAB	65	14.86 (1.85)	11 – 18	0 – 18
TM	64	136.84 (67.80)	45 – 240	– 240s
CWI	64	84.61(29.69)	39–180	– 180s
QoL-General Life	57	83.88 (28.83)	30 – 141	-96 – 160
QoL-General Health	58	62.10 (43.23)	-59 – 134	-96 – 160
QoL-Movement Disorders	55	96.96 (52.27)	-49 – 216	-144 – 240
PDQ-39	54	20.13 (11.57)	0.52 – 53.75	0 – 100
BRIEF-A Self	61	107.26 (19.62)	71 – 177	70 –210
Measures administered to the sub-group of PwPD with EF deficits	**N**	**M (SD)**	**Range**	**Min. and Max.**
D-KEFS Verbal Fluency	34	11.85 (3.47)	3 – 20	0 –
D-KEFS Design Fluency	34	85.00 (11.88)	42 – 100	0 – 100%
D-KEFS Sorting	30	28.43 (12.22)	6 – 53	0 – 64
D-KEFS 20 Questions	33	26.70 (11.44)	4 – 53	0 – 60
D-KEFS Word Context	33	24.55 (6.28)	9 – 36	0 – 50
D-KEFS Tower	33	15.39 (4.85)	4 – 24	0 – 30
D-KEFS Proverb	30	8.73 (2.79)	3 – 12	0 – 12
Measures administered to carers	**N**	**M (SD)**	**Range**	**Min. and Max.**
BRIEF-A Caregiver	47	97.87 (23.26)	70 – 166	70 – 210
CBI	42	12.45 (10.55)	0 – 46	0 – 96
Healthy older people	**n**	**M (SD)**	**Range**	**Min. and Max.**
ACE-R	43	92.86 (3.87)	82 – 99	0 –100
GDS-15	43	1.51 (1.59)	0 – 5	0 – 15
D-KEFS TM	42	110.60 (52.15)	42 – 240	– 240s
BRIEF-A Self	39	101.59 (18.91)	71 – 142	70 – 210
BRIEF-A Caregiver	39	97.87 (20.98)	70 – 151	70 – 210

Note. See Table 4.1 in Chapter 4 for details of which indices of performance were used for particular tests.

M – Mean; SD – Standard deviation; ACE-R – The Addenbrooke's Cognitive Examination - Revised; HADS – Hospital Anxiety and Depression Scale; FAB – Frontal Assessment Battery; TM – Trail Making; CWI – Color Word Interference; GDS-15 – Geriatric Depression Scale; BRIEF-A Self – BRIEF-A Global Executive Composite Self-rating (raw score); BRIEF-A Caregiver – BRIEF-A Global Executive Composite Caregiver rating (raw score); QoL – Quality of Life; PDQ-39 – Parkinson's Disease Questionnaire – 39; CBI – Caregiver Burden Inventory

2.4.3 Data transformation and dealing with outliers

Before conducting statistical analyses, all variables were inspected to identify potential outliers. The variables were converted into z-scores and the frequency of the absolute z-scores above the relevant cut-off values (1.96, 2.58, and 3.29; Field, 2005) was calculated for each variable of interest. Test performance scores were within the expected range of scores and there were no outliers impacting significantly on the analyses.

In order to decide on the most appropriate statistical methods for the planned inferential analyses, the properties of the variables were checked against the statistical assumptions relating to particular parametric tests. The variables were checked against assumptions of normality and homogeneity of variance, and more specific checks were performed for the regression analyses and the principal components analysis. The details of the specific assumption checks are presented at the appropriate points in the subsequent chapters. Where assumptions were violated, non-parametric equivalents were used (Field, 2005). One set of variables (performance ratios; see section 6.4.3. *Performance monitoring* in chapter 6) was logarithmically transformed to ensure a more symmetrical distribution for the statistical analysis (Trosset & Kaszniak, 1996).

2.4.4 Planned analyses

A range of statistical tests was used to address the research questions posed in the empirical studies. To investigate the pattern of performance on EF tests (Chapter 4) the results were analysed using data-driven approaches: cluster analysis and principal component analysis (PCA). Data-driven approaches are useful in exploring potential relationships in complex data sets where there is limited *a priori* knowledge of the data structure (Morris, Blashfield, & Satz, 1981; Ward, 1963). The associations between the study

variables of interest, as indicated in the specific research questions, were examined with the appropriate correlational analyses (chapters 4, 5, and 6). To establish the predictors of QoL, health status and caregiver burden (Chapter 5), multiple regression analyses were conducted. For the group comparisons in Chapter 6, one-way ANOVA were conducted with Bonferroni or Games-Howell post-hoc analyses as appropriate, depending on the results of the homogeneity of variance test. The rationale for selecting particular statistical tests and the details of the analyses are given at the appropriate points in the subsequent chapters. All analyses were performed in IBM SPSS Statistics 19.

Chapter 3

Executive functions in Parkinson's disease:

Systematic review and meta-analysis

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3.1 Abstract

Background: Impairment of executive function (EF) is commonly reported as a feature of PD. However, the exact pattern of executive impairment remains unclear. Also, there is an ongoing discussion surrounding the definition and conceptualization of EF, which might affect the clarity of research evidence on cognition in PD. The aim of this systematic review was to describe the pattern of executive impairment in early stage PD emerging from the research literature and to identify critical issues for improving consistency in this field.

Methods: The PsychInfo, Medline, Science Direct, CINAHL and Cochrane Library databases were searched using the term 'Parkinson's disease' combined with each of 14 cognitive abilities defined as representing aspects of executive function. The review was limited to studies that investigated EF as the central variable in early stage non-demented people with PD (PwPD).

Results: The review identified 33 studies of EF that were operationalised in terms of 30 abilities tested by 60 measures and variously interpreted. Many measures were used only once, so only a small part of the available research evidence could be synthesized in the meta-analysis. Meta-analysis was undertaken using data from 5 commonly-used tests of executive function drawn from 18 studies. This revealed consistent evidence for cognitive difficulties across all 5 EF tests.

Conclusions: Research on EF in PD is characterized by a considerable lack of clarity with regard to measure selection and interpretation. The findings support the view that EF impairments are evident in PD. However, the clinical significance of the cognitive abnormalities reported has yet to be clarified.

3.2 Introduction

Although motor impairment is the most profound feature of PD, cognitive deficits are also common and may add a considerable burden to the lives of people with PD (PwPD) and carers (Klepac et al., 2008; Schrag et al., 2000). Dopaminergic depletion leads to the disruption of frontostriatal circuits, which in turn may affect cognitive abilities (Zgaljardic et al., 2003). The severity of cognitive impairment ranges from difficulties in a single domain, through global decline, to dementia (Mindham & Hughes, 2000; Royall et al., 2002; Zgaljardic et al., 2003). Research on cognition in PD indicates that the disease may affect every cognitive domain: memory, language, attention, visuospatial and visuoconstructive abilities, and executive functions (Zgaljardic et al., 2003). However, executive dysfunction seems to be the most profound impairment. Some studies suggest that a proportion of broader cognitive deficits reported in the literature may actually be the manifestation of underlying executive impairment (Stuss & Alexander, 2000). The exact pattern of executive impairment in PD is still debated (Muslimovic, Schmand, Speelman, & De Haan, 2007), as numerous reports on executive dysfunction (Barnes & Boubert, 2008; Muslimovic et al., 2005) are accompanied by studies reporting normal performance on EF tests. For example, Zgaljardic et al. (2006), Uekermann et al. (2004), Dujardin et al. (2001), and Bouquet, Bonnaud, and Gil (2003) reported impaired performance in phonemic fluency, while Farina et al. (2000), Colman et al. (2009), Auriacombe et al. (1993), and Cools et al. (2001) found no significant differences between PwPD and controls. Dalrymple-Alford, Kalders, Jones, and Watson (1994) report central executive deficits, while Nathalie Fournet, Moreaud, Roulin, and Naegele (1996) claim that the central executive seem to be intact. Moreover, there are reports indicating the superior performance of PwPD in some tasks requiring executive control (Bialystok, Craik, & Stefurak, 2008; Cools et al., 2010). This inconsistency in results

may be influenced by a number of factors presumably related to the complex pathology of PD, including age of onset, severity and type of disease (Uekermann et al., 2004). Another reason for the inconsistency, however, may be the complexity of the EF construct itself. To provide the context for our review, we first present a brief overview of EF definitions and related concepts, and discuss the implications of the non-unitary character of EF for research.

3.2.1 Definitions of EF and related concepts

Researchers concur that the key elements of EF are successful coping with novelty and managing personal goals. Lezak (2004) describes EF in terms of capacities that enable successful, "independent, purposive, self-serving behavior" (p. 34) and responding in an "adaptive manner to novel situations" (p. 611), involving appropriate, socially responsible behavior. Burgess and Alderman (Burgess & Alderman, 2004) define EF as the abilities required for setting goals, determining strategies to achieve them and monitoring progression, as well as adjusting plans to changing circumstances. Other definitions accentuate the supervisory role of EF in coordinating 'lower-level' cognitive processes, and the significance of dealing with novelty in the non-automatic processing mode (Alvarez & Emory, 2006; Aron, 2008; Rabbitt, 1997). EF can also be explained as "a collection of anatomically and functionally independent but interrelated attentional control processes" (Stuss & Alexander, 2007, p. 901). Although expressing the essential concept of EF is relatively unproblematic, definitions remain rather broad and vague (see Salthouse (Salthouse, 2005) for a comprehensive list of definitions). One account aptly describes the issue by characterising EF as "a shorthand description of a complex set of processes that have been broadly and variously defined" (Strauss et al., 2006, p. 401).

Although executive function is frequently referred to as reflecting a homogenous ability (Costa et al., 2008; Edelstyn, Mayes, Condon, Tunnicliffe, & Ellis, 2007; Fama & Sullivan, 2002), most researchers acknowledge that EF serves as an umbrella term, and does not necessarily reflect a single, discrete cognitive function (2007). It is suggested that EF may be constituted by a number of abilities that are "separable but moderately correlated" (Miyake et al., 2000, p. 87). Lezak (2004) lists four components of EF: volition; planning; purposive action; and effective performance. She does not include concept formation and reasoning, which she considers as separate processes, although these abilities are included in other classifications of EF (Delis et al., 2001; Lafleche & Albert, 1995). Another frequently cited classification by Smith and Jonides (1999) proposes five components: attention and inhibition; task management (including switching attention between tasks); planning; monitoring; and coding. Stuss and Alexander (2000) note that although the great majority of recent studies seem to concentrate on 'cognitive' aspects of behavioral control (e.g. attention, set-shifting, inhibition), there are also other concepts at least equally important for successful behavior, such as personality, emotions, motivation, and awareness.

A concept commonly linked to EF is the multicomponent model of working memory (WM) introduced by Baddeley and Hitch (1974). This model distinguishes four components of WM: the visuospatial sketchpad; the phonological loop; the episodic buffer; and a central executive that controls attention and enables manipulation of information (Baddeley & Hitch, 1994). The central executive is closely related to the Supervisory Attentional System (SAS) described by Norman and Shallice (1986). Impairment of the SAS is linked to the 'frontal lobe syndrome'. The debate over the role of the central executive/SAS has contributed greatly to defining executive functions. The SAS framework (Norman & Shallice,

1986) divides cognitive functioning into routine activity and a non-routine, executive multicomponent system, labeled the Supervisory System (Stuss et al., 1995). In the context of Baddeley and Hitch's mode (1974), EF forms a component of working memory (the central executive). However, WM is also considered as an EF subcomponent or as a separate but related function (Alvarez & Emory, 2006; Royall et al., 2002). Another concept closely related to managing behavior (and to EF) is attention, as it plays a crucial role in managing behavior by regulating the appropriate distribution of cognitive resources (Stuss & Alexander, 2007).

3.2.2 Challenges in researching EF

The complex character of the EF construct creates challenges for EF research (Chan et al., 2008). Stuss and Alexander (2000) point out that problems may arise as a consequence of interchangeable and inconsistent use of terms and definitions of executive *versus* frontal functions. Moreover, terms such as EF (or 'executive control', 'supervisory system') are difficult to operationalize and 'executive' tests are characterized by low validity and reliability. EF are also multifactorial in nature, and thus impaired executive performance may be caused by dysfunctions in other cognitive domains (Stuss & Alexander, 2000). There are a number of tools described as "classic frontal" tests, developed to capture EF as a whole or selected components of it (e.g. tower tasks, Wisconsin Card Sorting Test, verbal fluency tasks, dual-task paradigms) and these are widely used in research and clinical practice (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Delis et al., 2001). However, there is an ongoing debate on approaches to measuring EF and no "gold standard" for tool selection has been agreed (Norman & Shallice, 1986; Royall et al., 2002).

3.2.3 Executive impairment in PwPD

Motor symptoms of PD are naturally the central concern in the care of PwPD. However, the effects of executive impairment may also have a significant impact on everyday life. PwPD with executive impairment have been compared to people with frontal lobe damage (Owen et al., 1993; Rogers et al., 1998), who may perform well in many cognitive tests and show no obvious signs of cognitive difficulties in structured settings, but fail in everyday situations (Lezak, 2004). It is important to investigate whether this is true for PwPD. Research in healthy older adults indicates a relationship between activities of daily living and performance on measures of executive functioning (Bell-McGinty et al., 2002; Jefferson, Paula, Ozonoffc, & Cohen, 2006). There is also evidence of a relationship between cognitive abilities and everyday functioning among PwPD in later stages of the disease (Bronnick et al., 2006; Cahn et al., 1998). Poliakoff and Smith-Spark (2008) found that PwPD without dementia do report being distractible and forgetting important information from the previous day more often than healthy controls. However, the impact of cognitive difficulties on PwPD' independence and well-being in the early stages of PD still needs to be better understood to facilitate appropriate support for PwPD and carers.

3.2.4 Rationale for the systematic review

In this review we aimed to describe the pattern of executive impairment in early PD by synthesizing existing research in a meta-analysis. In addition, we intended to explore which neuropsychological models, theories or conceptualizations of EF underlie research in PD, and to identify and clarify some of the possible factors contributing to the inconsistency in existing research findings. To control for the influence of complex disease characteristics as well as other methodological issues we aimed for a homogenous group of studies.

3.3 Method

A systematic literature search was performed in October 2009 and updated in May 2010 using the following databases: PsycInfo (CSA), Medline (Web of Knowledge), PubMed, CINAHL, and the Cochrane Library.

The search was performed in two stages: firstly using broad EF-related terms and then using specific EF subcomponents. Key words used were: 'Parkinson's disease' (in title/key words) combined with 'cognitive impairment', 'dysexecutive' or 'executive' (in title/abstract). The initial analysis identified 11 subcomponent functions commonly investigated in relation to or as a part of EF, and these were used in the second search: 'frontal', 'working', 'set-shifting', 'switching', 'fluency', 'inhibition', 'decision making', 'planning', 'flexib*', 'processing speed', 'cognitive speed' (in title/abstract/keywords) combined with 'Parkinson's disease' (in title). Only articles from peer-reviewed journals, written in English and published after 1990, were included.

The inclusion and exclusion criteria used in study selection are summarized in Table 3.1. In questionable cases, co-authors independently read the article and a joint decision was reached.

To narrow down the search only articles focusing specifically on EF in PD were included. We were interested in exploring the neuropsychological perspective which seems to link more directly to the everyday functioning of PwPD and their carers, rather than brain imaging or neuropharmacological studies. Working memory was considered to be related to EF only if the central executive component was directly investigated; otherwise the study was excluded. In making decisions in regard to the above criteria we referred to the theories and concepts of EF discussed in the introduction. Additionally, the review included only

those studies that clearly reported that all participating PwPD were in the early stages of the disease (Hoehn and Yahr stages I-III). Studies that included a broader range of PwPD, or did not specify the range, were not taken into consideration.

Table 3.1. Selection criteria for the literature search.

Inclusion criteria

Studies were included if:

1. The main aim of the study, as directly stated, was to investigate executive impairment in Parkinson's disease (overall, or its component(s), or EF distinguished as part of a general cognitive assessment)
2. The study was based on a neuropsychological perspective
3. Directly investigated abilities included executive functions, frontal lobe functions or at least one of the core subcomponents of EF
4. The severity of PD was stage I-III Hoehn & Yahr (as directly stated)
5. PwPD included in the study were not severely depressed and did not have a diagnosis of dementia (as directly stated)
6. The study was written in English, and published after 1990

Exclusion criteria

Studies were excluded if:

1. The study investigated only the neuronal or neurochemical basis of EF in PD
2. The study investigated the effect of a particular medical treatment
3. The study's aim was to verify the suitability of a particular EF measure for PD PwPD
4. The study investigated apathy (apathy may be interpreted as impairment of motivation or volition and may therefore be considered as an impairment of EF, but most studies consider apathy as a separate symptom)
5. The main interest of the study was not EF in PD
6. The study investigated general cognition in PD without distinguishing EF and/or no direct EF measure was used
7. The study concentrated on cognitive abilities without linking them directly to EF
8. A PwPD group served as a comparison group for another condition
9. The study presented results from a PD group without a control group or normative data (or did not provide full details of such a comparison)

In total, from 3264 hits, 393 articles were retrieved for detailed inspection and 33 fulfilled all inclusion criteria. See Figure 3.1 for a detailed flow chart of study selection for both searches. Key information was extracted from the articles considered at the final stage of the literature search and entered into a structured form for analysis (see appendix F, G, and H).

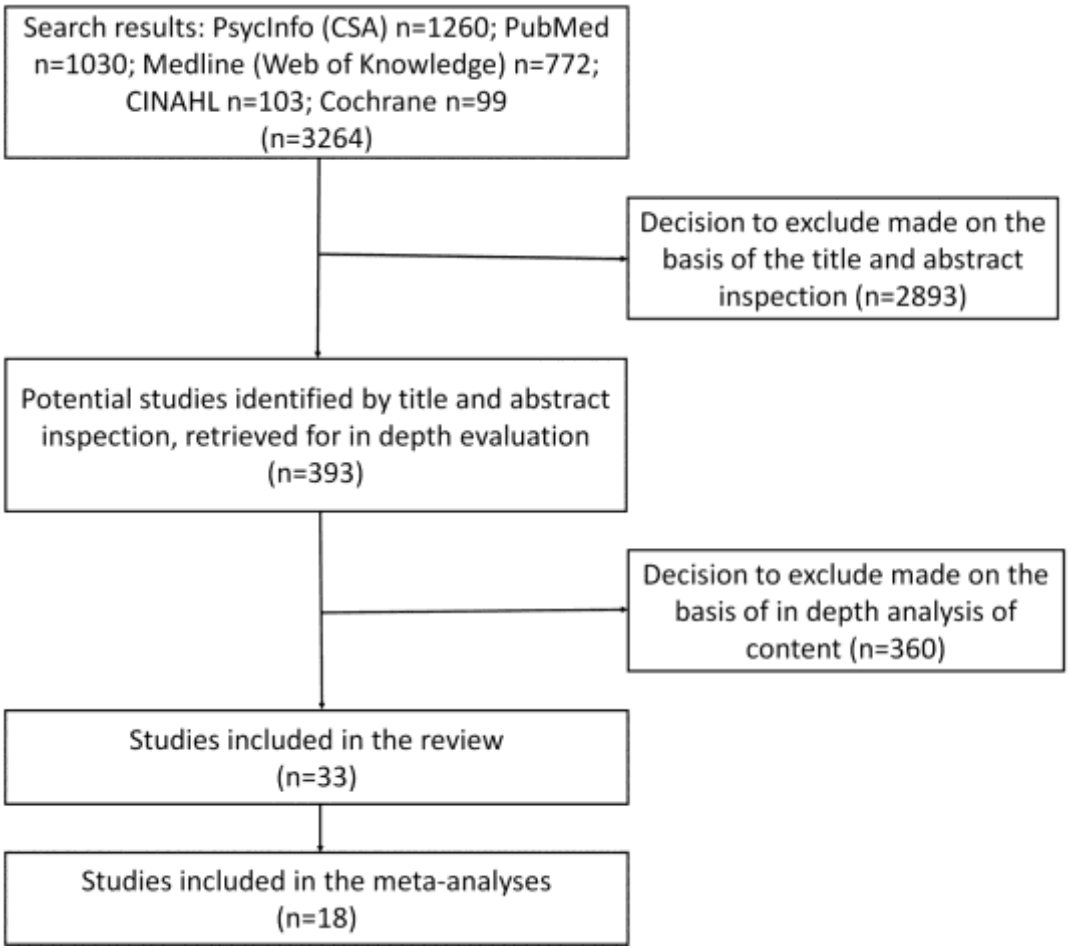

Figure 3.1. Study selection process.

To synthesize the results of the review articles, meta-analyses were performed for scores derived from five commonly-used tests (see Table 3.2). Analyses were carried out using Comprehensive Meta-Analysis software (Borenstein, Hedges, Higgins, & Rothstein, 2005). Results were compared using a random-effects model. First, the Standardised Mean

Difference (d) was computed and then the correction factor was applied to compute Hedges' g. Between-study heterogeneity for each cognitive measure was assessed by the Q statistic as well as an Index of Inconsistency (I^2). The Q statistic refers to the weighted squared deviation and provides a ratio of the total observed variation between studies to the variation that is a consequence of within-study errors. The I^2 statistic is the ratio of true heterogeneity to total observed variation (Borenstein et al., 2009).

3.4 Results

3.4.1 Executive functions and measures

Thirty-three articles met the inclusion criteria for the study, and these are briefly summarized in Table 3.2 (see also Appendix H for a more detailed summary). A detailed summary of studies examined at the final stage of the literature search and excluded from the review after in-depth analysis of content is presented in Appendix G. Amongst the studies included to the review there were three main approaches to investigating EF: exploring overall executive (or frontal) function; focusing on a single dimension of EF, frequently without discussing the EF concept; and exploring general cognition with EF distinguished as one of the abilities of interest. Several studies met inclusion criteria but had more than one of the following limitations: 1) background theories of executive/frontal domains were not discussed; 2) subcomponents of EF/frontal functions were not distinguished; 3) it was not specified which tests measure which subcomponents.

Table 3.2. Summary of articles included in the review.

First author	Participants n (men), mean age, years (SD or range, as reported), mean PD duration	EF components and measures List of EF components (as specified by authors) and measures of EF (also if it was not clear whether authors considered a test as an EF measure, if clearly EF related) *PD significantly lower than controls
Studies focused on executive or frontal functions as a whole, selectively or in relation to other factors.		
Zgaljardic et al. (2006)	32 PwPD (19 men), 66.9 (8.1) 29 controls (15 men), 66.7 (5.7)	**Anterior cingulate cortex*** (response monitoring, inhibition, initiation, apathy) Apathy Scale, Initial Fluency, Stroop test (Interference Index); **Dorsolateral prefrontal cortex*** (set-shifting, working memory, intrinsic response generation, and conditional associate learning) VF Category, DS, Executive Scale (Frontal Systems Behavior Scale), Phonemic Fluency, Odd Man Out, Petrides Conditional Associate Learning – Criterion (no. trials), Petrides Conditional Associate Learning – Errors, Spatial Span, VF Switching Accuracy; **Orbitofrontal cortex** (disinhibition, decision-making, impulsivity, and perseveration, depression) Beck Depression Inventory, Disinhibition Scale, Alternating Loops (no. errors), Twenty Questions Test – Abstraction Score, Total Questions, Weighted Score.
Farina et al. (2000)	20 PwPD (13 men), 57.9 (8.3) 18 controls (10 men), 56.6 (6.4) $M_{PD\ duration}$=28 months (3-96)	Abstract behavior and shifting ability: WCTS (2*of 4 variables); Concept formation and free recall: Test of categorization and recall (2*of 5 variables); Abstract non-verbal reasoning: Ravens Progressive Matrices*; Short-term verbal memory and attention: DS; Short-term visuo-spatial memory and attention: Corsi's block-tapping; Visuospatial long-term memory: Corsi's Supra span tapping*; Verbal long-term memory: Paired associated learning test; Measures not discussed: (Odd Man Out (1*of 2 variables), VF phonemic)
Uekermann et al. (2004)	20 PwPD (8 men), 55.9; 20 controls (9 men), 53.2 $M_{PD\ duration}$= 4.6 years (3.0)	**Initiation**: VF (phonemic*, semantic, alternating); **Planning and problem solving**: Key Search, Six Elements* and Zoo Map test (BADS, Behavioral Assessment of the Dysexecutive Syndrome); **Reasoning**: Temporal Judgment* and Cognitive Estimation task (BADS); **Inhibition**: Rule shift cards* of BADS, Hayling test*; **Self-reported behavioral problems**: Dysexecutive questionnaire of BADS)

(Table 3.2 continues)

(Table 3.2 continued)

Dujardin et al. (2001)	#12 sporadic PD (7 men), 65.92 (51-74) 12 familial PD (5 men), 63.42 (44-76) 12 controls (6 men), 59.25 (47-73) $M_{PD\ duration}$= 103/74 months	**Planning**: VF, spatial sequences generation* **Resistance to interference**: Brown-Peterson paradigm* **Set shifting**: WCST, VF alternate*, motor sequences*; **Memory**: immediate (DS forward and backward, spatial span, word span); working memory
Farina et al. (1994)	22 PwPD (11 men), 52.86 (39-72) 19 controls (6 men), 53.42 (33-66) $M_{PD\ duration}$=57.7 months	Organization, planning and memory: Classification* and recall of pictures
Price and Shin (2009)	12 mild PD (H&Y: I) 71.9 (2.0) #10 moderate PD (H&Y: II-III) 71.4 (1.4) 10 controls 70.5 (3.2) $M_{PD\ duration}$=4.0 (0.9)/9.7 (1.1) years	**Mental set-shifting**: mWCTS perseverative errors; **Concept formation**: number of categories on the Modified WCST; **Spontaneous cognitive flexibility**: VF semantic, COWAT (Controlled Oral Word Association Test)*; **Working memory**: CSpan test
Price (2010)	15 PwPD (10 men), 67.67 (1.42) 12 controls (8 men), 64.2 (1.67) $M_{PD\ duration}$= 6.47 (1.2)	**Problem solving**: Anagram task (baseline* and cued), Executive functions: Set shifting: WCST-64 (perseverative errors), **Inhibitory control**: Stroop interference (response time) Semantic verbal fluency: COWAT*, **Working memory**: CSpan (total correctly recalled)
Colman et al. (2009)	28 PwPD (16 men), 61.39 (8.8) 28 controls(16 men), 62.93 (9.04) $M_{PD\ duration}$=6.04 years (4.55)	**Attention**: 3 subtests of Testbatterie zur Aufmerksamkeitsprufung (sustained visual*, sustained auditory and divided attention); **Working memory**: DS forward and backward; **Cognitive set-switching**: TMT A and B + Odd Man Out (composite*); **Inhibititory control**: Stroop test; VF: phonemic, semantic, action; **Abstract structure processing**: experimental paradigm
Bondi, Kaszniak, Bayles, and Vance (1993)	19 PwPD (16 men), 67.32 (6.85) 19 controls (7 men), 69.26 (5.36) Median $_{PD\ duration}$=8 years (1-17)	**Frontal system tasks** (composite*): VF * (phonemic, semantic), Modified WCST *, California Sorting Test*, Verbal Temporal Ordering*.
Studies investigating subcomponents of executive (or frontal) functions, selectively or in relation to other factors.		
Altgassen, Phillips, Kopp, and Kliegel (2007)	16 PwPD (11men), 61.1 (6.9) 16 controls (8 men), 62.6 (9.1) $M_{PD\ duration}$ = 4.81 (3.0)	**Planning:** ToL*; **Working memory:** Phonological loop (VF forward), Visuospatial sketchpad (block span forward), Episodic buffer (logical memory*), **Central executive processes** (n-back task*)
Bouquet et al.	20 PwPD (12 men), 66.1(7.6)	Internal strategy generation and inhibition of unwanted response:

(Table 3.2 continues)

(Table 3.2 continued)

(2003)	20 controls (13 men), 63.5 (10.1) $M_{PD\ duration}$ =10.25 years (5.83)	Hayling test*, VF * (phonemic, semantic, alternating), TMT
Bublak, Müller, Grön, Reuter, and von Cramon (2002)	14 PwPD (5 men), 55.1 (14.7) 14 controls 55.2 (14.7) $M_{PD\ duration}$=47.3 months (50.0)	**Working memory**: experimental paradigm Working memory resources seem to diminish excessively with the increasing complexity of the task.
Gilbert, Belleville, Bherer, and Chouinard (2005)	14 PwPD (5 men), 66.29 (11.08) 14 controls 65.79 (10.33) $M_{PD\ duration}$= 7.29 years (4.53)	**Executive tasks:** Alphabetical recall* and updating memory tasks Storage Task: DS
McKinlay, Kaller, et al. (2008)	30 PwPD 65.77 (6.6) 30 controls 66.43 (5.3) $M_{PD\ duration}$= 7.3 (4.6)	**Planning**: ToL (computerised version) There was no evidence for general planning difficulties in the PD group when compared to controls. When the ambiguity of goal hierarchy increased (subgoals sequence was less predictable) the PD group performed worse than controls.
Cronin-Golomb, Corkin, and Growdon (1994)	15 non-medicated PwPD (14 men), 62.5 (44-73) 15 medicated PwPD (11 men) ,63.9 (44-79) 15 controls (10 men), 63.9 (42-77) $M_{PD\ duration}$=1.9 years (1-4)	**Problem solving**: Poisoned Food Problems* (set-shifting component), Hukok Logical Thinking Matrices Test, Mental Calculation; **Concept formation and comprehension**: Wechsler Adult Intelligence Scale - Revised Similarities, the Concept Comprehension Test, Proverb Interpretation
Downes, Sharp, Costall, Sagar, and Howe (1993)	20 PwPD (11 men), 60.05 (10.23) 14 controls (7 men), 60.0 (10.53) Median $_{PD\ duration}$= 30 months (15-156)	**Set shifting and attention**: VF: 2x single semantic/letter, 2x alternating semantic, 2x alternating letter, 2x alternating semantic/letter* (cued and uncued conditions for alternating conditions)
Kehagia et al. (2009)	13 PwPD (H&Y stage I) (10 men), 62.2 (9.1) #11 H&Y stage II (7 men), 66.6 (8.5) 16 control (10 men), 63.6 (8.3)	**Background neuropsychological profile**: VF phonemic, Spatial and Pattern (H&Y stage II group*) Recognition Memory **Switching**: task set switching procedure (H&Y stage II group*)
Euteneuer et al.	21 PwPD (7 men), 67.60 (7.31)	**EF and working memory**: Modified Cart Sorting Test, VF * (FAS and category (animal)), working

(Table 3.2 continues)

(Table 3.2 continued)

(2009)	23 controls (12 men), 64.4 (8.56) $M_{PD\ duration}$=85.7 months (72.70)	memory (DS reverse, DEMTect subtest (2* of 5 variables)); **Reasoning**: subtest of Leistungsprufsystem (German intelligence scale); **Decision-making under risk**: Game of Dice Task* (Rules of gains and losses are explicit) **Decision making under ambiguity**: Iowa Gambling Test; **ToM**: Reading the mind in the Eyes **Set-shifting**: task-set switching procedure **Background assessment**: The one-touch ToL Planning*, VF, Intra/Extra-Dimensional Set-Shifting task* (CANTAB), pattern* and spatial recognition memory (CANTAB).
Cools et al. (2001)	43 PwPD (31 men), 62.1 (1.2) 27 controls (18 men), 59.4 (1.8) $M_{PD\ duration}$= 6.9 years (7.2)	**Working memory**: Verbal span*, arithmetic span* **Strategic memory:** self-ordering pointing*, temporal ordering*, word recall*
Gabrieli, Singh, Stebbins, and Goetz (1996)	10 PwPD (6 men), 60.1 (7.5) 10 controls (2 men), 55.5 (9.7) $M_{PD\ duration}$= 2.9 years (1.6)	
Kliegel et al. (2005)	16 PwPD (11 men), 61.2 (6.9) 16 controls (11 men), 62.6 (9.1) $M_{PD\ duration}$=4.81 (3.00)	**Prospective memory** (formation, retention, initiation and execution of intention): experimental paradigm (planning phase*); **Cognitive resources:** divided attention (test battery of attention), short-term memory span (DS forward), working memory* (operation span measure), inhibition (Stroop task*)
Kobayakawa et al. (2008)	34 PwPD (12 men), 69.9 (8.9) 22 controls (13 men), 67.6 (6.9) $M_{PD\ duration}$=6.4 (3.4)	Decision making: Iowa Gambling Task* ; EF: WCTS; Short-term memory and attentional ability: DS; Emotional arousal: Skin Conductance Responses*
Mimura, Oeda, and Kawamura (2006)	13 PwPD (5 men), 68.9 (7)	**Set-shifting:** WCTS (2* of 3 variables); **Planning:** Maze-tracing of WISC-R*, Inhibition: Stroop test*, VF phonemic* and semantic; **Decision making**: Iowa Gambling Test *; **Mind-reading**: Reading the mind in the eyes test*

(Table 3.2 continues)

(Table 3.2 continued)

Witt et al. (2006)	20 PwPD (14 men), 59.25 (8.58) 20 older controls (12 men), 59.00 (5.70) 20 young controls (12 men), 25.90 (2.57) $M_{PD\ duration}$=3.25 years (4.40)	**EF:** Stroop test* (reading time and reading error only), VF* (semantic, phonemic), WCTS* **Switching abilities** in the predictable (cued) and unpredictable conditions*: task-switching paradigm
R. Tomer et al. (2002)	28 PwPD (18 men), 66.4 (9.5) 19 controls (10 men), 67.1 (9.1)	**Reactive flexibility** (set-shifting): WCST (3* of 4 variables) **Spontaneous flexibility** (ideas generation): Alternate uses*
S. Hsieh, Lee, and Tai (1995)	12 PwPD (8 men), 64.8 (7.1) 12 controls (5 men), 61.1 (8.6)	**Set-shifting**: Odd Man Out *
Studies focused on overall cognition with executive or frontal functions clearly distinguished.		
Muslimovic et al. (2005)	115 PwPD (61 men), 66.2 (10.1) 70 controls (37 men), 63.7 (7.30) $M_{PD\ duration}$: 18.8 (10.7) months	**EF*:** Modified WCST (number of categories achieved, errors, perseverative errors); VF (animals and supermarket items), WAIS-III Similarities; ToL-Drexel test (problems solved in minimum number of moves) **Attention:** DS forward and backward*; TMT-B*, Stroop test (interference condition)
Studies investigating executive/frontal functioning, but with two or more of the following weaknesses: 1) background theories of executive/frontal domains were not discussed; 2) subcomponents of EF/frontal functions were not distinguished; 3) It was not clear which tests measurde which subcomponents.		
Saltzman et al. (2000)	11 PwPD (6 men), 70.98 (13.43) 8 older controls (3 men), 71.61 (9.42) 9 young controls (3 men), 20.87 (2.53)	**EF:** California Card Sorting Task* (correct sorts), VF* (phonemic), Five-Point Fluency task* (figural fluency); Theory of mind tasks (composite*)
Costa et al. (2008)	23 PwPD (12 men), 63.5 (10.0) 25 controls (12 men), 65.0 (7.7) $M_{PD\ duration}$=7.69 (8.5) years	**EF:** Modified card sorting test, VF phonological; Short-term and working memory: DS forward and backward, Corsi test forward and backward; Prospective memory: experimental task *Almost 50% of PwPD were impaired in digit span tasks and almost 40% showed impairment in card sorting task. No formal group comparison for particular tests.

(Table 3.2 continues)

(Table 3.2 continued)

Edelstyn et al. (2007)	17 PwPD (11 men), 65.4 (8.9) 17 controls (9 men), 64.5 (7.4) $M_{PD\ duration}$ = 7.7 years (8.6)	**EF** (fluid intelligence): matrix reasoning*, the Hayling* and Brixton* Tests
Pagonabarraga et al. (2007)	35 PwPD (22 men), 67.2 (8.0) (19 stable and 16 fluctuating) 31 controls (16 men), 70.2 (10) $M_{PD\ duration}$= 8.4 years (5)	**Attention and executive prefrontal function:** digit span (forward, backward, WAIS-III), Stroop; **Limbic function**: Iowa Gambling Test*; **Global cognition**: MMSE, Mattis Dementia Rating Scale, VF phonemic, semantic. No group comparison for particular tests.
Cooper, Sagar, Jordan, Harvey, and Sullivan (1991)	60 PwPD (31 men) 59.8 (37.3-77.6) 37 controls (20 men), 59.6 (40.2-76.1) $M_{PD\ duration}$= 15.75 months (3-48)	**Frontal tasks:** WCST (1*/9), Picture Arrangement (WAIS); **Cognitive sequencing and working memory**: digit ordering*; **Memory**: DS forward and backward*, Rey-Osterreith and Taylor figures, Brown-Peterson paradigm; **Language**: VF* semantic, alternating
Woods and Tröster (2003)	18 PwPD without dementia (12 men), 69.39 (5.80) 18 PwPD with dementia (12 men), 69.67 (6.78) 18 controls (12 men), 68.76 (6.44) $M_{PD\ duration}$ = 5.50 (3.35)	**EF**: WCST (number of categories) Mattis Dementia Rating Scale (Conceptualization subtest) **Language**: COWAT, Boston Naming test *No comparison between non-demented PwPD and controls.

DS – digit span; H&Y – Hoehn and Yahr; WCST – Wisconsin Card Sorting Test; VF – verbal fluency; TMT AB – Trail Making Test A, B; ToL – Tower of London Test; UKPDSBB – UK PD Society Brain Bank

PD group included in the meta-analyses.

In the 33 included studies over 30 abilities were identified and measured as EF components or abilities related to EF, and these abilities were measured by over 60 tests and procedures. The most commonly investigated abilities were: executive functions as a whole (16 studies), set shifting (12 studies), working memory (11 studies), attention (8 studies), inhibition (6 studies), decision making (5 studies), and planning (4 studies). In many cases, however, there was no indication of which abilities were considered to represent EF and some abilities thought to be executive (Cools et al., 2001; Kehagia et al., 2009) were measured and interpreted along with others that did not come under that definition (e.g. both concept formation and the non-EF function of comprehension were measured by WAIS-R Similarities, the Concept Comprehension Test and Proverb Interpretation (Cronin-Golomb et al., 1994).

A broad selection of tests was used to measure EF-related functions. The majority of the studies used verbal fluency tasks (22 studies). Other frequently-used types of task included digit span (as well as spatial, verbal and arithmetic spans, 17 studies), card sorting tests (mostly the Wisconsin Card Sorting Test, used in 16 studies), Stroop tests (8 studies), tower tests (3 studies), and the Trail Making Test (5 studies). Apart from these, over 50 measures and experimental paradigms were each used only once. Some of these measures were variations on well-known 'executive tests' (e.g. different versions of a tower task), while others concentrated on a specific aspect of EF (e.g. experimental paradigms).

It is noteworthy that the interpretation of measures was inconsistent. The same tests were described as measuring different functions in different studies. For example, verbal fluency was variously described as measuring EF, as measuring a sub-component of EF (e.g. set-shifting, planning), as measuring a discrete function of verbal fluency, as

measuring language ability, or as measuring global cognition (Downes et al., 1993; Dujardin et al., 2001; Farina et al., 2000).

3.4.2 Meta-analysis of studies

It was not possible to undertake a meta-analysis of all the identified studies, as nearly 60 tests assessing 30 abilities were reported and the majority of tests were used only once. To synthesize the results, five commonly used tests were identified. See Table 3.3 for a summary of these tests and the associated abilities that are assessed. Where different variants or indices were used, these were treated individually. Meta-analysis was therefore performed for each of 11 separate measures.

Table 3.3. Demographic and clinical characteristics of PwPD in the study samples.

Measure	k	N	Age	Disease duration (months)	Heterogeneity		
					Q	p(Q)	I^2
Phonemic fluency (Bouquet et al., 2003; Colman et al., 2009; Cools et al., 2001; Downes et al., 1993; Dujardin et al., 2001; Euteneuer et al., 2009; Farina et al., 2000; Kehagia et al., 2009; Mimura et al., 2006; Muslimovic et al., 2005; Saltzman et al., 2000; Uekermann et al., 2004; Witt et al., 2006; Zgaljardic et al., 2006)	14	388	63.99	60.90	33.82	0.00	61.56
Semantic fluency (Bouquet et al., 2003; Colman et al., 2009; Cooper et al., 1991; Downes et al., 1993; Dujardin et al., 2001; Euteneuer et al., 2009; Mimura et al., 2006; Muslimovic et al., 2005; Price, 2010; Price & Shin, 2009; Uekermann et al., 2004; Witt et al., 2006; Zgaljardic et al., 2006)	13	393	64.17	66.11	48.16	0.00	75.08
Alternating fluency(Bouquet et al., 2003; Cooper et al., 1991; Downes et al., 1993; Dujardin et al., 2001; Uekermann et al., 2004; Zgaljardic et al., 2006)	6	164	63.88	59.59	45.19	0.00	88.94
Digit span backward(Colman et al., 2009; Cooper et al., 1991; Dujardin et al., 2001; Euteneuer et al., 2009; Muslimovic et al., 2005; Uekermann et al., 2004; Zgaljardic et al., 2006)	7	288	63.44	49.59	7.29	0.29	17.71
WCST categories achieved(Muslimovic et al., 2005) (Cooper et al., 1991; Mimura et al., 2006; Price & Shin, 2009; Witt et al., 2006)	5	223	63.96	24.52	6.80	0.15	41.22
WCST total errors(Cooper et al., 1991; Dujardin et al., 2001; Euteneuer et al., 2009; Muslimovic et al., 2005; Witt et al., 2006)	5	228	63.89	46.65	5.70	0.22	29.83
WCST perseverative errors(Cooper et al., 1991; Dujardin et al., 2001; Farina et al., 2000; Mimura et al., 2006; Muslimovic et al., 2005; Price, 2010; Price & Shin, 2009; Witt et al., 2006)	8	270	64.14	58.97	16.96	0.02	58.72
WCST cards to 1st category(Cooper et al., 1991; Farina et al., 2000)	2	80	63.74	21.88	0.03	0.86	0.00
Stroop interference time(Muslimovic et al., 2005; Price, 2010; Witt et al., 2006; Zgaljardic et al., 2006)	4	182	65.01	45.15	1.85	0.60	0.00
Stroop interference minus baseline(Kliegel et al., 2005; Mimura et al., 2006)	2	34	65.02	57.72	0.03	0.86	0.00
TMT B(Bouquet et al., 2003; Muslimovic et al., 2005)	2	135	63.54	70.90	0.30	0.58	0.00

k – number of studies; *N* – number of PwPD; *Q* – within domain heterogeneity; *p*(Q) – *p* value for heterogeneity; I^2 – percentage of heterogeneity due to study differences

Figure 3.2 presents numerical values and visual representation of the effect sizes and confidence intervals for each meta-analysis. The analyses showed that PwPD scored significantly lower than controls on all five tests (including all 11 separate indices), with differences reflecting medium to large effect sizes (Howell, 2007).

Measures	Hedges' g	Variance	CI	P*
Phonemic fluency	-0.55	0.02	-0.80 – -0.30	0.00
Semantic fluency	-0.75	0.03	-1.07 – -0.43	0.00
Alternating fluency	-0.87	0.15	-1.63 –-0.12	0.02
Digit span backward	-0.46	0.01	-0.67 – -0.26	0.00
WCST categories	-0.68	0.02	-0.97 – -0.39	0.00
WCST total errors	-0.57	0.02	-0.84 – -0.31	0.00
WCST persever. error	-0.69	0.03	-1.01 – -0.37	0.00
WCST cards to 1st category	-0.43	0.03	-0.77 – -0.09	0.01
Stroop interference	-0.54	0.01	-0.77 – -0.32	0.00
Stroop baseline - interference	-0.94	0.05	-1.39 – -0.49	0.00
TMT B	-0.67	0.02	-0.95 – -0.40	0.00

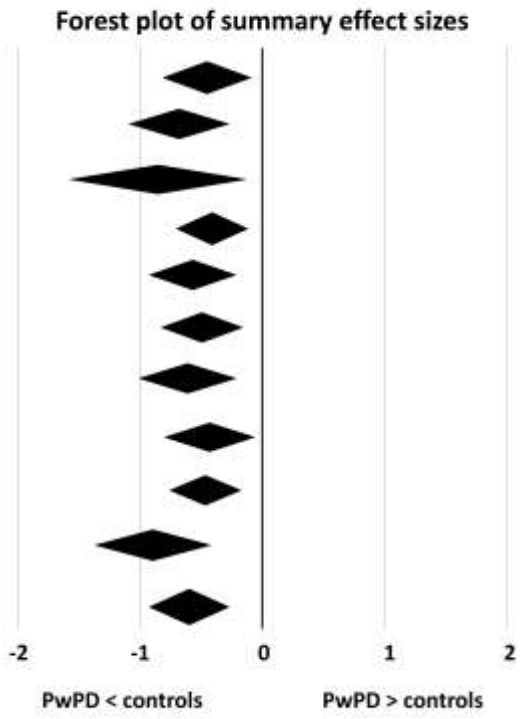

Figure 3.2. Numerical values and visual representation of the effect sizes and confidence intervals for each meta-analysis.

Hedges' g – corrected mean weighted effect size; CI – confidence interval; WCST – Wisconsin Card Sorting Test; TMT – Trail Making Test

* Test of null hypothesis (2-Tailed).

Descriptive statistics for PwPD and control groups (sample size, mean and standard deviations) were extracted from 18 studies. In four cases the effect sizes were calculated from t values as other data were not reported. Results from three studies were excluded as

there was no suitable group comparison reported despite the inclusion of a control group in the study. All variables included in the analysis were continuous data.

Participants were all in the early stages of the disease (I-III Hoehn and Yahr), without dementia and also without depression (unless this was controlled for in the analysis and found to have no influence on the results).

As presented in Table 3.3, the mean age of PwPD groups ranged from 63 to 66 years with an average PD duration of 5 years or less. Sample sizes for the meta-analyses were based on between 2 and 14 studies, with 34 to 388 PwPD in each analysis. For the three verbal fluency tasks, and WCST perseverative errors, variability was high, which means that effect sizes were substantially different between studies and the true effect size may differ from the one calculated. For alternating fluency in particular, the I^2 index indicates that a large proportion of the variance is not explained by random within-study error (see Table 3.3).

Table 3.4. Abilities tested by the measures included in the meta-analysis.

Measures and their indices		**Abilities tested**
Verbal fluency (3 variants: phonemic, semantic or alternating); 17 studies	Words named in 60 seconds	Initiation, simultaneous processing, rapid retrieval of lexical items, recalling of words, search strategy, attention, cognitive flexibility, organizing thinking. An alternating condition (switching between categories) additionally measures an ability to switch between cognitive sets.
Digit span backward; seven studies	Number of digits correctly repeated	Working memory, selective attention.
WCST; eight studies	*Categories achieved* – number of categories correctly identified, as indicated by 10 consecutive correct responses *Total errors* – total number of incorrect responses *Perseverative errors* – number of incorrect perseverative responses *Cards to 1st category* – number of cards presented before achieving 1st category	Abstraction ability, shifting, strategic planning, organized searching, using feedback, goal oriented behavior, modulating impulsive responses. Total number of errors and categories achieved refer to overall performance, and cards to achieve first category estimates concept formation.
Stroop Test; six studies	*Interference time* – time taken in the interference condition (seconds) *Interference minus baseline* – baseline time subtracted from time taken in the interference condition (seconds)	Concentration effectiveness, selective processing, selective attention, resistance to distractions, inhibition of unwanted responses. The baseline minus interference index gives a correction for the baseline speed.
TMT B; two studies	Time taken to complete Part B – Switching (seconds)	Complex visual scanning, conceptual tracking, cognitive flexibility, divided attention, speed.

Based on: Delis et al. (2001) Lezak (2004), and Strauss et al. (2006). See also Royall et al. (2002).

WCST – Wisconsin Card Sorting Test; TMT – Trail Making Test

3.5 Discussion

3.5.1 Meta-analysis of studies

The results provide consistent evidence for cognitive difficulties in PwPD in comparison to controls across all the EF tests included in the meta-analysis. These tests assess a broad range of executive functions, including abnormalities in cognitive flexibility (verbal fluency), and more specifically in set-switching (TMT B, WCST) and inhibition (Stroop), as well as in selective attention/working memory (digit span backward) and concept formation (WCST). The tests included in the meta-analysis cover a number of EF abilities. However, there is no rationale for assuming that they constitute a comprehensive assessment of EF. Therefore we can conclude only that performance on these particular tasks was impaired, and not that there is impairment across the whole spectrum of executive abilities.

3.5.2 Methodological challenges in researching EF in PD

The clinical heterogeneity of PwPD groups may be one reason for contradictory reports in the literature, as complex pathology in PD may influence cognition in various ways (Colman et al., 2009; Kobayakawa et al., 2008). As the reviewed studies had PwPD groups that were similar in terms of general cognition, depression level and disease stage, this may account for the consistent findings from the meta-analyses. Aiming for homogenous groups of PwPD may facilitate more consistent results and better understanding of cognitive deficits.

It was noteworthy that only a proportion of the available research evidence could be synthesized in the meta-analysis. The limited potential for summarizing findings across studies seems to be related to the methodological challenges inherent in measuring EF (Miyake et al., 2000; Salthouse, 2005). The systematic review demonstrated that only a few studies based their methods on a formal theory of EF that could serve as a framework for

distinguishing EF subcomponents and selecting appropriate measures. The most commonly discussed theory was working memory (Baddeley, 1986), which was referred to in four studies (Altgassen et al., 2007; Bublak et al., 2002; Gilbert et al., 2005). In most studies, either a definition of EF was presented or one of the frequently-used shorthand terms was adopted, such as 'frontal-like abilities', or dysfunction similar to that "found in patients with frontal lobe damage" (Farina et al., 1994, p. 34). The definitions were usually followed by a list of functions that constitute EF. However, these lists tended to be left open by ubiquitous phrases: 'such as', 'like' or 'for example' (Altgassen et al., 2007; Euteneuer et al., 2009). As a consequence, it is not possible to be certain precisely what was meant by executive or 'frontal' functions, or what subcomponents of EF were investigated.

Additionally, the interpretation of EF measures was inconsistent. The same tests were used to measure various functions depending on the study. Some studies explicitly specified which test is supposed to measure which particular ability (Colman et al., 2009; Farina et al., 2000; Uekermann et al., 2004; Zgaljardic et al., 2006), but others did not. In many cases there were comprehensive lists of abilities tested (e.g. working memory, set-shifting, verbal fluency, inhibition, short-term memory) as well as an outline of measures supposed to tap these abilities, but it often remained unclear which of these were regarded as 'executive'.

A large proportion of studies was excluded in the early stages of the search, as study reports lacked basic information such as details of disease severity and presence of dementia. At the same time, we attempted to include a broad spectrum of studies referring to EF, which affected the number of studies available for meta-analysis of particular tests. However, the range of EF measures reflects the complexity of executive control and

highlights a key challenge of research on EF in PD. Given the variability in the way that different measures are interpreted, and the frequent absence of a clearly-articulated theoretical framework, it is difficult to synthesize the results of these studies. However, it is important to acknowledge that many of these studies do indicate some abnormalities in PwPD performance and may be useful in understanding cognitive functioning of PwPD.

In the included studies there was little consideration of how impaired performance on neuropsychological tests impacts on the quality of life of PwPD and their carers (Siegert et al., 2008). There is an urgent need to understand the everyday impact of cognitive impairment to provide appropriate support for PwPD and their families (Clare, 2008). The meta-analysis showed consistent differences in all EF measures. However, the differences were small and their impact on everyday life may or may not be significant. It might be helpful for future research to focus more on the subjective experience of cognitive decline and the impact of cognitive impairment on everyday functioning.

3.5.3 Conclusions

A meta-analytic approach has the potential to synthesize and clarify evidence regarding executive deficits in PD. This review provides consistent evidence for the presence of executive deficits in PD. Increased precision in reporting PD characteristics of PwPD groups and defining executive abilities in future studies will facilitate better understanding of observed cognitive changes. An important question that has yet to be addressed is how observed deficits translate into everyday functioning and affects PwPD well-being, and whether there is a need for specific support for those people with PD who demonstrate EF impairment.

Chapter 4

Pattern of executive impairment in early stage Parkinson's disease

Kudlicka, A., Clare, L., & Hindle, J. V. (in press). Pattern of executive impairment in mild to moderate Parkinson's disease. *Dementia and Geriatric Cognitive Disorders*

4.1 Abstract

Background: The exact pattern of impairment in executive functions (EF) among people with Parkinson's disease (PD) is still debated. Using a data-driven approach we investigated which areas of EF are particularly problematic in mild to moderate PD.

Methods: Thirty-four people with mild to moderate PD, who scored in the normal range on general cognition screening tests, but displayed frontal-type deficits indicated by Frontal Assessment Battery (FAB) screening, completed the nine tests that comprise the Delis-Kaplan Executive Function System. Patterns of performance were explored using cluster analysis and Principal Component Analysis (PCA), and the frequency of impairments was established using normative data.

Results: Both cluster analysis and PCA identified two distinct groups of EF tests. The first group included tests requiring time-efficient attentional control (e.g. the Trail Making test). The second group included tests measuring abstract reasoning and concept formation abilities (e.g. the 20 Questions test). Impairment was more frequent on the attentional control tests than on the abstract thinking tests.

Conclusions: PD pathology in the mild to moderate PD appears to affect the attentional control aspect of EF to a greater extent than abstract reasoning. Understanding the nature of executive deficits in PD is important for the development of targeted pharmacological and cognitive interventions for cognitive disturbances.

4.2 Introduction

Parkinson's disease (PD) is a heterogeneous neurodegenerative movement disorder associated with a number of non-motor difficulties, including neuropsychiatric, autonomic and gastrointestinal symptoms, sleep disturbance, and fatigue. There are three commonly identified subtypes of PD, based on the main motor symptoms: tremor dominant, postural instability gait disorder (PIGD) and akinetic-rigid (Jankovic et al., 1990; Marras & Lang, 2013). Cognitive decline is frequently observed in people diagnosed with PD (PwPD) even at the onset of the disease, with over 80% having some cognitive impairment or dementia within 15 years of onset (Hely et al., 2005). The impairment ranges from single domain difficulties (e.g. in memory, language, attention, or executive functions), through global decline, to dementia (Janvin, Aarsland, Larsen, & Hugdahl, 2003; Mindham & Hughes, 2000; Owen, 2004; Zgaljardic et al., 2003), and is particularly evident in the executive function (EF) domain (McKinlay et al., 2009; Muslimovic et al., 2005). EF is an umbrella term for complex attentional processes and cognitive abilities regulating independent goal-oriented behaviour (Burgess & Alderman, 2004; Lezak, 2004; Strauss et al., 2006). Reports indicate that many aspects of EF are impaired in PD, including planning, concept formation, decision making, cognitive flexibility, set-switching, inhibition and selective attention (Altgassen et al., 2007; Bouquet et al., 2003; Cools et al., 2001; Dujardin et al., 2001; Kobayakawa et al., 2008; Muslimovic et al., 2005; Zgaljardic et al., 2006). However, the research evidence is not consistent with regard to the reported level of impairment. There have been varying reports of performance on verbal fluency, a task commonly employed to estimate abilities related to frontal lobe function, with some studies reporting impaired performance (Bouquet et al., 2003; Dujardin et al., 2001; Uekermann et al., 2004; Zgaljardic et al., 2006), and other studies reporting no difference between PwPD and controls (Colman et al., 2009; Cools et

al., 2001; Farina et al., 2000). The verbal fluency task has been variously reported to measure EF, set-shifting, planning, language ability, or global cognition (Auriacombe et al., 1993; Downes et al., 1993; Dujardin et al., 2001; Farina et al., 2000). As similar inconsistencies exist in the evidence relating to other executive abilities, it is difficult to determine how prevalent particular EF deficits are, and whether there is any consistent pattern in the way in which PD pathology affects EF.

The inconsistency in reports of executive functioning in PwPD may reflect the complex pathology of PD, which includes not only profound dopaminergic deficiency in the striatum (Dauer & Przedborski, 2003), but also widespread Lewy body pathology and cell loss in many brain regions, and abnormalities in noradrenergic, cholinergic, and serotonergic systems. EF deficits observed in PD may result from the multifaceted influences of these abnormalities on frontostriatal circuitry. Alexander, DeLong and Strick (1986) proposed that specific aspects of motor, cognitive and behavioural control are mediated by five frontostriatal circuits that interconnect specific areas of the prefrontal cortex (PFC) with separate, well-defined areas of the striatum (Dubois & Pillon, 1997). The disruption of PFC circuits may result in specific cognitive, emotional and motivational deficits. In particular, the dorsolateral prefrontal circuit (DLPFC) seems to be essential for some aspects of EF (Alexander et al., 1986; Dauer & Przedborski, 2003; Royall et al., 2002; Tekin & Cummings, 2002; Zgaljardic et al., 2004). The impact that PD-related neurochemical imbalance has on cognition might change throughout the course of the disease as the neurodegeneration of dopaminergic regions progresses, and might be complicated by the effects of dopaminergic medication (Cools et al., 2010; Leh et al., 2010). In addition it seems that the EF deficits

develop as a function of PD severity, while more posterior functions including memory have a different trajectory (Williams-Gray et al., 2009).

The inconsistency in the research evidence may also reflect the complexity of the EF construct, as there is ongoing debate regarding both definitions of EF and the neuronal basis of EF, with a plethora of abilities described as 'executive', and no gold standard measure of EF available (Kudlicka, Clare, & Hindle, 2011; see previous chapter). The term 'executive functions' tends to be used interchangeably to describe either one of a range of specific cognitive abilities involved in behavioural control, or the whole group of such abilities and processes (Miyake et al., 2000). At the behavioural level EF may be defined in terms of successfully coping with novelty and managing personal goals in a socially appropriate manner, and this is linked to non-cognitive capacities like personality, motivation and emotions (Ardila, 2008; Stuss & Alexander, 2000). More frequently, EF is considered in the context of attentional control, for instance in terms of attentional processes controlling 'lower level' cognitive functions (Alvarez & Emory, 2006; Aron, 2008; Krpan et al., 2007), or as a concept closely related to the central executive component of the multicomponent model of working memory and the supervisory attentional system (SAS) (Baddeley & Hitch, 1974; Norman & Shallice, 1986). It has been suggested that to improve the consistency of reports of EF deficits in PD, there is a need for careful consideration of EF test selection, as well as meticulous precision in reporting and interpreting tests results (Kudlicka et al., 2011; see previous chapter).

In summary, there is good evidence for EF deficits in PwPD, but some inconsistency remains, possibly related to multifaceted PD pathology and the complexity of the EF concept. More in-depth understanding of executive functioning in PD comes from studies

that have examined how the results of various EF tests relate to each other. For example, in one study (Zgaljardic et al., 2006), researchers analysed the performance of non-demented PwPD on 20 measures of frontal-type abilities classified as relating to the function of one of the three non-motor frontostriatal circuits (Alexander et al., 1986), and reported the DLPFC to be affected more than other circuits. However, the classification of measures was based on a literature review, rather than being data-driven, and included standard tests of EF as well as measures of mood and self-reported behavioural problems, which might have implications for interpretation of the findings. In another study (Weintraub et al., 2005), factor analysis identified two factors relating to EF in non-demented PwPD. The Planning factor included three indices of the Tower of London test, with lower scores associated with higher apathy. The Inhibitory Control factor included three measures (TM errors, Stroop errors and rule violations in the Tower of London test), with lower scores associated with lower education and greater motor impairment. There was little consideration of how PwPD differed across the two dimensions, and there was no measure of behavioural control or abstract thinking included. Cluster analysis has previously been employed to explore the heterogeneity of PD symptoms and patterns of cognitive functioning in PD, but has not been applied specifically to the investigation of EF in PD (Lewis, Foltynie, et al., 2005; McKinlay et al., 2009; van Rooden et al., 2010).

In the present study we aimed to address some of the limitations in the existing evidence by examining EF with a broad range of standard EF measures, and focusing exclusively on people with mild to moderate PD, without dementia, but with frontal-type deficits indicated by screening using the Frontal Assessment Battery (Dubois et al., 2000). To establish the clinical significance of EF deficits we compared performance on EF tests to

normative data. We used Cluster Analysis and Principal Component Analysis to investigate which areas of executive functioning are particularly problematic in PD, and whether there is any consistent pattern of performance on EF tests. A good understanding of the nature of executive deficits in PD is important for tailoring treatment plans to the specific needs of PwPD, as different aetiology of cognitive impairment in PD may require different medication (Wurtman, 2012). It might also provide a basis for developing cognitive interventions that would support PwPD and their families in coping with the deficits. This is particularly important in the context of growing evidence that particular EF deficits may help to distinguish those PwPD who are at risk of developing dementia (Janvin et al., 2006; Williams-Gray et al., 2009; Woods & Tröster, 2003).

4.3 Method

4.3.1 Design

The study employed a cross-sectional design to examine the pattern of EF in PwPD shown during screening to have frontal-type deficits. As reported in Chapter 1, the assessment presented here was part of a wider study of PwPD and included some measures not reported here. Ethical approval was obtained from the relevant University and National Health Service (NHS) ethics committees. All participants provided written informed consent.

4.3.2 Participants

As described in Chapter 1, a sample of PwPD in the mild to moderate stages of PD (Hoehn and Yahr stage I-III; Hoehn & Yahr, 1967), diagnosed according to the UKPDS Brain Bank criteria (Daniel & Lees, 1993) was identified by the consultant physician (JVH) from Movement Disorders clinics in North-West Wales. Over 18 months of recruitment, 75 PwPD agreed to take part in the study. Sixty-five of them met the inclusion criteria of normal

general cognition, indicated by an Addenbrooke's Cognitive Examination – Revised (ACE-R) score ≥ 82 (Mioshi et al., 2006) and a MMSE score ≥ 24 (Folstein et al., 1975), and no clinically significant depression, indicated by a Hospital Anxiety and Depression Scale (HADS) score ≤ 11 (Snaith & Zigmond, 1994). Forty (61.1%) of the 65 participants screened had a Frontal Assessment Battery (FAB) score ≤ 15, indicating possible frontal type cognitive deficits (Dubois et al., 2000), and were thus eligible for the in-depth EF assessment. Six of these participants did not complete the EF assessment, three due to elective withdrawal and three due to fatigue, leaving a sample of 34 who completed the assessment. All participants had adequate eyesight and hearing, and were fluent in English.

The following measures from the wide database were used in this analysis.

4.3.3 Screening measures

The Addenbrooke's Cognitive Examination - Revised (ACE-R; Mioshi et al., 2006) validated for use in PD (Reyes et al., 2009) was employed to screen general cognition in five domains: attention and orientation, memory, verbal fluency, language and visuospatial abilities. The maximum total score of 100 indicates accurate performance. The study adopted a conservative cut-off of ≥ 82 suggested for screening purposes, with 84% sensitivity and 100% specificity for dementia diagnosis (Mioshi et al., 2006).The ACE-R also provides an MMSE score (Folstein et al., 1975).

The Frontal Assessment Battery (FAB; Dubois et al., 2000) was used for screening purposes to identify PwPD with frontal-type deficits. The scale consists of six components measuring different aspects of frontal-type abilities. The maximum score of 18 indicates accurate performance. The study adopted a cut-off of 15 for probable frontal-type deficits,

which is 2 SD below the mean reported for healthy controls (M = 17.3, SD = 0.8) (Dubois et al., 2000).

Mood was assessed with the Hospital Anxiety and Depression Scale (HADS; Snaith & Zigmond, 1994) (Appendix F), a self-rating questionnaire consisting of two 7-item subscales, HADS-Depression and HADS-Anxiety. Scores for each subscale range from 0 to 21, with higher scores indicating higher levels of self-rated anxiety/depression. The study adopted the cut-off of 11 suggested for depression screening purposes (Crawford et al., 2001).

In addition, an estimate of pre-morbid IQ was obtained for each participant. The National Adult Reading Test (NART; Nelson & Willison, 1991) estimates lifelong intellectual ability by assessing the ability to correctly pronounce 50 phonetically irregular words. The number of words pronounced incorrectly is converted into an estimated IQ score. More errors produce a lower estimated IQ score.

4.3.4 Assessment of EF

Executive functions were assessed with the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001), which is a set of nine tests assessing important aspects of EF with some well-known tests of EF (Trail Making, Verbal Fluency, Tower) as well as more novel tasks (20 Questions, Proverb). The test administration procedure and clinical interpretation of the indices used in the study are described in Table 4.1. The results of standard EF tests from the D-KEFS were converted to scaled scores derived from a large normative sample. Using scaled scores allows for both evaluation of performance in terms of impairment and direct comparison of the results across the different tests (Homack et al., 2005; Strauss et al., 2006).

Table 4.1. Description of EF tests and indices.

Test	**Index**	**Task description and interpretation of performance index**
Trail Making Test (TM): Switching	*Time to complete*	TM consists of four conditions assessing lower-level cognitive abilities, and a higher-level switching condition, in which participants draw a line connecting numbers and letters in ascending order, while alternating between numbers and letters. A low scaled contrast score (composite score of two baseline conditions *vs.* switching condition) indicates that poor lower-level cognitive abilities may account for poor performance in the higher-level condition. Shorter time to complete indicates better flexibility in thinking and switching between mental sets.
Verbal Fluency (VF): Switching	*Number of correct words*	Participants produce words from phonemic and semantic categories, according to given rules and within the time limit. In the switching condition they alternate between two semantic categories. A higher score indicates better initiation, systematic retrieval, simultaneous processing, and flexibility in shifting.
Design Fluency (DF)	*Percentage accuracy*	Participants draw different designs according to given rules and within a time limit. They are presented with pages containing a number of boxes with identical arrays of dots (different arrays in each of the 3 conditions) and asked to connect the dots with four straight lines. The ratio between correct *vs*. attempted designs was chosen rather than a score based on the number of designs drawn, as the former is less affected by hand dexterity. Higher percentage accuracy indicates better initiation of problem solving, and better performance in establishing and maintaining cognitive set.
Colour Word Interference (CWI): Switching	*Time to complete*	CWI consists of four parts, with two baseline and two higher-level conditions. In the switching condition participants need to either name the dissonant ink colour (traditional Stroop task) or read the word, according to the given rules. A shorter time indicates better inhibition of unwanted reactions and greater cognitive flexibility.

(Table 4.1 continues)

(Table 4.1 continued)

Sorting: Recognition	*Description score*	Participants are presented with six cards of various colours, shapes and inscriptions, and asked to either sort the cards into two groups of 3 cards that are similar in some respect (Free Sorting) or recognise and describe such sorts when these are presented by the examiner (Recognition). Higher description scores reflect better flexibility in thinking and ability to perceive and express abstract concepts and conceptual relationships.
Test	**Index**	**Task description and interpretation of performance index**
20 Questions	*Initial abstraction score*	Participants ask yes-no questions to identify which object, out of 30 presented, has been chosen by the examiner. The initial abstraction score indicates how many objects are eliminated with the first question. A higher score indicates more efficient categorical clustering and abstract thinking.
Word Context	*Total consecutively correct score*	Participants guess the meaning of made-up words from the context of the consecutively presented sentences. A higher number of consecutively correct answers is indicative of better deductive reasoning, hypothesis testing, and flexibility in thinking.
Tower	*Total achievement score*	Participants need to move discs between 3 pegs in order to build target towers. They need to follow a set of rules and complete the task with as few moves as possible. One point is assigned for a correct tower and up to 3 extra points for minimum-moves solutions. A higher score indicates better spatial planning, rule learning, performance in establishing and maintaining instructional set, and inhibition.
Proverb: *Uncommon*	*Achievement score*	Participants explain the meaning of proverbs. Achievement score in uncommon proverbs was used rather than the total achievement score that includes common proverbs, as with uncommon proverbs participants rely on abstract thinking more than on learnt descriptions, which might be the case in common proverbs. This is therefore a more sensitive measure of verbal abstract thinking, semantic integration, and generalisation. Higher scores assigned for abstraction and accuracy reflect better performance.

Note. Description based on the D-KEFS manual (Delis et al., 2001).

4.3.5 Procedure and data collection

Participants were assessed during their 'on' medication phase, usually in their own homes (four participants preferred to come to the University). After completing a screening session lasting 2 to 3 hours, participants who scored below the cut-off for frontal-type deficits on the FAB and otherwise met inclusion criteria were invited to complete the further in-depth assessment of EF, consisting of two to three visits, each lasting approximately 2 hours.

4.3.6 Planned analysis

The frequency of clinically significant deficits was established using D-KEFS normative data. Correlational analysis (Spearman's *Rho*) was used to explore the extent of any association between EF tests. The pattern of performance on EF tests was examined using cluster analysis, a data-driven approach that is useful in exploring potential relationships within complex data sets, when there is little a priori knowledge of the data structure (Morris et al., 1981; Ward, 1963). In the cluster analysis similar participants or variables are grouped together to form clusters of variables or cases that are most similar to each other. The identified clusters can then be further examined to reveal characteristics that discriminate between the groups (Morris et al., 1981; Ward, 1963). The approach offers various methods of assessing similarity and establishing number of clusters and several of them were explored to ensure that the method presented in the study (Ward hierarchical grouping, based on squared Euclidean distance) provided results that were generally representative across the range of methods. Two cluster analyses were run, the first examining associations between tests (variables) and the second examining associations between participants (cases). In the cluster analysis of variables, scaled scores were used to minimise the impact of age on the observed relationships between EF tests. However, in the cluster analysis of cases, raw scores were used, as age might be an important characteristic that would

differentiate between groups. To verify the results of the cluster analysis, an exploratory principal component analysis (PCA) was conducted on the EF tests. Oblimin rotation was employed as it was expected that various aspects of EF might be correlated (Miyake et al., 2000). Associations between EF tests and other group characteristics were explored with correlational analysis (Spearman's *Rho*). All analyses were performed in IBM SPSS statistics 19.

4.4 Results

Thirty-four PwPD (15 men, 44.1%) with frontal-type deficits indicated by FAB screening completed the assessment. According to the Hoehn and Yahr classification (Hoehn & Yahr, 1967), the majority of PwPD (n=19; 55.9%) were in stage I of the disease, 11 participants were in stage II (32.4%), and 1 person (2.9%) was in stage III. Information was unavailable for 3 participants (8.8%). Symptoms started on the left side in 12 participants, on the right side in 16, and bilaterally in 6. Demographic information and details of disease characteristics and medication use are presented in Table 4.2. Raw scores and scaled scores achieved on EF tests are presented in Table 4.3.

Table 4.2. Demographic information, disease characteristics, and medication use in PwPD (n=34).

	M (SD)	**Range**
Age	72.62 (8.27)	48 – 89
Education (years)	13.04 (3.04)	5 – 19
NART-estimated IQ	114.56 (7.70)	100 – 128
Socio-Economic Status[1]	2.41 (1.02)	1 – 4
MMSE	29.41 (1.10)	25 – 30
ACE-R	94.18 (4.65)	82 – 100
FAB	13.74 (0.96)	12 – 15
HADS-Depression	4.18 (2.04)	1 – 9
HADS-Anxiety	5.29 (3.16)	1 – 12
Hoehn and Yahr stage n = 31	1.42 (0.56)	1 – 3
PD duration (months)[2]	68.21 (52.39)	10 – 204
LED n = 33	596.21 (626.55)	100 – 3125
Medication	n (%)	
Levodopa	21 (61.8)	
Dopamine agonists	20 (58.8)	
Rasagiline	20 (58.8)	
Entecapone	6 (17.6)	
Amantadine	3 (8.8)	
Apomorphine	1 (2.9)	

M – Mean; SD – Standard deviation; NART – National Adult Reading Test; ACE-R – The Addenbrooke's Cognitive Examination - Revised; HADS – Hospital Anxiety and Depression Scale; FAB – Frontal Assessment Battery; LED – Total Daily Levodopa Equivalent Dose, based on Tomlinson et al. (2010); Dopamine agonists – Non ergot-derived dopamine-receptor agonists

[1]1 – Professional; 2 – Managerial/technical; 3 – Skilled, non-manual; 4 – Skilled, manual; 5 – Partly skilled; 6 – Unskilled.

[2]Time since the diagnosis, as reported by PwPD.

Table 4.3. Mean raw and scaled scores on EF tests.

		Raw		Scaled	
Test	**n**	**M (SD)**	**Range**	**M (SD)**	**Range**
TM	33	151.88 (69.45)	50 – 240	7.94 (4.83)	1 – 15
Verbal Fluency	34	11.85 (3.47)	3 – 20	10.00 (4.08)	1 – 19
Design Fluency	34	85.00 (11.88)	42 – 100	9.91 (2.23)	4 – 14
CWI	34	88.03 (29.52)	48 – 180	9.32 (3.22)	1 – 14
Sorting	30	28.43 (12.22)	6 – 53	10.53 (3.58)	3 – 18
20 Questions	33	26.70 (11.44)	4 – 53	10.70 (2.73)	5 – 17
Word Context	33	24.55 (6.28)	9 – 36	10.85 (2.61)	4 – 16
Tower	33	15.39 (4.85)	4 – 24	10.36 (3.30)	2 – 16
Proverb	30	8.73 (2.79)	3 – 12	12.53 (2.40)	8 – 16

Note. See Table 4.1 for details of which index was used for each test. The range of possible scaled scores is 1 – 19.

M – Mean; SD – Standard deviation; TM – Trail Making; CWI – Color Word Interference

Table 4.4 presents a comparison of the two PwPD groups identified on the basis of their performance on the Frontal Assessment Battery (FAB) screening tool. One group consists of PwPD who scored 15 or below on the FAB (FAB-poor, n = 40), and the second group consists of PwPD who scored above 15 on the FAB (FAB-normal, n = 25). Independent samples t-tests indicated that PwPD with poor performance on the FAB were older on average than PwPD with normal FAB scores, and performed significantly worse on the switching condition of the Trail Making test. There was also a trend toward a difference in PD severity; PwPD with lower FAB scores tended to be at more advanced Hoehn and Yahr stages, but this was not significant.

Table 4.4. Comparison of PwPD who scored 15 or below and PwPD who scored above 15 on the FAB.

	PwPD FAB-poor (n=40)[5]		PwPD FAB-normal (n=25)		Independent sample t-test	*p*
	M (SD)	Range	M (SD)	Range		
Age	72.35 (8.34)	48–89	66.52 (8.79)	49–82	t(63) = 2.69	**.009**
Education (years)	12.81 (3.03)	5–19	13.22 (2.94)	8–20	t(63) = -0.53	.596
NART-estimated IQ[1]	113.64 (8.39)	95–128	113.96 (7.64)	92–127	t(62) = -0.15	.878
MMSE	29.38 (1.06)	25–30	29.64 (0.64)	28–30	t(63) = -1.13	.262
ACE-R	93.25 (4.74)	82–100	94.76 (3.72)	88–100	t(63) = -1.35	.181
PD duration (months)[2]	69.68 (56.81)	10–216	60.04 (45.70)	1–192	t(63) = 0.72	.477
Hoehn and Yahr stage[3]	1.49 (0.59)	1–3	1.24 (0.50)	1–3	t(52.70) = 1.73	.090
LED[4]	574.62 (599.85)	0–3125	586.32 (492.64)	0–2145.75	t(62) = -0.08	.935
HADS-Depression	4.53 (2.45)	1–10	4.28 (2.64)	0–9	t(63) = 0.38	.705
HADS-Anxiety	5.50 (3.49)	1–14	5.28 (3.64)	1–16	t(63) = 0.24	.808
TM switching (seconds)	154.31 (68.31)	50–240	109.60 (58.38)	45–240	t(62) = 2.70	**.009**
TM switching (scaled)	7.74 (4.84)	1–15	10.36 (3.81)	2–15	t(59.32) = -2.41	**.019**
CWI inhibition (seconds)	76.60 (24.81)	46–147	66.13 (31.21)	39–180	t(62) = 1.48	.143
CWI inhibition (scaled)	9.58 (3.57)	1–14	11.08 (3.90)	1–15	t(62) = -1.58	.119
CWI inhibition/ switching (seconds)	88.50 (28.44)	48–180	78.13 (31.19)	39–180	t(62) = 1.36	.178
CWI inhibition/ switching (scaled)	9.20 (3.26)	1–14	10.13 (3.79)	1–15	t(62) = -1.03	.305

M – Mean; SD – Standard deviation; NART – National Adult Reading Test; ACE-R – The Addenbrooke's Cognitive Examination - Revised; HADS – Hospital Anxiety and Depression Scale; FAB – Frontal Assessment Battery; LED – Total Daily Levodopa Equivalent Dose; HADS – Hospital Anxiety and Depression; TM – Trail Making; CWI – Color Word Interference Scale

[1]Pre-morbid IQ of PwPD (n=64) was estimated with the National Adult Reading Test (NART; Nelson & Willison, 1991).

[2]Time since the diagnosis, as reported by PwPD.

[3]PwPD FAB poor (n=36), PwPD FAB normal (n=23).

[4]Based on Tomlinson et al. (2010), n=64.

[5]Includes 6 PwD who did not complete in-depth assessment of EF, 3 due to fatigue and 3 due to elective withdrawal

Scaled scores for the EF tests were calculated using normative data published in the D-KEFS manual. Scaled scores ≤ 5 (comparable to ≤ the 5th percentile and ≤ 1.5 SD below the mean) were classified as impaired. Scaled scores of 6 and 7 (comparable to the 9–24 percentile the percentile and 1.3-0.7 SD below the mean) are traditionally interpreted as potentially indicative of clinically significant deficit or as borderline in the context of a comprehensive evaluation (Delis et al., 2001; Strauss et al., 2006), and were here labelled as 'poor'. The percentage of clinically significant deficits on the various EF tests is presented in Figure 4.1. The mean percentage of scaled scores ≤ 5 across all EF tests was 7.4%. Examination of performance on all tests for individual participants shows that 55.8% of PwPD performed within the normal range on all of the tests, 29.4% had impaired performance in one of the nine tests, and 14.7% had impaired performance on 2 to 5 of the tests (overall 44.2%). Impairment was most frequent in TM, with 18.2% of PwPD exhibiting impaired performance (after excluding the 15.2% of PwPD whose impaired performance in the switching condition could be explained by poor performance in the baseline conditions). In contrast, none of the participants scored below the cut-off for poor or impaired performance on the Proverb test.

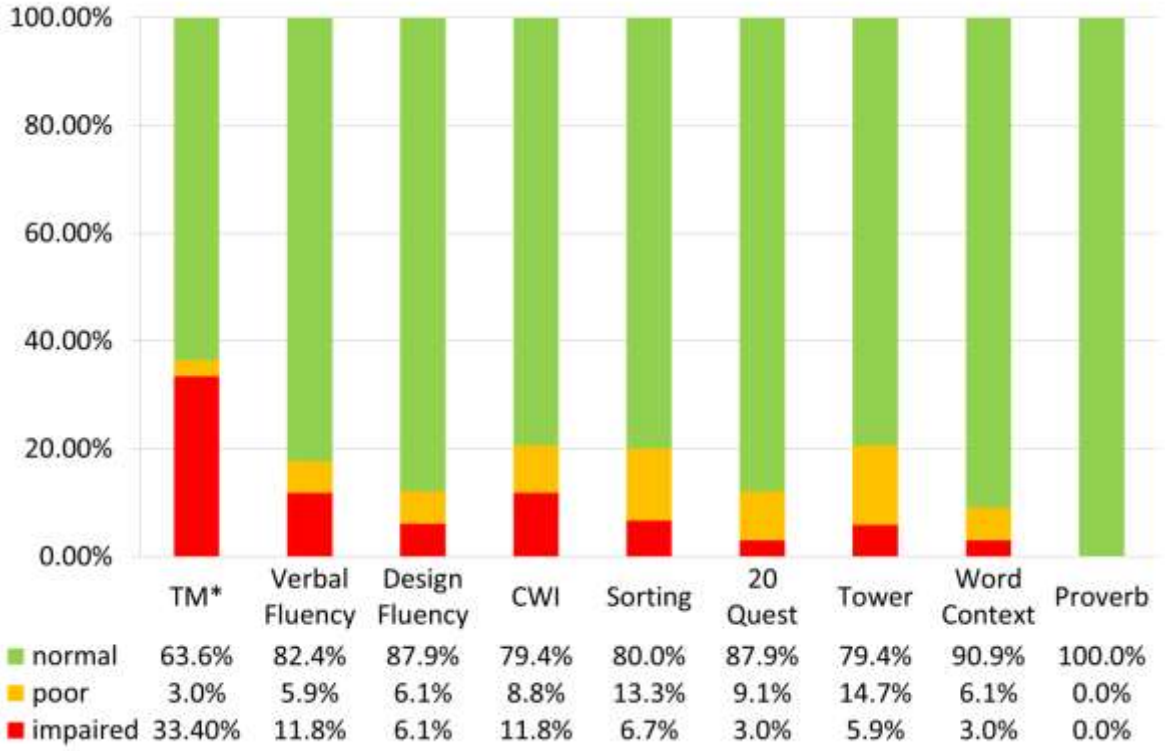

Figure 4.1. Frequency of EF impairment on EF tests in PwPD who scored below the cut-off for frontal type cognitive deficits on the FAB.

Note. See Table 4.1 for information about which index was used for each test. On all EF tests performance was classified as impaired for scaled scores ≤ 5, and as poor for scaled scores of 6 and 7.

TM – Trail Making; CWI – Color Word Interference; 20 Quest – 20 Questions.

* Low scores on TM seem to specifically reflect EF deficits rather than poor dexterity or other non-EF deficits in 18.2% of participants, according to the contrast measure analysis (Delis et al., 2001).

Correlational analysis (Spearman's *Rho*) was used to explore the extent of any association between EF tests. The CWI test was strongly correlated with TM and Verbal Fluency, and the Tower Test was strongly correlated with TM, Verbal Fluency and CWI. There were also moderate correlations between the TM and Verbal Fluency tests, between

the Sorting and 20 Questions tests, and between the Proverb and Verbal Fluency tests, but these were not statistically significant after Holm-Bonferroni correction. See Table 4.5 for details of the correlational analysis.

Table 4.5. Spearman's Rho correlation coefficients for associations between the EF tests.

EF Tests	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1. TM								
2. Verbal Fluency	.459**							
3. Design Fluency	.261	.185						
4. CWI	**.706****	**.654****	.302					
5. Sorting	.172	.316	-.075	.196				
6. 20 Questions	-.133	.033	-.016	-.080	.419*			
7. Word Context	.316	-.108	-.073	.017	-.009	.229		
8. Tower	**.669****	**.608****	.197	**.684****	.310	.007	.086	
9. Proverb	.085	.376*	.252	.203	.245	.105	.212	.107

Note. See Table 4.1 for information which index was used for each test. Bold typeface indicates significance after Holm-Bonferroni correction for multiple comparisons (p = .05/50 = 0.001).

TM – Trail Making; CWI – Color Word Interference

Cluster analysis of variables, based on Ward hierarchical grouping using squared Euclidean distance (Morris et al., 1981; Ward, 1963), identified two groups of tests (see Figure 4.2). Cluster 1 consists of five tests: CWI, Tower, Verbal Fluency, Design Fluency and TM. Cluster 2 consists of the remaining four tests: Sorting, 20 Questions, Word Context and Proverb. Analysis of the test characteristics suggests that Cluster 1 tests primarily focus on attentional control, while Cluster 2 tests seem to require predominantly abstract reasoning abilities. Scaled scores for the tests included in each of the two clusters were averaged to provide two composite scores. A dependent t-test indicated that on average performance

was significantly better on the Cluster 2 tests (M = 11.33, SD = 1.81) than on the Cluster 1 tests (M = 9.86, SD = 2.71), t(26) = -2.53, *p* = .018.

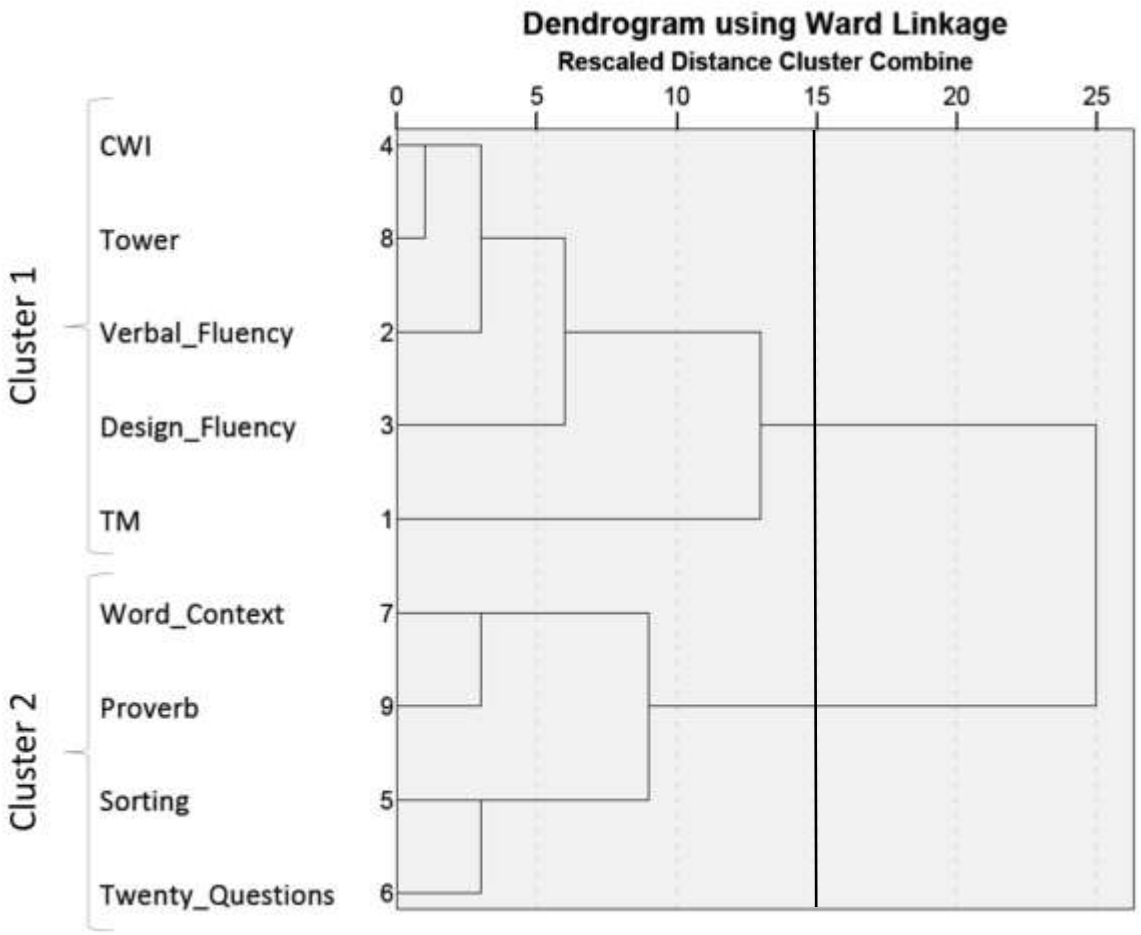

Figure 4.2. Hierarchical cluster analysis examining associations between EF tests (variables). *Note.* See Table 4.1 for information on which index was used for each test.

TM – Trail Making Test; CWI – Color Word Interference

The Kaiser-Meyer-Olkin (KMO) measure of .609 indicated acceptable sampling adequacy for the PCA, and Bartlett's test of sphericity (χ^2 (36) = 89.41, $p < .001$) indicated a sufficient degree of correlation between the tests. A three-component solution was retained, based on the Kaiser's eigenvalues > 1 criterion and the scree plot examination. The three components with eigenvalues > 1 together explained 66.76% of the variance. Table

4.6 shows the factor loading after rotation (pattern matrix). Component 1 includes all tests that were grouped in the Attentional Control cluster in the cluster analysis. Component 2 includes Sorting, Twenty Questions and Proverb tests, reflecting abstract reasoning abilities. Component 3 includes only the Word Context test, which also requires abstract reasoning, but may rely more strongly on language abilities.

Table 4.6. Summary of principal component analysis of EF test scores (factor loading after oblimin rotation).

	Component		
	1	**2**	**3**
CWI	.901		
Tower	.868		
TM	.812		
Verbal Fluency	.681		
Design Fluency	.478		
Sorting		.804	
20 Questions		.777	
Proverb		.558	
Word Context			.941

Note. See Table 4.1 for information on which index was used for each test. Values below the suggested cut-off value of .40 were removed to increase clarity (Field, 2005).

TM – Trail Making; CWI – Color Word Interference

Cluster analysis of cases, based on Ward hierarchical grouping and squared Euclidean distance (Morris et al., 1981; Ward, 1963), identified three groups of PwPD (see Figure 4.3).

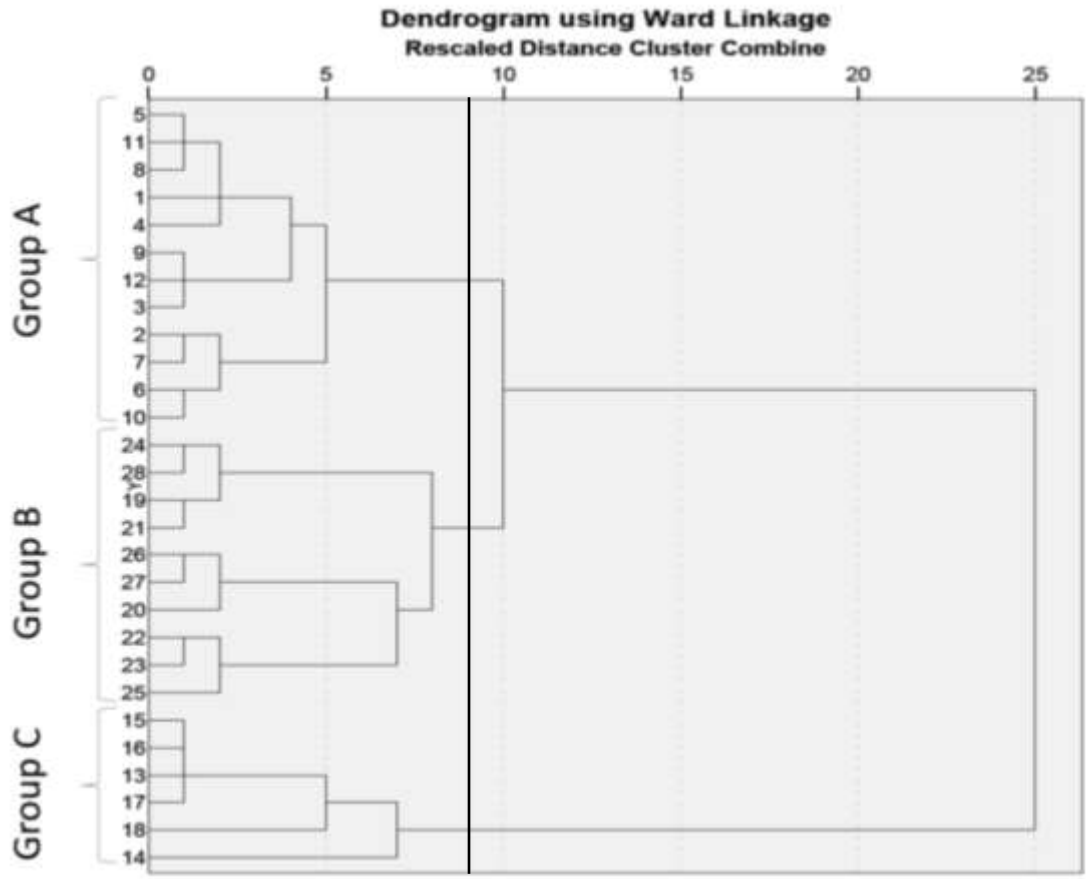

Figure 4.3. Hierarchical cluster analysis examining associations between participants (cases) in EF test performance.

Note. Missing values excluded listwise, n = 28.

Scaled scores on each test for all participants in each group are presented in Table 4.7. The groups were compared with regard to the two composite scores for EF tests, and to demographic and PD characteristics. Kruskal-Wallis comparison of Cluster 1 composite scores across the three groups indicated a significant group effect, with Mann-Whitney post-hoc analysis showing that Group C performed significantly worse than Groups A and B. For the Cluster 2 composite scores, there was a trend towards a between-group difference, with Mann-Whitney post-hoc analysis indicating that Group A performed significantly worse than Group B. There was also a significant difference in ACE-R scores, with Group C

performing significantly worse than Groups A and B. There were no other significant differences between the groups. See Table 4.8 for details.

Table 4.7. Comparison of the three groups identified by the cluster analysis of cases.

	Group A M (SD)	**Group B M (SD)**	**Group C M (SD)**	**Statistics[1]**	**Post-hoc[2]**
Cluster 1 (Attentional control)	11.08 (1.78)	10.78 (1.10)	5.08 (1.11)	H(2) = 12.07, *p* = .002	A, B > C
Cluster 2 (Abstract reasoning)	10.44 (1.49)	12.40 (1.83)	10.88 (1.81)	H(2) = 4.74, *p* = .094	A=C; B=C; A < B
Age	70.67 (9.95)	71.50 (8.66)	76.17 (1.94)	H(2) = 2.50, *p* = .287	
Education (years)	13.33 (3.75)	13.20 (3.02)	12.58 (3.07)	H(2) = 0.78, *p* = .678	
NART-estimated IQ	114.75 (7.26)	114.20 (8.04)	115.50 (7.42)	H(2) = 0.15, *p* = .927	
HADS Anxiety	5.75 (3.49)	4.40 (2.95)	5.17 (3.55)	H(2) = 0.94, *p* = .626	
HADS Depression	3.75 (1.66)	3.70 (2.50)	4.00 (1.14)	H(2) = 0.25, *p* = .881	
ACE-R	96.00 (2.86)	96.50 (2.88)	90.50 (5.82)	H(2) = 6.07, *p* = .048	A, B > C
Hoehn and Yahr stage	1.45 (0.69)	1.22 (0.44)	1.60 (0.55)	H(2) = 1.77, *p* = .414	
PD duration (months)	52.66 (45.04)	70.30 (51.16)	79.00 (53.45)	H(2) = 1.79, *p* = .409	
LED	604.33 (826.48)	350.44 (279.45)	770.58 (524.19)	H(2) = 3.47, *p* = .177	

M – Mean; SD – Standard deviation; NART – National Adult Reading Test; ACE-R – The Addenbrooke's Cognitive Examination - Revised; HADS – Hospital Anxiety and Depression Scale; LED – Total Daily Levodopa Equivalent Dose (Tomlinson et al., 2010)

[1] Kruskal Wallis test; [2] Mann-Whitney; Group A: n=12; Group B: n=10; Group C: n=6.

Scaled scores on each test for all participants in each group are presented in Table 4.7.

Table 4.8. Scaled scores of EF tests grouped by clusters identified in the cluster analyses of variables (EF tests) and cases.

		Attentional Control					Abstract Reasoning			
	Case	CWI	Tower	Verbal Fluency	Design Fluency	TM	Word Context	Proverb	Sorting	20 Quest
Group A	5	12	11	11	13	14	13	11	7	10
	11	11	11	9	10	9	10	9	5	10
	8	10	12	11	10	12	10	11	9	8
	1	9	10	11	10	7	10	9	3	8
	4	12	16	14	11	15	15	15	6	10
	9	13	15	14	11	14	12	15	12	10
	12	13	13	11	12	13	13	14	10	6
	3	14	11	10	12	13	8	13	13	9
	2	10	12	11	5	11	11	12	8	9
	7	12	12	9	10	11	12	16	9	10
	6	8	6	5	10	8	10	15	8	7
	10	10	10	15	9	11	12	16	14	8
Group B	24	8	10	12	12	9	8	15	10	13
	28	7	11	12	13	2	10	15	12	11
	19	12	12	19	11	1	9	15	13	13
	21	12	12	18	8	3	8	14	12	11
	26	12	10	14	10	13	12	13	18	16
	27	11	12	11	11	12	13	15	17	17
	20	7	12	9	8	10	16	13	17	11
	22	12	15	14	8	13	10	9	13	11
	23	11	15	11	9	12	11	10	14	11
	25	10	14	8	11	10	6	8	14	12
Group C	15	7	7	6	9	2	12	13	10	14
	16	4	7	3	7	2	12	12	10	12
	13	4	8	5	8	2	14	12	7	13
	17	8	8	8	4	1	14	13	11	13
	18	8	6	9	1	2	8	9	7	10
	14	1	3	1	10	2	12	9	9	5
Cases not classified due to missing data										
	29	1	2	7	7	1	4	13	-	10
	30	8	10	9	12	1	7	-	9	7
	31	8	7	1	12	-	13	-	-	14
	32	11	-	11	14	8	12	-	9	14
	34	12	10	11	9	9	11	12	-	10
	34	9	12	10	11	9	-	-	-	-
		poor (scaled scores 6-7)					impaired (scaled scores ≤ 5)			

TM – Trail Making; CWI – Color Word Interference; 20 Quest – 20 Questions

Spearman's correlational analysis indicated only two moderate correlations, between Cluster 1 composite score and premorbid IQ estimated with NART, and between Cluster 2 composite score and Hoehn and Yahr stage, which were not significant after Holm-Bonferroni correction for multiple comparisons (p = .05/19 = 0.0026). See details in Table 4.9.

Table 4.9. Bivariate correlations between disease-related and demographic characteristics and EF composite scores (Spearman's Rho).

		Cluster 1		**Cluster 2**
	N	**(Attentional control)**	**N**	**(Abstract reasoning)**
Cluster 2	27	.099		
Age	28	.195	31	-.100
Education (years)	28	.360	31	.219
NART-estimated IQ	28	.435*	31	.056
HADS Anxiety	28	.143	31	.298
HADS Depression	28	.287	31	-.001
ACE-R	28	.226	31	.270
PD duration (months)	28	-.092	31	-.073
Hoehn and Yahr stage[1]	25	-.088	29	-.411*
LED	27	-.066	30	-.232

NART – National Adult Reading Test; HADS – Hospital Anxiety and Depression Scale; ACE-R – The Addenbrooke's Cognitive Examination - Revised; LED – Total Daily Levodopa Equivalent Dose (Tomlinson et al., 2010)

[1]There was no rating available for 3 participants (8.8%).

* significant at p = .05.

4.5 Discussion

In the present study we investigated patterns of performance on EF tests in people with mild to moderate PD without dementia, who screened positive for frontal-type deficits. The frequency of impaired performance (1.5 SD or more below the mean) ranged from 18.2% in the TM to none in the Proverb test. Almost 30% of PwPD had impaired performance in one of the nine tests and 15% had impaired performance in 2 to 5 tests, while over 55% of PwPD scored within the normal range on all tests. Cluster Analysis identified two groups of tests, which we interpreted as reflecting attentional control (Cluster 1) and abstract reasoning (Cluster 2). PwPD performed significantly worse on attentional control than on abstract reasoning tasks, suggesting that the two aspects of EF may be differentially affected in mild to moderate PD.

4.5.1 Frequency of clinically significant EF deficits

Nearly 45% of PwPD in our study performed below the normal range (1.5 SD or more below the mean) on at least one of the tests, while 14.7% had impaired scores on two or more tests. Similar rates have been reported previously; however, as studies employ different definitions of impairment, focus on various aspects of EF, and include PwPD at different PD stages and with differing cognitive status, some of the reports might not be directly comparable. The 45% rate of impairment (at least one test score at least 1.5 SD below the mean) is similar to the results of another study (McKinlay et al., 2009), where about 50% of non-demented PwPD exhibited impairment on executive and problem solving tests. In that study (McKinlay et al., 2009), impairment in the EF domain was defined as performance 1.5 SD below the control group mean, presumably on at least one of the tests, but this criterion was not stated directly. EF impairment is frequently assumed on the basis of performance

on one test only. For example, approximately 9% of non-demented PwPD, who performed at least 1.5 SD below the mean on the Stroop test, were reported as having impaired EF (Caviness et al., 2007), and this was further interpreted as reflecting mild cognitive impairment. In another study (Foltynie et al., 2004) almost 30% of non-demented PwPD were described as having EF impairment on the basis of scores on the Tower of London test (ToL), but no rationale for the choice of the cut-off score for impaired performance was given. The authors suggested that, in 17% of the impaired group, impaired performance on the ToL might reflect underlying deficits in recognition memory.

In the present study, the range of impaired performance varied from none in the Proverb test to 18.2% in the TM. Even greater variability in performance on tests assessing various aspects of EF has been reported previously (Costa et al., 2008), with impaired performance (below the lower limit of the 95% tolerance interval of the normative sample, approximately 2 SD below the mean) observed in 39% of PwPD on the Card Sorting test (categories achieved), but only in 4% on the Phonological Fluency test. In line with our findings, one other study (Muslimovic et al., 2005) reported that the TM had the highest level of impairment in comparison to other EF tests, with impaired performance (2 SD or more below the mean) seen in 16% of non-demented PwPD in early stages of PD.

Cluster analysis of cases identified three groups of PwPD. Group C performed significantly worse than other groups on Cluster 1 tests and on a test of general cognition (ACE-R). One possibility is that this group differed from the other groups in terms of global cognitive impairment, rather than specifically in terms of EF. However, this is unlikely to be the case as all participants had normal general cognition. Hence it is more likely that for this

group the greater deficits in EF affected performance on the ACE-R. The relationship between general cognition and performance on EF tests needs to be further investigated.

There are varying views on how to define cognitive impairment, what cut-off is appropriate for classifying a score as impaired, and how many scores in a set of tests need to be in the impaired range to indicate impairment in a given cognitive domain (Binder, Iverson, & Brooks, 2009; Ingraham & Aiken, 1996). It has been demonstrated (Liepelt-Scarfone et al., 2011) that different criteria for diagnosing mild cognitive impairment in PD (performance 1 SD, 1.5 SD or 2 SD below the mean, in at least one test or at least two tests in a cognitive domain) result in the frequency rates ranging from 9.9% to 92.1% in the same group of PwPD. The more measures that are used, both in terms of the number of tests and the number of indices for each test, the higher the chances are of observing an abnormal score. A single abnormal score might not reflect genuine cognitive problems, as some abnormal scores are commonly observed in healthy people (Binder et al., 2009; Ingraham & Aiken, 1996). In the present study we aimed to minimise the risk of reporting a random abnormal score as impaired, while comprehensively assessing EF, by limiting the use of performance indices to one index per test only. Nevertheless, it remains debatable whether one impaired score is sufficient to classify a person as having impaired EF. Further studies in healthy older adults might offer some clarification. In clinical practice impairment is diagnosed on the basis of convergent evidence from elements of a comprehensive clinical evaluation, for example medical history, observation, and different measures involving similar cognitive processes (Strauss et al., 2006). As such an approach is not usually considered feasible in research projects, single impaired scores may be useful in indicating areas of possible difficulties, but the lower figure of 14.7% (at least two scores falling 1.5 SD

or more below the mean) might more reliably estimate the frequency of EF impairment in our group of PwPD.

4.5.2 Pattern of EF performance

Cluster analysis and PCA both identified similar groups of tests, which seem to reflect two distinctive aspects of EF: attentional control (Cluster 1) and abstract reasoning (Cluster 2). The interpretation of performance on EF tests is not straightforward, as it typically involves a number of EF as well as lower-level cognitive functions, but since EF tests are typically designed to elucidate some distinctive features of executive control, they enable more specific analysis. The majority of EF tests in both clusters are defined as measuring, among other executive abilities, cognitive flexibility. However, it seems that cognitive flexibility might be understood differently in the two aspects of EF.

In Cluster 1 tests (CWI, Tower, Verbal Fluency, Design Fluency and TM) cognitive flexibility seems to reflect time-efficient distribution of attention between various aspects of a test (switching). Time-efficiency is an important aspect of performance in all these tests, with time to complete the test being a primary index of performance in the CWI and TM. The subtasks may be relatively simple (e.g. connecting numbers or letters in ascending order), while the key challenge of the test is associated with the switching itself (e.g. switching between numbers and letters). This is particularly evident in TM, CWI and Verbal Fluency (switching conditions), which specifically require switching, while other tests in Cluster 1 rely more strongly on abilities such as inhibition and simultaneous processing that are related to switching (Miyake et al., 2000).

In the Cluster 2 tests (Sorting, 20 Questions, Word Context and Proverb), flexibility in thinking seems to be equivalent to the cognitive processes of abstract reasoning. All these

tests require the ability to perceive various aspects of abstract concepts, adopt different interpretations and understandings, and implement various strategies to approach the task. For example, in the Word Context test examinees deduce the meaning of a made-up word based on the context given by the clue sentences in which the word appears. The key challenge of these tests seems to be associated with the complexity of the particular cognitive processes involved, rather than the flexibility aspect. While the Cluster 1 tests rely on time-efficient distribution of attention, the majority of Cluster 2 tests have no time limit. Only the Sorting test in Cluster 2 is timed, and noticeably, it is the task with the highest impairment rate among the Cluster 2 tests. What seems to distinguish the Sorting test from the timed tests of Cluster 1 is the abstract reasoning aspect, involving perceiving conceptual relationships between various features of the cards in order to deduce the logic behind the presented grouping.

The Cluster 2 tests seem to require more verbal abilities than the Cluster 1 tests. This might be interpreted as showing that the differences between the two clusters reflect verbal abilities in PD rather than EF. However, this interpretation seems unconvincing as some of the sorts in the Sorting test included in the mostly verbal Cluster 2 are purely visuo-spatial, while the mostly non-verbal Cluster 1 includes the Verbal Fluency test, which assesses an essentially verbal ability of word production.

Interestingly, PwPD performed significantly worse on the attentional control tests than on abstract reasoning tasks, suggesting that the two aspects of EF might be differentially affected in mild to moderate PD. The results seem to be in line with the current understanding of the neuronal basis of EF and the potential role of striatal dopaminergic depletion in EF (Goldman-Rakic, 1992). As proposed by Miller and Cohen

(2001) the striatum and mesocortical dopaminergic modulation of PFC may be critical for the appropriate updating of goal representation in PFC, as it seems to modulate the balance between responsiveness to changing circumstances and the resistance to distraction (E. K. Miller & Cohen, 2001; Seamans & Yang, 2004). Therefore, the disruption of that system might result in disturbances in the inhibitory control and attentional shifting that seem to be important for the tests in the attentional control cluster. In contrast, the aspect of EF related to abstract reasoning and concept formation seem to have stronger associations with anterior and frontopolar regions of PFC and the interconnections of PFC with other cortical sensory systems (Badre, Kayser, & D'Esposito, 2010; Green, Fugelsang, Kraemer, Shamosh, & Dunbar, 2006; Kopp, 2012; Krawczyk, McClelland, & Donovan, 2011). The observed pattern of performance might therefore be interpreted as reflecting the progression of dopaminergic depletion in PD that spreads from the striatum toward the mesocorticolimbic dopaminergic system (Kish & Shannak, 1988; N. Sawamoto et al., 2008). The proposed interpretation could be further investigated by comparing the two aspects of EF in PwPD in more diverse stages of PD and in a prospective study.

4.5.3 Limitations

There are several limitations of the present study that need to be taken into account when interpreting the results. The study aimed to identify the aspects of EF that are particularly problematic in PD, rather than to provide comprehensive frequency rates. The frequency rates given here apply only to the subgroup of PwPD who underperformed in the screening test (FAB) and might not be the same for the whole group of non-demented PwPD in mild to moderate stages of PD. The FAB is a well-established screening tool with good psychometric properties (Lima et al., 2008), but may have distinguished PwPD with a specific profile of executive abilities. A proportion of PwPD who underperformed on FAB had normal scores

on all standard tests of EF and it is possible that some PwPD who have EF deficits not captured by this screening tool were not included in this study. There might be recruitment bias, as PwPD who felt less confident about their cognitive abilities might have chosen not to take part in a study that explicitly focused on cognition. The study employed a cross-sectional design, and a longitudinal follow-up could demonstrate how executive functioning changes as the disease progresses. The analyses were performed on a relatively small sample of PwPD and the findings need to be further validated. However, the convergent evidence from two different analyses (Cluster Analysis and PCA) does increase the likelihood that the identified EF dimensions might generalise to other groups of PwPD. A larger sample would enable more detailed characterisation of factors associated with executive functioning in the subgroups of PwPD distinguished by cluster analysis, for example with regard to motor impairment, medication, age, genetic factors, or PD subtype. We have attempted to control for the impact that lower-level cognition and motor functioning might have on observed executive performance by including PwPD with normal general cognition and choosing measures less affected by motor speed, but some non-executive deficits may still have a potential impact on performance on EF tests. Finally, it should be noted that while the ability to cope with novelty is described as central for EF, this might not be effectively assessed in a firmly structured testing situation (Manchester et al., 2004).

4.5.4 Conclusions

In summary, more than half of PwPD in our sample performed within the normal range on all nine EF tests. The highest rate of impaired scores, 18.2%, was observed for TM, and the lowest for Proverb, with all PwPD performing within the normal range. Cluster analysis identified two groups of tests that seem to reflect two distinctive sets of abilities: attentional control and abstract reasoning. Both aspects of EF are typically included in broad

definitions of EF (Alvarez & Emory, 2006; Ardila, 2008; Aron, 2008; Krpan et al., 2007; Stuss & Alexander, 2000), but they seem to rely on fundamentally different cognitive processes, possibly reflecting regional specialisation within the PFC and frontostriatal circuits. It seems that PD pathology in the mild to moderate stages affects the attentional control aspect of EF to a greater extent than the abstract reasoning aspect. Better understanding of the nature of executive deficits may facilitate development of targeted pharmacological treatment and provision of the adequate support for PwPD and their families.

Chapter 5

Quality of life, health status and caregiver burden in Parkinson's disease: Relationship to executive functioning

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5.1 Abstract

Background: High-quality person-centred care for people with Parkinson's disease (PwPD) and their families relies on identifying and addressing factors that specifically impact on quality of life (QoL). Deficits in executive functions (EF) are common in Parkinson's disease, but their impact on PwPD and their caregivers is not well understood. The present study evaluated how EF contributes to QoL and health status for the PwPD, and caregiver burden.

Methods: Sixty-five PwPD completed measures of QoL, health status and EF, and 50 caregivers rated the EF of the PwPD and their own burden. Multiple regression analyses examined predictors of QoL (General life, Health, and Movement disorders domains), health status and caregiver burden.

Results: QoL in the Health and Movement disorders domains was best explained by caregiver-rated EF, while QoL in the General life domain was best explained by level of depression. Health status was predicted by self-rated EF, with an objective EF measure also included in the regression model. Caregiver burden was best explained by caregiver-rated EF and disease severity, with general cognition and other factors also included in the regression model.

Conclusions: EF-related behavioural problems may contribute to QoL and health status in PwPD, and affect caregiver burden. The findings support the view that the concepts of subjective QoL and self-assessed health status are only partially related and should not be seen as identical. Adequate strategies to reduce the impact of EF deficits are needed as this may have the potential to improve QoL in PwPD.

5.2 Introduction

People diagnosed with Parkinson's disease (PwPD) are affected by the disease in numerous ways. The typically profound motor symptoms (tremor, rigidity and postural instability) are accompanied by a plethora of non-motor symptoms: neuropsychiatric problems (e.g. depression, apathy and cognitive deficits), sleep disturbances, and various autonomic symptoms (including gastrointestinal problems), as well as widespread slowness and fatigue (Chaudhuri et al., 2005; Poewe, 2008). Impairment in executive functions (EF) is one of the most commonly reported cognitive deficits in PD, observed even in the early stages of the disease (Muslimovic et al., 2005). EF is an umbrella term for a number of processes involved in regulating goal-oriented behaviour (Strauss et al., 2006). PwPD are reported to have deficits in cognitive flexibility, set-switching, inhibition and selective attention, as well as concept formation, planning, and decision making (Altgassen et al., 2007; Bouquet et al., 2003; Cools et al., 2001; Dujardin et al., 2001; Kobayakawa et al., 2008; Kudlicka et al., 2011; Muslimovic et al., 2005; Zgaljardic et al., 2006). Executive deficits may affect functional abilities (Bronnick et al., 2006; Cahn et al., 1998; Hobson et al., 1999; Sabbagh et al., 2007; Schrag et al., 2000) and the use of coping strategies, with implications for the subjective health status of PwPD (Hurt et al., 2012). One-third of PwPD assessed in a large multi-centre study reported difficulties with maintaining concentration (Barone et al., 2009). Many PwPD complain about forgetfulness and slowness of thinking (Brod et al., 1998; Poliakoff & Smith-Spark, 2008). Despite their ubiquity and possible implications for everyday life (Hely et al., 2005; Leiknes, Tysnes, Aarsland, & Larsen, 2010), cognitive deficits and other non-motor symptoms have received attention only in recent decades and still tend to be under-diagnosed (Chaudhuri & Schapira, 2009; Shulman, Taback, & Weiner, 2002). There is also

limited evidence regarding the specific impact that executive deficits may have on PwPD and their families.

Studies evaluating the impact of PD on PwPD and their families frequently consider quality of life (QoL) or health-related QoL. QoL is defined as a subjective evaluation of various aspects of life, such as health, family, or occupation, in the context of the person's needs and expectations (Den Oudsten et al., 2007a; Sprangers & Schwartz, 1999; WHOQOL group, 1998). However, the questionnaires used for assessing health-related QoL tend to ask about magnitude and/or frequency of symptoms, rather than about satisfaction with health (Den Oudsten et al., 2007a). It has been suggested that subjective perception of symptom severity might be more accurately referred to as subjective health status, and that this is only partially related to the QoL concept (Den Oudsten et al., 2007a). People can adjust and reconceptualise their internal standards and values, and their expectations, to incorporate the illness (Foley et al., 2006; Sodergren & Hyland, 2000; Sprangers & Schwartz, 1999; Thornton, 2002). Therefore persons acknowledging similar levels of symptom severity (subjective health status) may express different levels of satisfaction with health and with life in general (QoL), depending on their expectations about health, after being diagnosed with PD.

Only two of the 61 studies identified in a systematic literature review of studies on QoL in PD (Den Oudsten et al., 2007a) employed a measure assessing QoL specifically, rather than subjective health status, and these studies reported a possible role for depression (Lee et al., 2006) and PD duration and severity (Schestatsky et al., 2006). Subjective health status seems to be most strongly associated with depression and there is some evidence for the

influence of insomnia, medication use and surgery (Den Oudsten et al., 2007a; Soh, Morris, & McGinley, 2011).

Only a small proportion of studies found cognition relevant to QoL or health status (Leroi et al., 2011; Leroi, McDonald, Pantula, & Harbishettar, 2012), but the limited number of significant findings may result from the fact that many studies assessed cognition only with the MMSE (Folstein et al., 1975) or other screening tools, which are not sensitive to the more subtle executive impairment observed in PD (Folstein & Folstein, 2010).

When considering the impact of PD on a person's life, it is important to acknowledge the role of family members, as particularly in the later stages PwPD depend on the care provided by family members in order to continue living at home. Given their critical role in supporting PwPD, caregivers' specific needs should be well-understood and addressed alongside the needs of PwPD. Severity of motor symptoms is often reported as an important predictor of burden associated with caring for PwPD (Cifu et al., 2006; D'Amelio et al., 2009; Martínez-Martín et al., 2007; Schrag et al., 2006). Other studies highlight the importance of various non-motor symptoms, particularly depression (Aarsland et al., 1999; Martinez-Martin et al., 2005; E. Miller et al., 1996). Some studies have found a relationship between caregiver burden and cognition (Aarsland et al., 1999; Leroi, Harbishettar, et al., 2012; Martinez-Martin et al., 2005; Thommessen et al., 2002), while other found no association (D'Amelio et al., 2009; E. Miller et al., 1996; Peters et al., 2011; Schrag et al., 2006). As in the studies of QoL and health status in PwPD, cognition was in many cases assessed using screening instruments only.

In summary, the adequate support of PwPD and their families relies upon identifying and targeting factors that specifically impact on the QoL and health status of PwPD and on

the burden associated with caring for PwPD. Cognitive functioning, and more specifically EF, may influence the functioning of PwPD and the well-being of caregivers, but to evaluate this relationship, measures sensitive to EF need to be employed. In the present study we evaluated the extent to which executive impairment contributes to QoL, subjective health status and self-reported caregiver burden.

5.3 Method

5.3.1 Design

As described in Chapter 1, the study employed a cross-sectional design, and the assessment presented here was part of a wider study, approved by the relevant University and National Health Service (NHS) ethics committees.

5.3.2 Participants

The same sample as that reported in Chapter 3 and the same inclusion/exclusion criteria were used. A sample of people with early stage PD (H&Y stage I-III, Hoehn & Yahr, 1967), diagnosed according to UKPDS Brain Bank criteria (Daniel & Lees, 1993), were identified by the consultant physician (JVH) from local Movement Disorders clinics in North-West Wales. Over 18 months of recruitment, 75 PwPD agreed to take part in the study and 65 of them met the inclusion criteria of normal general cognition, indicated by an Addenbrooke's Cognitive Examination – Revised (ACE-R) score ≥ 82 (Mioshi et al., 2006) and a MMSE score ≥ 24 (Folstein et al., 1975), and no clinically significant depression, as indicated by a Hospital Anxiety and Depression Scale (HADS) score ≤ 11 (Snaith & Zigmond, 1994). PwPD were on stable medication and had no serious comorbid neurological or psychiatric conditions, such as stroke, epilepsy or schizophrenia. Caregiver ratings were provided by people who lived with PwPD and/or knew the participants very well (e.g. spouses or adult children). Although

some of these people would not identify themselves as 'caregivers' the term has been used in this chapter to refer to individuals providing support to a PwPD as it is a widely-understood and accepted construct. Caregiver data is not available in all cases as a proportion of PwPD lived alone and did not specify a suitable informant, and some family members who lived with PwPD and were invited to participate did not return the questionnaires. All participants had adequate eyesight and hearing, and were fluent in English.

5.3.3 Measures

The following measures from the wide database were used in this analysis.

Quality of life (QoL)

PwPD completed the Questions on Life Satisfaction scale (Henrich & Herschbach, 2000; Kuehler et al., 2003) (Appendix H), validated for use in PD, which examines subjective quality of life in three dimensions**:** general life satisfaction (QoL-Life, 8 items), satisfaction with health (QoL-Health, 8 items), and satisfaction with health in relation to movement disorders (QoL-MD, 12 items). This seems to be the only PD-specific measure of QoL rather than subjective health status (Den Oudsten et al., 2007b). On two separate 5-point scales participants indicate the subjective importance of a specific area of life or health (importance rating), and the degree of satisfaction in that area (satisfaction rating). The two ratings for each item are used to calculate a weighted satisfaction score and summed to provide global ratings for each of the three dimensions. Negative values indicate a predominance of "dissatisfaction".

Health status

PwPD completed the Parkinson's Disease Questionnaire (PDQ-39; Jenkinson et al., 1998), a widely-used PD-specific questionnaire assessing subjectively perceived severity of various PD symptoms (health status). Participants indicate how often they have been affected by each of 39 problems listed. A summary index ranges from 0 to 100, with higher scores indicating higher levels of problems.

Caregiver Burden

Caregivers of PwPD completed the Caregiver Burden Inventory (CBI; Novak & Guest, 1989) (Appendix I), a 24-item self-rating questionnaire providing a detailed picture of the caregiver's feelings and responses to the burden of care, used previously in PD studies (D'Amelio et al., 2009). A maximum score of 96 indicates the highest level of burden.

Mood

PwPD completed the Hospital Anxiety and Depression Scale (HADS; Snaith & Zigmond, 1994), a self-rating questionnaire assessing levels of depression (HADS - Depression) and anxiety (HADS-Anxiety), widely used in PD studies (Schrag et al., 2007). Scores for each of the 7 item subscales range from 0 to 21, with higher scores indicating higher levels of self-rated anxiety/depression. The study adopted the cut-off of 11 suggested for depression screening purposes (Crawford et al., 2001).

Cognitive screening

PwPD completed the Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi et al., 2006), which estimates general cognition in five cognitive domains: attention and orientation, memory, verbal fluency, language and visuospatial abilities. It also provides an

MMSE score (Folstein et al., 1975). The maximum total score of 100 indicates errorless performance.

Executive functions (EF)

PwPD completed two tests from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001): the Trail Making Test (TMT) and the Color-Word Interference test (CWI), both known to be sensitive to EF deficits in PD (Kudlicka et al., 2011; see chapter 2). In TMT participants draw a line connecting numbers (TMT-Numbers) or numbers and letters in alternating sequence (TMT-Switching) in ascending order. A ratio score TMT-Switching /TMT-Numbers (comparable to the widely used TMTB /TMTA) has been identified as the most accurate estimation of EF, differentiating EF from visuospatial and motor abilities (Arbuthnott & Frank, 2000). CWI is based on the traditional Stroop task, where participants name the dissonant ink colour instead of reading the word (colour name). In CWI inhibition/switching condition participants switch between naming the dissonant ink colour (Stroop task) and reading the word, which tests the ability to inhibit unwanted reaction as well as cognitive flexibility. Longer completion times indicate poorer performance.

EF-related behavioural problems

PwPD and their caregivers completed parallel versions of the Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A; Roth et al., 2005), which estimates the ability to efficiently regulate behaviour and emotional responses, and to appropriately distribute attention to sustain task-completion efforts and systematically solve problems. On a 3-point scale participants indicate which of the 75 behaviours described has been a problem during the past month. Higher scores indicate more difficulties.

5.3.4 Procedure and data collection

Participants were assessed at home, except for six participants who preferred to meet at the University. Some participants opted to send the self-completion questionnaires by post. The assessment reported here took 1.5-3 hours, split over two visits when needed. Visits were arranged during the 'on' medication phase.

5.3.5 Planned analysis

The associations between the variables were evaluated with bivariate correlational analyses (Pearson's correlation). Predictors of QoL and health status in PwPD, and of caregiver burden, were identified with multiple regression analyses. Stepwise backward regression was selected as most suitable for addressing the exploratory aims of the study. The multiple regression analyses were performed in SPSS v.20 (IBM Corporation, NY, USA) with the default criterion probability of F-to-remove ≥.10.

5.4 Results

Sixty-five PwPD were included in the study, and 50 caregivers also contributed. Table 5.1 presents demographic and disease characteristics, and Table 5.2 shows a summary of scores on all study measures.

Table 5.1. Descriptive statistics of the study measures in PwPD (n=65).

a) Demographic characteristics

	M (SD)	Range
Age	70.11 (8.92)	48–89
Education (years)	12.97 (2.98)	5–20
NART-estimated IQ* (n=64)	113.77 (8.04)	92–128
MMSE	29.48 (0.92)	25–30
	n (%)	
Gender (Male)	30 (46.2)	
Socio-economical status		
I Professional	10 (15.4)	
II Managerial/technical	28 (43.1)	
III N Skilled, non-manual	13 (20.0)	
III M Skilled, manual	11 (16.9)	
IV Partly skilled	3 (4.6)	
V Unskilled	0	
Relationship with caregiver**		
Spouse/Partner	45 (69.2)	
Parent/Child	3 (4.6)	
Friend	2 (3.1)	
Caregiver did not participate	15 (23.1)	

b) Disease characteristics and medication use

	M (SD)	Range
PD duration (months)[1]	71.97 (50.42)	7–216
Hoehn and Yahr stage[2]	1.34 (0.57)	1–3
LED[3]	579.19 (556.35)	0–3125
	n (%)	
Hoehn and Yahr stage[2]		
Stage I	41 (63.1)	
Stage II	16 (24.6)	
Stage III	2 (3.1)	
Side of onset		
Left	24 (36.9)	
Right	31 (47.7)	
Bilateral	10 (15.4)	
Levodopa	39 (60.0)	
Dopamine agonists	40 (61.5)	
Rasagiline	33 (50.8)	
Entacapone	11 (16.9)	
Amantadine	4 (6.2)	
Apomorphine	1 (1.5)	
None	3 (4.6)	

M – Mean; SD – Standard deviation; LED – Total Daily Levodopa Equivalent Dose; Dopamine agonists – Non ergot-derived dopamine-receptor agonists

[1]Mean value of the time since first symptoms and the diagnosis, as reported by PwPD.

[2]There was no rating available for 6 participants (9.2%).

[3]Based on Tomlinson et al. (2010), n=64.

* Pre-morbid IQ of PwPD was estimated with the National Adult Reading Test (NART; Nelson & Willison, 1991). The number of phonetically irregular words pronounced incorrectly is converted into an estimated IQ score. Based on the NART, 31% of PwPD had an average IQ and 69% had an above average IQ. **92% of caregivers lived with PwPD.

Table 5.2. PwPD and caregiver scores on all measures.

	n	M (SD)	Range	Min. and Max.
QoL-General Life	57	83.88 (28.83)	30–141	-96–160
QoL-General Health	58	62.10 (43.23)	-59–134	-96–160
QoL-Movement Disorders	55	96.96 (52.27)	-49–216	-144–240
PDQ-39	54	20.13 (11.57)	0.52–53.75	0–100
Caregiver Burden Inventory	42	12.45 (10.55)	0–46	0–96
ACE-R	65	93.83 (4.41)	82–100	0–100
HADS-Depression	65	4.43 (2.51)	0–10	0–21
HADS-Anxiety	65	5.42 (3.52)	1–16	0–21
TMT ratio	64	2.25 (0.79)	0.71–4.14	n/a
CWI inhibit/switch (seconds)	64	84.61 (29.68)	39–180	–180s
CWI inhibit/switch (scaled)	64	9.55 (3.37)	1–15	1–19
BRIEF-A Self	61	107.26 (19.62)	71–177	70–210
BRIEF-A Caregiver	47	97.87 (23.26)	70–166	70–210

M – Mean; SD – Standard deviation; QoL – Quality of Life; PDQ-39 – Parkinson's disease Questionnaire - 39; ACE-R – The Addenbrooke's Cognitive Examination - Revised; HADS – Hospital Anxiety and Depression Scale; TMT ratio– Trail Making Test (D-KEFS), TMT-Switching/TMT- Numbers; CWI – Color Word Interference (D-KEFS); BRIEF-A Self – BRIEF-A Global Executive Composite Self-rating (raw score); BRIEF-A Caregiver – BRIEF-A Global Executive Composite Caregiver rating (raw score)

The three QoL domains were strongly correlated with each other, and health status was related to QoL–Movement Disorders and QoL–Health but not to QoL-Life. Caregiver burden was not related to QoL domains or health status. Details of the bivariate correlations are presented in Table 5.3.

Table 5.3. Pearson's correlation coefficients for quality of life, health status and caregiver burden, and other study variables.

	QoL-Life	QoL-Health	QoL-Movement Disorders	Health status (PDQ-39)	Caregiver burden (CBI)
QoL Health	**.693*****				
QoL MD	.441***	**.709*****			
Health status (PDQ-39)	-.207	**-.521*****	**-.625*****		
Caregiver burden (CBI)	.001	-.240	-.316	.398*	
Age	-.076	.125	-.160	-.078	.036
Hoehn and Yahr stage	-.068	.062	.075	.014	.413*
HADS-Depression	**-.453*****	**-.492*****	-.377**	.403**	.453**
ACE-R	-.028	-.175	-.021	.156	-.314*
NART-estimated IQ	-.269*	-.174	-.147	.092	-.205
TMT ratio	.026	.144	.158	-.174	-.144
CWI inhibit/switch (scaled)	.108	.105	.034	-.055	-.416**
BRIEF-A Self	-.254	-.351**	-.441***	**.586*****	.282
BRIEF-A Caregiver	-.163	-.447**	-.466**	.368*	**.723*****

Note. Bold indicates significance after Holm-Bonferroni correction for multiple comparison p = .05/65 = 0.00077.

QoL – Quality of Life; PDQ-39 – Parkinson's disease Questionnaire - 39; HADS – Hospital Anxiety and Depression Scale; ACE-R – The Addenbrooke's Cognitive Examination - Revised; TMT ratio– Trail Making Test (D-KEFS), TMT-Switching /TMT-Numbers; CWI – Color Word Interference (D-KEFS); BRIEF-A Self – BRIEF-A Global Executive Composite Self-rating (raw score); BRIEF-A Caregiver – BRIEF-A Global Executive Composite Caregiver rating (raw score)

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

*** Correlation is significant at the 0.001 level (2-tailed).

Prior to the multiple regression analyses the data were checked against assumptions for multilinear regression (Field, 2005). To control for collinearity problems, scales that were highly correlated with others were removed when possible. Decisions were made as follows. The H&Y score was included, as a more direct indication of PD severity than LED and PD duration. The HADS Depression scale was included rather than HADS Anxiety as the variable of primary interest, based on previous studies (Den Oudsten et al., 2007a). To control for a strong age effect in CWI inhibition/switching, the scaled score was used.

Multiple regression analyses were performed for the following dependent variables: QoL–Life, QoL–Health, QoL–Movement Disorders, PDQ-39 (health status) and the Caregiver Burden Inventory. The following independent variables were included: HADS-Depression; ACE-R (general cognition); CWI inhibition/switching scaled score and TMT ratio (executive functions); self- and caregiver ratings of BRIEF-A (EF-related behavioural difficulties); and H&Y stage (PD severity). The models that were statistically significant and accounted for the greatest variance (adjusted R^2) were selected in each case, and these are summarised in Table 5.4.

Table 5.4. Results summary for the backward regression analyses.

	QoL–Life		**QoL–Health**		**QoL–Movement Disorders**		**Health status (PDQ-39)**		**Caregiver burden**	
R^2	.279		.393		.364		.388		.736	
R^2 adj	.225		.323		.262		.343		.661	
F	5.22		5.61		3.57		8.55		9.76	
p	.012		.004		.019		.001		.000	
Predictors	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Age					-.173	.290				
H&Y									**.377**	.008
HADS-D	**-.454**	.010	-.330	.061	-.203	.262			.204	.151
ACE-R									-.168	.188
NART IQ	-.271	.109	-.294	.080	-.282	.107			.224	.113
TMT ratio							-.211	.172		
CWI inhibit/ switch (scaled)										
BRIEF-A Self							**.599**	.000	-.230	.148
BRIEF-A Caregiver			**-.400**	.032	**-.468**	.018			**.754**	.000

R^2 adj – R^2 adjusted; β – standardized coefficient; QoL – Quality of Life; PDQ-39 – Parkinson's disease Questionnaire - 39; HADS – Hospital Anxiety and Depression Scale; ACE-R – The Addenbrooke's Cognitive Examination - Revised; TMT ratio – Trail Making Test (D-KEFS), TMT-Switching /TMT-Numbers; CWI – Color Word Interference (D-KEFS); BRIEF-A Self – BRIEF-A Global Executive Composite Self-rating (raw score); BRIEF-A Caregiver – BRIEF-A Global Executive Composite Caregiver rating (raw score)

The depression rating was the strongest and the only individually significant predictor of QoL-Life. The model explained 23% of the variance in QoL-Life.

The BRIEF-A caregiver rating was the strongest and the only individually significant predictor of QoL-Health, while the depression rating only approached significance. The model explained 32% of the variance in QoL-Health.

The BRIEF-A caregiver rating was the strongest and the only individually significant predictor of QoL-Movement Disorders. The model explained 26% of the variance in QoL-Movement Disorders.

The BRIEF-A self-rating was the strongest and the only individually significant predictor of health status. The model explained 34% of the variance in health status.

The BRIEF-A caregiver rating and PD-stage were the strongest and the only two individually significant predictors of caregiver burden. The model explained 66% of the variance in caregiver burden.

5.5 Discussion

The present study has addressed the complex variety of factors influencing quality of life and health status in PwPD, and the burden associated with caring for PwPD. The findings show that behavioural problems related to executive functioning, as indicated by the BRIEF-A rating, contribute to QoL and health status in PwPD and to burden in caregivers of PwPD.

Depression was the only individually significant predictor of QoL in the General Life domain in PwPD. This is in line with the study by Lee et al. (2006), where depression was the only predictor of subjective QoL in PwPD, while disease severity was not included in the model. That suggests that there is no straightforward relationship between general QoL and health, as has been reported in other conditions, particularly in cancer research (Foley et al., 2006; Sodergren & Hyland, 2000; Thornton, 2002).

The best predictor of QoL in both the general health and the movement disorders domains was executive functioning, as rated by the caregiver on the BRIEF-A questionnaire.

As far as can be determined, this is the first study suggesting that EF-related behavioural problems may impact on QoL related to health in PD.

Consistent with other studies reporting a close relationship between health status and depression in PD (Den Oudsten et al., 2007a; Soh et al., 2011), we observed a strong relationship between depression and health status in the correlational analysis. However, depression was not included in the regression model. The only individually significant predictor included in the regression model of health status was BRIEF-A self-rating, which indicates EF-related behavioural problems, as perceived by PwPD themselves.

Standard tests of EF were not included in any of the regression models, which might reflect the generally low ecological validity of such tests and the limited relationship between EF test scores and everyday functioning (Goldberg & Podell, 2000). The BRIEF-A questionnaire was developed specifically to address this limitation of standard EF tests, and it is therefore not surprising to see BRIEF-A ratings and not standard EF tests emerging as relevant for QoL and subjective health status (Koerts et al., 2012; Manchester et al., 2004).

There are several possible explanations for the observed relationship between QoL, health status and executive functioning. One explanation might be that QoL in health domains is affected by the caregiver's critical perception of the PwPD (illustrated by a low BRIEF-A rating) rather than executive deficits. However, the lack of such relationship in the general life domain, and the non-significant relationships between QoL and health status, and caregiver burden, make this explanation less plausible.

Another possible explanation for the relationship between QoL, health status and EF is that particular EF-related difficulties (e.g. poor planning or problems with prioritising

activities) and behavioural disturbances hinder everyday functioning and impact directly on QoL (Leroi et al., 2011). Alternatively, difficulties in regulating behaviour and emotions, and solving problems, as indicated by low BRIEF-A ratings, may influence QoL indirectly, resulting in less effective use of strategies to overcome PD-related limitations or less effective coping with the psychological consequences of the illness (Frazier, 2000; Montel, Bonnet, & Bungener, 2009; Sanders-Dewy, Mullins, & Chaney, 2001). Adequate behavioural, cognitive, and affective processes (e.g. positive reappraisal, reordering goals or adjusting expectations) may help in adjusting to the illness and sustaining good QoL despite physical problems (Sprangers & Schwartz, 1999). These mechanisms can be seen as coping or self-regulation strategies, and might rely on EF (Baumeister & Vohs, 2003). The role of EF in coping has not been specifically assessed in PD, but there is some evidence that the use of specific coping strategies may be related to general cognition in PwPD (Hurt et al., 2012). Moreover, coping styles are related to EF in other patient groups, for example in people with traumatic brain injury (Krpan et al., 2007), multiple sclerosis (Goretti et al., 2010), and schizophrenia (Wilder-Willis, Shear, Steffen, & Borkin, 2002).

Interestingly, the regression model for caregiver burden explained a large proportion of the variance, despite including only patient-related variables. In line with other studies investigating caregiver burden in PD, the regression model included disease severity (Cifu et al., 2006; D'Amelio et al., 2009; Martínez-Martín et al., 2007; Schrag et al., 2006). However, the strongest individually significant predictor of caregiver burden in our study was caregiver-rated behavioural problems related to EF. As far as can be determined, this is the first study to demonstrate such a relationship in PD. EF deficits have been reported to specifically impact on caregiver burden in dementia (Davis & Tremont, 2007; Rymer et al.,

2002). It is particularly interesting to observe such a relationship in people in mild to moderate stages of PD, where only a limited amount of care would be required with regard to physical symptoms.

Health status was not related to general QoL, and was predicted by variables different to those included in the models for QoL domains. These findings support the view that the concepts of subjective QoL and self-assessed health status are only partially related and should not be seen as identical (Foley et al., 2006; Sodergren & Hyland, 2000; Sprangers & Schwartz, 1999; Thornton, 2002).

5.5.1 Limitations

Some limitations need to be taken into account when interpreting these results. Our study employed a relatively small sample and the results of our analyses need to be validated in a larger study. The BRIEF-A has been used in many clinical groups, including Alzheimer's and MCI (Roth et al., 2005), but as far as can be determined it has not been employed in PD studies. Models of QoL domains and health status accounted for a modest proportion of the variance, and a broader range of variables may need to be considered, for example apathy, quality of relationship and activities of daily living, alongside a more comprehensive assessment of EF. Including more caregiver-related variables may also help to produce a more comprehensive model. In the present sample the average level of depression was relatively low and this might account for a less extensive impact of depression on the constructs we evaluated. The Hoehn and Yahr classification of PD severity is widely used, but a more detailed disease characterisation might give a better insight into how physical difficulties influence QoL and health status in PD.

5.5.2 Conclusions

In summary, the study suggests that EF-related difficulties may influence QoL and health status in PwPD, as well as the burden associated with caring for PwPD. The results support the view that assessing QoL and health status separately is relevant to understanding how PwPD perceive the impact of PD on their life. Further research is needed to clarify the mechanisms whereby executive deficits affect QoL and health status in PD, and to inform development of adequate strategies to reduce the impact of EF deficits on PwPD and caregivers. Addressing difficulties related to EF offers the potential to improve QoL in PwPD (National Collaborating Centre for Chronic Conditions, 2006; Van der Eijk, Faber, Al Shamma, Munneke, & Bloem, 2011), which should be the overall aim of high-quality person-centred healthcare.

Chapter 6

Awareness of executive deficits

in people with Parkinson's disease

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6.1 Abstract

Background: Executive functioning is frequently impaired among people with Parkinson's disease (PD). Little is known about awareness of executive functioning, in the sense of being able to accurately appraise functioning or performance, in people with PD, or about whether awareness is particularly affected in those who have impaired executive functioning.

Method: This study explored awareness of executive functioning at the levels of evaluative judgment (comparison of self- and informant ratings of executive functioning), and performance monitoring (comparison of performance on cognitive tests and self-ratings of that performance). Awareness levels were assessed in people with PD with and without executive deficits, and in healthy controls.

Results: When the level of agreement between self- and informant ratings was considered, people with PD in both groups appeared as accurate in evaluating their overall executive functioning as healthy controls. When appraising their performance as the specific tasks were completed, people with PD who had impairments in executive functioning appeared less accurate than controls and people with PD without executive impairments.

Conclusions: People with PD who have executive deficits may lack the ability to recognise their limitations while performing specific tasks, which may have implications for their functional abilities.

6.2 Introduction

Inaccurate appraisal of one's condition and its consequences, which may be referred to in terms of reduced awareness, insight, metacognition, anosognosia or denial, is frequently reported in conditions involving cognitive impairment, such as dementia, or following brain injury or stroke, where it may interfere with treatment, add to carer burden and lead to problem escalation (Aalten, van Valen, Clare, Kenny, & Verhey, 2005; Nelis et al., 2011). Inaccurate self-appraisal may be observed in healthy people, and may be related to psychosocial factors (Clare et al., 2012), but is most commonly seen as a consequence of brain lesions (in particular where the prefrontal cortex is involved) and is often associated with impairment in executive functions (EF) (Bramham, Morris, Hornak, Bullock, & Polkey, 2009; Stuss, Picton, & Alexander, 2001; Wheeler, Stuss, & Tulving, 1997).

Frontal lobe functions involved in the performance of executive tasks are frequently compromised in Parkinson's disease (PD) as dopamine depletion in the striatum causes a disruption of frontostriatal networks. This affects the motor loop (connecting the putamen and the supplementary motor area), as well as the cognitive loop (connecting the dorsolateral prefrontal cortex and the dorsal caudate nucleus, associated with executive deficits) (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Leh et al., 2010). A significant proportion of people diagnosed with PD (PwPD) experience cognitive decline, particularly in EF, that may impact negatively upon quality of life (Klepac et al., 2008; Schrag et al., 2000) and activities of daily living (Cahn et al., 1998). Little is known about the extent of awareness of cognitive problems shown by PwPD. Lack of awareness might mean that impairments are unrecognised by PwPD and not reported to the clinician, with possible implications for treatment outcomes (Koerts et al., 2012).

Executive deficits and poor awareness of one's own limitations may impact on various aspects of everyday life in PD, including driving (Devos et al., 2007; Rizzo et al., 2010; Stolwyk, Charlton, Triggs, Iansek, & Bradshaw, 2006; Uc et al., 2007) and adherence to medication regimes (Grosset, Bone, & Grosset, 2005; Grosset et al., 2006; Kulkarni et al., 2008; Leopold, Polansky, & Hurka, 2004). Where the view of cognitive functioning held by the PwPD is discrepant from that held by the carer, there may be particular stresses in the caregiving relationship. Understanding how cognitive problems are perceived by both the PwPD and the carer is therefore crucial for providing appropriate support.

The Levels of Awareness Framework proposed by Clare, Marková, Roth, and Morris (2011) describes awareness in terms of dynamic perceptual and appraisal processes operating at various levels: sensory registration, performance monitoring, evaluative judgment and meta-representation. Sensory registration relates to core consciousness and attentional processes; performance monitoring reflects an immediate judgement about performance on a specific task as it is completed; evaluative judgement refers to more general judgements about functioning in a particular area; and meta-representation is a complex reflection on the situation, which integrates individual knowledge, emotions and attitudes. The phenomena of awareness elicited at each level are different. They may be influenced by a number of internal (e.g. mood, personality) and external (e.g. social norms, carer responses) factors, and are additionally shaped by the object in relation to which awareness is assessed (e.g. cognitive deficits or the experience of illness and its implications); hence they are not directly comparable. To understand the implications of someone's level of awareness for everyday functioning, it is useful to know how accurately

the individual perceives his/her overall cognitive functioning and appraises his/her performance in particular tasks.

Studies of awareness in PD to date have focused exclusively on the evaluative judgement level, with informant ratings being used as a benchmark against which self-ratings are compared, and less frequent comparisons to objective measures. Only a few studies have directly explored awareness of cognitive problems in PwPD; Seltzer et al. (2001) and Sitek, Soltan, et al. (2011) reported good agreement between self- and informant ratings of general cognition and of memory, respectively. Ivory et al. (1999) analysed the accuracy of evaluative judgments about memory and attention by correlating performance on three cognitive tests with responses on a metamemory questionnaire. Only one out of 11 correlations was significant, suggesting limited accuracy of evaluative judgment in PwPD. While the above studies have investigated awareness of cognitive functions in PD, they did not focus specifically on EF. It would be particularly relevant to focus on awareness in relation to EF, as this is the cognitive domain commonly impaired in PwPD (Kudlicka et al., 2011; Muslimovic et al., 2007).

Three studies which did not refer directly to awareness have explored evaluative judgment of EF in PwPD by comparing self- and informant questionnaire-based ratings. In McKinlay, Grace, et al. (2008) PwPD reported more difficulties than their carers, while Koerts et al. (2012) and Mathias (2003) revealed good agreement between ratings. The inconsistency might be related to differences in cognitive status in the study samples. Poor awareness is commonly described in relation to executive deficits (Stuss et al., 2001), and studying awareness in PwPD without distinguishing those with actual executive deficits may produce mixed findings. The observed inaccuracies might be clarified by establishing how

the awareness level in PwPD compares to awareness in a similar but healthy population. There are two studies on executive and neurobehavioural functioning that examined self- and informant ratings in PwPD and controls (Koerts et al., 2012; Mathias, 2003), but without direct comparison of the actual level of agreement between participants and informants.

In summary, studies on awareness in PD have only considered the level of evaluative judgement, have rarely investigated awareness in relation to well-specified EF impairment, and have not compared awareness levels in PD and healthy controls. The present study aimed to address these issues by distinguishing PwPD with and without EF impairments, and by comparing their performance to healthy controls. Awareness phenomena were examined in relation to the two levels of evaluative judgement and performance monitoring. The following research questions were addressed:

1. How accurate are PwPD with and without EF impairments in assessing their overall executive functioning and performance in a given task, in comparison to controls?

2. What are the correlates of awareness in PwPD?

6.3 Method

6.3.1 Design

The study employed a cross-sectional design comparing PwPD with and without EF deficits, and healthy controls. Awareness of EF was assessed at the two levels of evaluative judgement and performance monitoring. In relation to evaluative judgment, awareness was assessed as follows: a) discrepancy between self- and informant ratings on a questionnaire evaluating executive functioning (BRIEF-A; Roth et al., 2005); b) relationship between BRIEF-A ratings and EF test performance. In relation to performance monitoring, awareness was assessed through comparison of test performance on two EF tests (Trail Making Test and Colour Word Interference; Delis et al., 2001) with self-ratings of that performance, made immediately after the tasks had been completed. As described in Chapter 1, ethical approval was granted by the relevant University and National Health Service ethics committees and written informed consent was obtained from all participants.

6.3.2 Participants

The same sample as that reported in previous chapters and the same inclusion/exclusion criteria were used. People with Parkinson's disease, recruited from local Movement Disorders clinics, were diagnosed according to the UKPDS Brain Bank criteria (Daniel & Lees, 1993), and were in the mild to moderate stages of the disease (Hoehn & Yahr, 1967). They had normal general cognition, as indicated by an Addenbrooke's Cognitive Examination – Revised (ACE-R) score ≥ 82 (Mioshi et al., 2006) and an MMSE score ≥ 24 (Folstein et al., 1975), and no significant depression, as indicated by a Hospital Anxiety and Depression Scale depression score ≤ 11 (Snaith & Zigmond, 1994). Controls were recruited from various community sources (e.g. over-50s clubs, University of the Third Age branches, church

groups), had normal general cognition, as indicated by an ACE-R score ≥ 82 (Mioshi et al., 2006) and an MMSE score ≥ 24 (Folstein et al., 1975), and no significant depression, as indicated by a Geriatric Depression Scale (GDS-15) score ≤ 5 (Burke et al., 1991; Sheikh & Yesavage, 1986). Informant ratings were provided by people who knew the participants very well (e.g. spouses, adult children or close friends). All participants were fluent in English and had adequate eyesight and hearing.

6.3.3 Measures

The following measures from the wide database were used in this analysis.

Cognitive screening

The Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi et al., 2006) assesses five cognitive domains: attention and orientation, memory, verbal fluency, language and visuospatial abilities. The maximum total score of 100 indicates error-free performance. The ACE-R also provides an MMSE score (Folstein et al., 1975).

Executive functions

The Trail Making Test (TMT) of the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) consists of five visual-motor tasks assessing basic visuospatial and motor skills (TMT 1, 2, 3, and 5), and flexibility in thinking (TMT 4), which is regarded as one of the core EF abilities (Royall et al., 2002). In TMT 1 participants cross out all instances of the number 3 on a sheet of paper. In the following three conditions participants draw a line connecting numbers (TMT 2), letters (TMT 3) or numbers and letters in alternating sequence (TMT 4) in ascending order. In TMT 5 participants draw a line connecting circles in the indicated order. Greater time to complete each task indicates poorer performance. A ratio score TMT 4/TMT 2 is suggested as the most accurate index of EF that differentiates EF from visuospatial and

motor abilities (equivalent to TMT B/TMT A in a widely used version of the TMT) (Arbuthnott & Frank, 2000; Delis et al., 2001). Raw scores for each condition (in seconds) are converted to age-scaled scores (M = 10, SD = 3). For the purposes of this study, the age-scaled scores were classified into five bands: impaired (≤ 5), below average (6-8), average range (9-11), above average (12-14) and superior (≥15). The five bands formed a five-point scale (1 to 5) with lower scores indicating worse test performance. The scale was used for comparing test performance with self-appraisal of that performance (as reported in Martyr et al., 2012). See details in the 'Planned analyses' section below.

The Color-Word Interference test (CWI) of the D-KEFS (Delis et al., 2001) assesses inhibition and flexibility in thinking. There are two baseline conditions (naming the ink colour of colour patches – CWI 1, and reading a list of colour names in black ink – CWI 2), and two higher-level conditions, naming the dissonant ink colour instead of reading the colour name (CWI 3, inhibition; the traditional Stroop task), and switching between naming the dissonant ink colour and reading the word (CWI 4, inhibition and flexibility in thinking). As in the TMT, raw scores (time to complete the task) are converted to age-scaled scores. For the purposes of this study, scores were then classified into five bands. PwPD completed both the TMT and the CWI, and controls completed the TMT only.

EF-related behavioural problems

The Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A; Delis et al., 2001) provides information about executive functioning (self-regulation skills) in the everyday environment, as rated by participants and informants in two parallel questionnaires (self and informant versions). Using a 3-point scale (never, sometimes, often; scored 1, 2, 3 respectively) participants indicate which of the 75 behaviours described have

been a problem during the past month. Higher Global Executive Composite scores (GEC, range 70-210) indicate more reported problems in regulating behaviour and emotional responses, distributing and sustaining attention, and solving problems. The GEC scores are converted to age-scaled T scores (M = 50, SD = 10), which indicate whether the reported level of difficulty suggests clinically significant problems in EF (T ≥ 65, 1.5 SD above the mean).

Premorbid IQ

The National Adult Reading Test (NART; Nelson & Willison, 1991) estimates lifelong intellectual ability. Participants read aloud 50 phonetically irregular words. The number of words pronounced incorrectly is converted into an estimated IQ score, with more errors producing a lower estimated IQ score.

Mood

PwPD completed the Hospital Anxiety and Depression Scale (HADS; Snaith & Zigmond, 1994), a self-rating questionnaire assessing levels of depression and anxiety, validated for use in PD (Schrag et al., 2007). The 14 questions form two subscales: HADS-Anxiety and HADS-Depression. Higher scores indicate higher levels of self-rated anxiety/depression. This study adopted the cut-off of 11 that has been suggested for depression screening purposes (Crawford et al., 2001). Healthy controls completed the Geriatric Depression Scale (GDS-15; Sheikh & Yesavage, 1986) (Appendix J), a 15-item scale assessing levels of depression, with higher scores indicating higher levels of self-rated depression. The study adopted the cut-off of ≤ 5 recommended for depression screening (Burke et al., 1991).

Caregiver Burden

Informants of the PwPD completed the Caregiver Burden Inventory (CBI; Novak & Guest, 1989), a 24-item questionnaire describing caregivers' feelings about and responses to the burden of care. The maximum score of 96 indicates the highest levels of caregiver stress.

6.3.4 Procedure and data collection

The majority of participants were visited at home; six PwPD and nine controls chose to meet at the University. PwPD were assessed during their 'on' phase. The assessment took between 1.5 and 3h and was part of a wider study, which included some measures not reported here. Some participants completed the assessment over two shorter visits and some opting to send the self-completion questionnaires by post.

6.3.5 Planned analysis

Prior to analysis the normality of distributions and the homogeneity of variance were assessed (using the Shapiro-Wilk test and a Q-Q plots, and the Leven test, respectively), and non-parametric statistics were employed where appropriate.

Evaluative judgment analysis

Self- versus informant rating of executive functioning. The level of agreement between self- and informant ratings was calculated for the BRIEF-A summary score (GEC) in the form of a Corrected Discrepancy score, which is a rigorous measure correcting for between-subject differences in actual level of scoring (Clare, Whitaker, & Nelis, 2010). The corrected discrepancy score was calculated by subtracting the self-rating from the informant rating (BRIEF-A Informant raw score – BRIEF-A Self raw score) and dividing the difference by the mean value of the two ratings [(BRIEF-A Informant + BRIEF-A Self)/2]. The possible range of corrected discrepancy scores is -1 to 1, with positive values indicating that self-rating is

more positive than informant rating (taken to indicate an overestimation of executive functioning ability), and negative values indicating that self-rating is less positive than informant rating (taken to indicate an underestimation). Discrepancy scores close to 0 indicate close agreement. The discrepancy scores in the three study groups were compared using one-way ANOVA and Bonferroni post-hoc analysis. BRIEF-A summary scores were compared using the Kruskal-Wallis test, and self- and informant ratings within each group were compared using the Wilcoxon Signed Ranks test.

Evaluative judgment of executive functioning versus EF test performance. Correlational analyses (Spearman's *Rho*) examined the relationship between performance on executive tests (TMT 4, CWI 3, and CWI 4; raw scores) and the overall judgment of executive functioning (BRIEF-A score), separately for PwPD with and without executive deficits.

Performance monitoring analysis

Awareness at the performance monitoring level was established by calculating Performance Ratios – the self-evaluation of test performance divided by the test performance band score, for each TMT and CWI condition.

Participants evaluated their performance on TMT and CWI immediately after a task was completed, using a 5-point scale: very poor, poor, alright, good, or very good (scored 1 to 5, respectively) (Appendix K). PwPD and controls rated their performance on each TMT condition and PwPD also rated their performance on CWI. Test performance on each condition was classified into one of five bands, based on the age-scaled scores: impaired, below average, average, above average and superior. This formed a five-point scale (1 to 5) with lower scores indicating worse test performance (as reported in Martyr et al., 2012).

A Performance Ratio score of 1 indicates perfect agreement between test performance and self-appraisal of that performance; values above 1 suggest overestimation of actual performance, and values below 1 indicate underestimation. As the interpretation of the scaled scores of EF tests in terms of the five self-appraisal categories is somewhat arbitrary, the actual values of the ratio need to be interpreted with caution. In contrast, the group comparison of the ratios provides an objective indication of whether PwPD are as accurate as healthy controls in self-appraising their task performance. Performance ratios were logarithmically transformed to ensure a more symmetrical distribution for statistical analysis (Trosset & Kaszniak, 1996) and averaged to provide summary indices separately for TMT and CWI (Mean Performance Ratios). Performance ratios in the three study groups (PwPD with and without executive impairment, and the control group) were compared using one-way ANOVA and Bonferroni or Games-Howell post-hoc analysis.

The relationships between the indicators of awareness (BRIEF-A Discrepancy Scores and Mean Performance Ratios) and other variables of interest were explored using correlational analyses (Spearman's *Rho*).

6.4 Results

6.4.1 Participants

Sixty-five PwPD and 43 controls were included in the study. One person was excluded from the PwPD group due to severe hearing difficulties and one control participant aged 94 was excluded as there are no normative data for the D-KEFS tests and BRIEF-A for people over 90. One-way ANOVA found no significant differences between controls and PwPD with regard to age ($t(106) = -1.23$, $p = .220$), years of education ($t(106) = -1.91$, $p = .059$), NART-

estimated IQ ($t(106) = 1.18$, $p = .240$) or general cognition (as indicated by ACE-R, $t(106) = 1.17$, $p = .243$). See Table 6.1 for demographic characteristics.

PwPD were allocated to one of two groups on the basis of their performance on EF tests: PwPD with normal performance on all three EF tests (TMT 4, CWI 3, and CWI 4) were allocated to the group with normal EF (PwPD_EF+), and PwPD who had impaired performance on one or more of the above tests (scaled score ≤ 5, 1.5 SD below the mean) were allocated to the group with EF deficits (PwPD_EF-). Two participants who did not complete CWI (due to colour blindness) or TMT (due to difficulties with the alphabet) were allocated to PwPD_EF+ on the basis of their normal performance on the other tests.

Table 6.1. Demographic characteristics of the study groups.

	PwPD (n=65)		PwPD_EF- (n=23)		PwPD_EF+ (n=42)		Control (n=43)	
	M (SD)	**Range**	**M (SD)**	**Range**	**M (SD)**	**Range**	**M (SD)**	**Range**
Age	70.11 (8.92)	48-89	72.91(7.25)	57-86	68.57 (9.44)	48-89	72.02 (6.05)	63-86
Education (years)	12.97 (2.98)	5-20	12.41(2.78)	8-18.5	13.27 (3.07)	5-20	13.98 (2.15)	10-16
NART-estimated IQ	113.77 (8.04)[1]	92-128	113.09 (9.13)	92-127	114.15 (7.45)[1]	98-128	111.63 (10.65)	79-126
MMSE	29.48 (0.92)	25-30	29.30 (0.88)	27-30	29.57 (0.41)	25-30	28.63 (1.02)	26-30
ACE-R Total	93.83 (4.41)	82-100	91.61 (4.65)	82-100	95.05(3.80)	88-100	92.86 (3.87)	82-99
Attention/orientation	17.91 (0.34)	16-18	17.91 (0.29)	17-18	17.90 (0.37)	16-18	17.88 (0.32)	17-18
Memory	23.91 (2.32)	15-26	23.00 (2.86)	15-26	24.40 (1.81)	18-26	23.70 (1.97)	18-26
Verbal fluency	11.58 (2.16)	4-14	10.87 (2.49)	4-14	11.98 (1.88)	7-14	11.35 (2.24)	6-14
Language	25.29 (1.05)	22-26	24.87 (1.25)	22-26	25.52 (0.86)	23-26	24.56 (1.37)	21-26
Visuospatial abilities	15.14 (1.06)	12-16	14.96 (0.98)	13-16	15.24 (1.10)	12-16	15.37 (0.85)	13-16
HADS-Depression	4.43 (2.51)	0-10	4.74 (2.65)	1-10	4.26 (2.44)	1-10		
HADS-Anxiety	5.42 (3.52)	1-16	5.35 (3.94)	1-16	5.45 (3.31)	1-14		
GDS							1.51 (1.59)	0-5

(Table 6.1 continues)

(Table 6.1 continued)

	PwPD (n=65) n (%)	PwPD_EF- (n=23) n (%)	PwPD_EF+ (n=42) n (%)	Control (n=43) n (%)
Gender (Male)	30 (46.2)	10 (43.5)	20 (47.6)	18 (41.9)
IQ Below average (<90)	0	0	0	1 (2.3)
IQ Average (90-100)	20 (30.8)	6 (26.1)	14 (33.3)	16 (37.2)
IQ Above average (>110)	45 (69.2)	17 (73.9)	28 (66.7)	26 (60.5)
Socio-economical status				
I Professional	10 (15.4)	2 (8.7)	8 (19.0)	9 (20.9)
II Managerial/technical	28 (43.1)	13 (56.5)	15 (35.7)	20 (46.5)
III N Skilled, non-manual	13 (20.0)	4 (17.4)	9 (21.4)	10 (23.3)
III M Skilled, manual	11 (16.9)	1 (4.3)	10 (23.8)	2 (4.7)
IV Partly skilled	3 (4.6)	3 (13.0)	0	1 (2.3)
V Unskilled	0	0	0	1 (2.3)
Relationship with informant				
Spouse/Partner	45 (69.2)	17 (73.9)	28 (66.7)	34 (79.1)
Parent/Child	3 (4.6)	1 (4.3)	2 (4.8)	3 (7.0)
Other family member	0	0	0	2 (4.7)
Friend	2 (3.1)	1 (4.3)	1 (2.4)	3 (7.0)
No informant	15 (23.1)	4 (17.4)	11 (26.2)	1 (2.3)

PwPD_EF- – PwPD with EF deficits; PwPD_EF+ – PwPD with normal EF; M – Mean; SD – Standard deviation; ACE-R – The Addenbrooke's Cognitive Examination - Revised; HADS – Hospital Anxiety and Depression Scale; GDS – Geriatric Depression Scale; [1]n=64 in PwPD and n=41 in PwPD_EF+

One-way ANOVA found no significant differences between the control group, PwPD_EF+ and PwPD_EF- in age (F(2,105) = 3.11, p = .049, not significant in post-hoc analysis), years of education (F(2,105) = 2.60, p = .079) or NART-estimated IQ (F(2,105) = 0.79, p = .457). There was a significant group difference in general cognition (ACE-R, F(2,105) = 6.19, p = .003; PwPD_EF-, controls < PwPD_EF+, significant at p < .05 in post-hoc analysis). The comparison of ACE-R subscales indicated no group effect for Attention and orientation, Verbal fluency and Visuospatial abilities. There was a significant group effect for Memory (F(2,105) = 3.35, p = .039; not significant in post-hoc analysis) and for Language (F(2,105) = 7.42, p = .001; PwPD_EF-, controls < PwPD_EF+ significant at p < .001 in post-hoc analysis. PwPD_EF+ and PwPD_EF- were similar in terms of disease duration (t(33.99) = 1.07, p = .294) and the Total Daily Levodopa Equivalent Dose (t(62) = 1.11, p = 270), as indicated by an independent-samples t-test. See Table 6.2 for detailed PD characteristics.

Table 6.2. Disease characteristics and EF test performance in PwPD groups.

	PwPD			PwPD_EF-			PwPD_EF+		
	n	**M (SD)**	**Range**	**n**	**M (SD)**	**Range**	**n**	**M (SD)**	**Range**
PD duration (months)[1]	65	71.97 (50.42)	7-216	23	81.93 (61.60)	7-216	42	66.51 (42.96)	11-180
LED[2]	64	579.19 (556.35)	0-3125	22	685.84 (690.38)	0-3125	41	523.32 (471.36)	0-2145.75
H&Y	59	1.34 (0.57)	1-3	18	1.53 (0.55)	1-2.5	41	1.33 (0.57)	1-3
CBI	42	12.45 (10.55)	0-46	18	17.61 (10.38)	5-46	24	8.58 (9.08)	0-39
TMT4 (scaled)[3]	64	8.77 (4.62)	1-15	23	4.04 (4.00)	1-13	41	11.41 2.18)	7-15
CWI3 (scaled)	64	10.14 (3.74)	1-15	23	7.13 (4.33)	1-14	41	11.83 (1.89)	7-15
CWI4 (scaled)	64	9.55 (3.47)	1-15	23	6.61 (3.38)	1-12	41	11.20 2.22)	6-15

(Table 6.2 continues)

(Table 6.2 continued)

	PwPD n (%)	**PwPD_EF-** n (%)	**PwPD_EF+** n (%)
PD Medication			
Levodopa	39 (60.0)	18 (78.3)	21 (50.0)
Dopamine agonists	40 (61.5)	11 (47.8)	29 (69.0)
Rasagiline	33 (50.8)	10 (43.5)	23 (54.8)
Entacapone	11 (16.9)	4 (17.4)	7 (16.7)
Amantadine	4 (6.2)	3 (13.0)	1 (2.4)
Apomorphine	1 (1.5)	1 (4.3)	0
None	3 (4.6)	1 (4.3)	2 (4.8)
Hoehn and Yahr[4]:			
Stage I	41 (63.1)	9 (39.1)	32 (76.2)
Stage II	16 (24.6)	9 (39.1)	7 (16.7)
Stage III	2 (3.1)	0	2 (4.8)
Side of onset:			
Left	24 (36.9)	9 (39.1)	15 (35.7)
Right	31 (47.7)	9 (39.1)	22 (52.4)
Bilateral	10 (15.4)	5 (21.7)	5 (11.9)

PwPD_EF- – PwPD with EF deficits; PwPD_EF+ – PwPD with normal EF; M – Mean; SD – Standard deviation; TMT – Trail Making Test (D-KEFS); CWI – Color Word Interference (D-KEFS); LED – Total Daily Levodopa Equivalent Dose; H&Y – Hoehn and Yahr stage; CBI – Caregiver Burden Inventory; Dopamine agonists – Non ergot-derived dopamine-receptor agonists

[1]Mean value of the time since first symptoms and the diagnosis, as reported by PwPD.

[2]Based on Tomlinson et al. (2010).

[3]TMT4 in the control group: n=42, M=10.83, SD=3.57, Range: 2-15.

[4]There was no rating available for 6 participants (9.2%).

6.4.2 Evaluative judgment

BRIEF-A Self-rating versus BRIEF-A Informant rating

The largest corrected discrepancy scores were observed in PwPD_EF+ (PwPD_EF+ > PwPD_EF > Controls), but the differences were not statistically significant. See details of the one-way ANOVA in Table 6.3a and scaled scores in Figure 6.1.

There was no significant difference in how participants in the three study groups rated their own executive functioning (BRIEF-A Self), or in how informants rated the executive functioning of the participants (BRIEF-A Informant). See details of the Kruskal-Wallis tests in Table 6.3b.

Self- and informant BRIEF-A ratings (compared *within* each study group) were similar in controls and PwPD_EF-, while in PwPD_EF+ participants reported significantly more problematic behaviours than did their informants. See details of the Wilcoxon Signed Ranks test in Table 6.3b.

Table 6.3. Comparisons of BRIEF-A self- and informant summary scales.

a) Between-group comparisons of corrected discrepancy scores for BRIEF-A scales

	PwPD_EF- (n=21)[1]	**PwPD_EF+ (n=40)[2]**	**Control (n=39)[3]**		
	M (SD) range	**M (SD) range**	**M (SD) range**	**Statistics**	***p***
BRIEF-A CD	-0.05 (0.20) -0.38–0.28	-0.14 (0.22) -0.53–0.54	0.04 (0.18) -0.41–0.42	$F(2,79) = 2.31$	.106

Note: The corrected discrepancy scores were calculated for both scales by subtracting the self-rating from the informant rating and dividing the difference by the mean value of the two ratings (BRIEF-A Informant – BRIEF-A Self)/[(BRIEF-A Informant + BRIEF-A Self)/2] to correct for between-subject differences in actual level of scoring. Possible range of scores is -1 to 1.

b) Between-group (PwPD_EF- vs. PwPD_EF+ vs. Control) and within-group (self- vs. informant rating) comparisons of BRIEF-A scales

	PwPD_EF- (n=21)[1]	**PwPD_EF+ (n=40)[2]**	**Control (n=39)[3]**		
	M (SD)	**M (SD)**	**M (SD)**	**Statistics**	***p***
BRIEF-A _R Self	110.38 (24.53)	105.62 (16.09)	101.59 (18.91)	H(2) = 3.33	.189
BRIEF-A _R Inf	107.06 (26.57)	92.67 (19.79)	97.87 (20.98)	H(2) = 3.87	.144
Self *vs* Inf[4]	T = 43.50, *p* = .348	T = 66.50, ***p* = .001**	T = 208, *p* = .195		

Note: Prior to the analyses, the three BRIEF-A validity scales (for both self- and informant ratings) were inspected. Three participants in PwPD had a marginally elevated Inconsistency scale and one participant in PwPD had an elevated Infrequency scale. As directed in the BRIEF-A manual, BRIEF-A responses from all four participants were inspected, and as no further evidence for atypical or unreliable answers was found, these participants' data were included in further analyses.

PwPD_EF- – PwPD with EF deficits; PwPD_EF+ – PwPD with normal EF; M – Mean; SD – Standard deviation; CD – Corrected Discrepancy score

[1]Informants in PwPD_EF- n_i=17.

[2]Informants in PwPD_EF+ n_i =30.

[3]Informants in Control n_i =39.

[4]Wilcoxon Signed Ranks test, based on positive ranks.

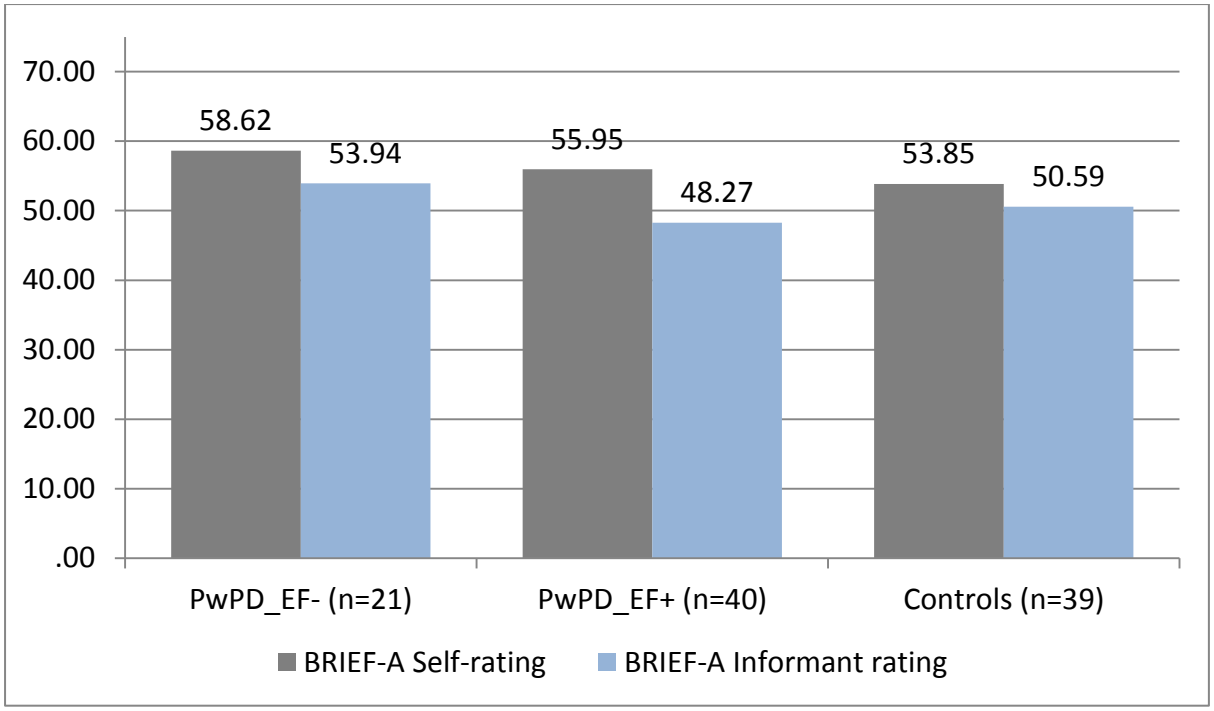

Figure 6.1. Mean age-scaled T scores on the BRIEF-A (M = 50, SD = 10) in the three study groups.

Note. Informants in PwPD_EF- n_i=17; Informants in PwPD_EF+ n_i =30; Informants in Control n_i =39; PwPD_EF- – PwPD with EF deficits; PwPD_EF+ – PwPD with normal EF

Evaluative judgment of cognitive functioning versus objective test performance

The correlational analyses revealed that in PwPD_EF- BRIEF-A self-rating was negatively related to performance on CWI 3, with poorer performance on CWI 3 related to fewer difficulties reported. In PwPD_EF+ both self- and informant BRIEF-A ratings were positively related to performance on CWI 4, with poorer performance associated with more difficulties reported. See details of Spearman's *Rho* correlational analyses in Table 6.4.

Table 6.4. Bivariate correlations between ratings of executive functioning (BRIEF-A) and objective EF test performance.

	PwPD_EF-				PwPD_EF+			
	BRIEF-A_R Self		BRIEF-A _R Inf		BRIEF-A _R Self		BRIEF-A _R Inf	
	r_s	n	r_s	n	r_s	n	r_s	n
TMT ratio	-.027	21	-.217	17	.039	39	-.099	29
CWI 3_R	-.439*	21	-.315	17	.026	40	.191	30
CWI 4_R	-.359	21	-.302	17	.390*	40	.423*	30

Note. Cases excluded pairwise in the event of missing data.

PwPD_EF- – PwPD with EF deficits; PwPD_EF+ – PwPD with normal EF; r_s – Spearman's correlation coefficient; BRIEF-A_R – BRIEF-A raw score; CWI 3_R – Color Word Interference (D-KEFS) raw score; TMT ratio – TMT4/TMT2

* significant at $p < .05$; No Bonferroni adjustment has been made in order to minimise the risk of Type II error (Bender & Lange, 2001; Perneger, 1998).

6.4.3 Performance monitoring

TMT and CWI Performance Scores *versus* Self-ratings

The comparison of mean Performance Ratios for TMT and CWI indicates that PwPD_EF- were significantly less accurate (more positive) in appraising their performance than other study groups. While mean test performance of PwPD_EF- was significantly worse than in other groups, their self-appraisals were comparable to those of other groups. See details of the one-way ANOVAs (TMT) and the t-tests (CWI) in Table 6.5.

Table 6.5. Descriptive information on variables used for calculating performance ratios and comparison of performance ratios in the study groups.

a) Mean scaled scores, test performance band scores, and self-evaluation of test performance for TMT and CWI.

	PwPD_EF-		PwPD_EF+		Control		
Mean scores	**M (SD)**	**Range**	**M (SD)**	**Range**	**M (SD)**	**Range**	***p***
TMT SS	6.28 (1.91)	3.20-9.20	10.08 (2.12)	5.40-13.20	10.43 (2.31)	5.40-14.00	<.000[1]
TMT TP band	1.98 (0.50)	1.40-2.80	3.05 (0.67)	1.80-4.00	3.17 (0.70)	1.40-4.20	<.000[2]
TMT Self-evaluation	3.20 (0.51)	2.40-4.00	3.26 (0.50)	2.40-4.00	3.16 (0.53)	2.20-4.00	.778[3]
	n=10		n=20		n=42		
CWI SS	7.70 (2.67)	2.50-11.25	10.97 (1.60)	7.50-13.50			<.000[4]
CWI TP band	2.38 (0.72)	1.25-3.50	3.40 (0.59)	2.50-4.25			<.000[5]
CWI Self-evaluation	3.78 (0.58)	3.00-4.75	3.80 (0.53)	3.00-5.00			.661[6]
	n=11		n=23				

SS – Mean Scaled Score; TP band – Mean test performance band score based on scaled score; Self-evaluation – Mean Self-evaluation of test performance score

[1] $F(2,69) = 514.54$, PwPD_EF- < PwPD_EF+, Control.

[2] $F(2,69) = 512.93$, PwPD_EF- < PwPD_EF+, Control.

[3] $F(2,71) = 50.25$.

[4] $t(32) = 524.39$, PwPD_EF- < PwPD_EF+.

[5] $t(32) = 524.52$, PwPD_EF- < PwPD_EF+.

[6] $t(31) = 520.44$.

b) Between-group comparison of TMT and CWI Performance Ratios (PR).

	PwPD_EF-		PwPD_EF+		Control			
	n	**M (SD)**	**n**	**M (SD)**	**n**	**M (SD)**	***F***	***p***	**Post-hoc[1]**
TMT1 PR	11	2.60 (1.43)	21	2.17 (1.04)	42	1.87 (1.09)	$F(2,71) = 2.56$	.085	ns
TMT2 PR	11	2.56 (1.20)	21	1.28 (0.31)	41	1.25 (0.52)	$^{1}F(2,71) = 17.22$	<.000	EF->EF+,Ctrl
TMT3 PR	11	2.13 (1.35)	21	1.23 (0.38)	42	1.28 (0.62)	$^{1}F(2,71) = 5.50$	.006	ns in post-hoc
TMT4 PR	11	1.85 (0.96)	21	1.01 (0.32)	42	1.20 (0.51)	$F(2,71) = 7.69$	.001	EF->EF+,Ctrl
TMT5 PR	10	1.78 (0.55)	20	1.55 (0.67)	42	1.35 (0.46)	$F(2,71) = 3.14$	.050	ns in post-hoc
TMT MPR	10	2.22 (0.70	20	1.41 (0.39)	41	1.37 (0.38)	$F(2,68) = 12.03$	<.000	EF->EF+,Ctrl
CWI1 PR	11	2.14 (1.17)	23	1.48 (0.57)			$t(32) = 2.07$	.047	EF->EF+
CWI2 PR	11	1.52 (0.56)	23	1.39 (0.38)			$t(32) = 0.60$	.553	ns
CWI3 PR	11	2.03 (0.95)	23	0.95 (0.20)			$t(12.90) = 4.74$	<.000	EF->EF+
CWI4 PR	11	1.58 (0.63)	23	0.91 (0.28)			$t(32) = 4.22$	<.000	EF->EF+
CWI MPR	11	1.82 (0.66)	23	1.18 (0.26)			$t(32) = 4.02$	<.000	EF->EF+

Note. The Performance Ratio scores were transformed using natural logarithms to improve distribution prior to comparison analyses.

PwPD_EF- – PwPD with EF deficits; PwPD_EF+ – PwPD with normal EF; M – Mean; SD – Standard deviation; PR – Performance Ratio; TMT – Trail Making Test (D-KEFS); CWI – Color Word Interference (D-KEFS); TMT MPR – Mean Performance Ratio for TMT subtests; CWI MPR – Mean Performance Ratio for CWI subtests

[1]Games-Howell post-hoc correction for unequal variances.

Bivariate Correlations of Awareness Indicators and Other Variables of Interest

Table 6.6 shows Spearman's correlations between the awareness indicators and other variables in the PwPD group. Higher BRIEF-A corrected discrepancy scores (greater differences between self- and informant ratings) were associated with higher stress reported on the Caregiver Burden Inventory. Higher Mean Performance Ratios (greater discrepancies between self-appraisal and actual test performance) were associated with poorer general cognition (lower ACE-R).

Table 6.6. Spearmans's rho correlations of awareness indicators and other variables in PwPD.

		Age	NART IQ	CBI	HADS-D	HADS-A	ACE-R	H&Y	LED	PD duration
BRIEF-A	r_s	-.029	-.284	**.526****	-.065	.057	-.279	-.058	-.116	.051
CD	n	45	44	39	45	45	45	41	45	45
logTMT	r_s	.142	.115	.420	.102	.030	**-.502****	.254	.097	.101
MPR	n	30	30	22	30	30	30	27	30	30
logCWI MPR	r_s	.175	.093	.046	-.116	.075	**-.471****	.254	.240	.105
	n	34	34	25	34	34	34	30	34	34

Note. Cases excluded pairwise in the event of missing data. The Performance Ratio scores were transformed using natural logarithms to improve distribution prior to analysis. No Bonferroni adjustment has been made in order to minimise the risk of Type II error (Bender & Lange, 2001; Perneger, 1998).

BRIEF-A CD – Corrected Discrepancy for BRIEF-A BRI; BRIEF-A MI CD – Corrected Discrepancy for BRIEF-A MI; logTMT_MPR –logarithm of Mean Performance Ratio for TMT subtests; logCWI MPR – logarithm of Mean Performance Ratio for CWI subtests; CBI – Caregivers Burden Inventory; HADS-A – HADS Anxiety; HADS-D – HADS Depression; LED – Total Daily Levodopa Equivalent Dose

** significant at $p < .01$.

6.5 Discussion

The present study investigated awareness of executive functioning in PwPD with and without EF deficits, and in healthy controls. At the evaluative judgment level PwPD with EF deficits were found to be as accurate as PwPD with normal EF and healthy older people. At the performance monitoring level, PwPD_EF- were found to significantly overestimate their performance on EF tests in comparison to PwPD_EF+ and healthy older people, which is a novel finding in PwPD. The overestimation was particularly profound in the more demanding tasks, and might be related to deficits in executive control processes. Larger BRIEF-A discrepancies were related to higher levels of caregiver burden, and higher performance ratios were related to poorer general cognition.

6.5.1 Evaluative judgment level

Self-rating versus informant rating. At the evaluative judgment level, awareness of executive functioning was operationalised with a discrepancy score between self- and informant ratings. The BRIEF-A corrected discrepancy scores were similar in all study groups, suggesting that PwPD (with and without EF deficits) are as accurate in self-appraisal of their executive functioning as healthy older people. As far as can be determined, this is a new finding, as a discrepancy score approach has not been previously used to compare awareness in PwPD and healthy controls. The examination of the discrepancy scores is different from the direct comparison of self *vs.* informant ratings, as it clarifies whether the level of agreement is similar across groups, regardless of whether the two ratings in a particular study group are comparable or not. Sitek, Soltan, et al. (2011) used a discrepancy score approach to investigate memory awareness in PD, but they examined the score in relation to objective memory tests, and not to a control group. Clare et al. (2010) compared

memory awareness in people with Alzheimer's disease (AD) and healthy controls using a corrected discrepancy score approach and found that the discrepancies were significantly greater in the AD group than in controls, suggesting decreased awareness of memory impairment. At the same time, the AD participants did rate their memory significantly less positively than controls, suggesting some acknowledgment of their deficits. In the present study, all three participant groups reported on average the same number of EF-related difficulties, while it was expected that PwPD_EF- would report more EF-related difficulties. Given their impaired performance in EF tests, the absence of difference may suggest that PwPD_EF- acknowledge their difficulties only partially.

In the present study, all self-reports were higher than corresponding informant reports, which is consistent with studies comparing self- and informant ratings of executive functioning (Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Rabin et al., 2006; Roth et al., 2005). The difference was statistically significant only in PwPD_EF+, in line with the study of McKinlay, Grace, et al. (2008), where PwPD with normal general cognition (MMSE score > 25, no EF tests included) self-reported *more* difficulties than their informants. PwPD_EF+ may in fact have some subtle deficits experienced internally as a change in cognitive processing, which is impossible for the carer to observe, hence resulting in discrepant appraisals (McKinlay, Grace, et al., 2008). In contrast, deficits in PwPD_EF- may be more substantial and therefore evident to the carers, resulting in more similar ratings.

Self- and informant ratings versus objective measures. The interpretation of discrepancies between self- and informant ratings in terms of degree of awareness is not straightforward, as it depends on the accuracy of informant ratings prone to influence by social and interpersonal factors or the degree of stress or burden experienced (Clare, 2004), and may

be affected by the impossibility of observing some aspects of internal cognitive processing (McKinlay, Grace, et al., 2008). It has been argued that comparing self-ratings to objective test performance provides a useful approach, as it eliminates that bias (Dalla Barba, Parlato, Iavarone, & Boller, 1995; McLoughlin, Cooney, Holmes, & Levy, 1996).

In PwPD_EF+, higher BRIEF-A ratings (both self- and informant) were related to poorer performance in CWI 4, while in PwPD_EF- there was a significant correlation between BRIEF-A self report and CWI 3. These correlations would suggest that the BRIEF-A ratings offer a degree of accuracy, and that inhibition and switching abilities assessed by CWI may overlap with some aspects of the executive difficulties elicited in the BRIEF-A. However, the pattern of correlations between BRIEF-A and EF tests was not consistent, as other correlations were non-significant. Non-significant relationships between EF tests and questionnaire-based ratings have previously been reported (Koerts et al., 2012; Rabin et al., 2006), and have been interpreted as a consequence of the generally low ecological reliability of EF tests and a lack of overlap between the difficulties assessed by EF tests and the kinds of cognitive failures listed in the BRIEF-A (Goldberg & Podell, 2000; Manchester et al., 2004).

6.5.2 Performance monitoring level

As far as can be determined, this is the first study to report on the accuracy of self-appraisal of executive task performance in PwPD. PwPD_EF- overestimated their performance in EF tests significantly more than PwPD_EF+ and controls, particularly in more challenging tasks (TMT 4, CWI 3 & 4). While the exact values of the ratios might reflect the calculation method, the group comparison *objectively* demonstrates that PwPD_EF- were significantly less accurate. It has been argued that cognitive processes have greater impact on self-appraisal of performance on a given task than on general evaluation of cognitive

functioning, as the former requires an EF-related ability to efficiently distribute attention between the task itself and self-appraisal (Clare, Marková, et al., 2011). This notion is supported by the present study where poorer performance monitoring was associated with poorer general cognition, in line with studies reporting an association between overestimation of test performance and poorer general cognition and EF in people with dementia (Bettcher, Giovannetti, Macmullen, & Libon, 2008; Clare et al., 2010; Graham, Kunik, Doody, & Snow, 2005). Executive control has been previously reported as impaired in PwPD (West, Ergis, Winocur, & Saint-Cyr, 1998; Zgaljardic et al., 2006); it is therefore not surprising that PwPD_EF- exhibited difficulties in self-appraisal of task performance, even though they were allocated to the impaired group based on tasks which do not specifically assess task-monitoring abilities (Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004; Zgaljardic et al., 2006).

6.5.3 Correlates of decreased awareness

Awareness is shaped by a number of factors, and might be prone to psychosocial influences, especially at the evaluative judgment and meta-representational levels (Clare, Marková, et al., 2011). This notion was illustrated in the correlational analysis; while poorer performance monitoring was associated with poorer general cognition, lower level of agreement between ratings (greater discrepancy in BRIEF-A) was related to higher levels of caregiver burden. Caregiver burden has not been previously examined in relation to awareness in PD, but it might have a profound impact on informant ratings, as is consistently reported in dementia studies (Clare et al., 2012; Jorm et al., 1994; Rymer et al., 2002). Discrepancy scores were not correlated with depression, which is different to findings from other PD studies (Koerts et al., 2012; Sitek, Soltan, et al., 2011) and might result from the relatively low levels of depression in the study groups.

6.5.4 Limitations

Some limitations of the present study must be taken into account when interpreting the findings. The interpretation of EF test results is complicated as performance may reflect various lower and higher level cognitive functions. We included PwPD with normal global cognition and controlled for potential motor impairment on the TMT, which increases the reliability of test interpretation. However, the potential role of non-executive deficits for EF performance and awareness level in PwPD needs to be acknowledged, as the two groups distinguished on the basis of performance on EF tests may possibly differ from each other in respect to other non-executive abilities, such as language. Further research might be needed to clarify the relationship between awareness and non-executive abilities. Only two tests of EF were used to distinguish between participants with normal and impaired EF. TMT and CWI capture only some aspects of EF related to inhibitory control and mental switching, and including more tasks would facilitate more accurate identification of PwPD with EF deficits. Our sample of PwPD with EF impairments was relatively small, which limits the potential to generalise these findings. EF tests are different from tasks encountered by PwPD in daily life, and this might have added to the inaccuracy of self-appraisal. It would be interesting to examine the accuracy of performance monitoring in more ecologically valid tasks, and investigate how that accuracy relates to everyday functioning (e.g. driving, medication adherence).

6.5.5 Conclusions

Accurate self-appraisal and performance monitoring are crucial for independent and safe day-to-day functioning. This study demonstrates that while PwPD accurately acknowledge their deficits at the general level, they may lack capacity to recognise their limitations while performing specific tasks, which may have implications for functional abilities. Performance

monitoring is a new approach in assessing awareness in PD, with the results supporting the view that awareness at the evaluative judgment level involves different processes than those required for accurate monitoring of one's own performance. Future studies could explore the potential consequences of inaccurate self-appraisal for everyday functioning and examine strategies to prevent possible excess disability associated with limited awareness of functioning and performance.

Chapter 7

Discussion

7.1 Introduction

This thesis aimed to extend our understanding of executive functions in people with PD by clarifying the pattern of executive impairment in early stage PD, establishing the impact of executive deficits on quality of life in PwPD and their families, and assessing the accuracy of PwPD in acknowledging their limitations. These areas were important to investigate to facilitate better understanding of the subjective experience of PD and identification of specific needs. These are the key objectives for arranging health services around the subjective needs of PwPD, which is regarded as a priority by policy makers and service users (Department of Health, 2001; Institute of Medicine, 2001; Van der Eijk et al., 2011).

In the following sections the results of the thesis will be summarised and discussed with regard to the research questions and existing research evidence. Then, theoretical implications will be considered and recommendations for future research presented. Finally, implications for clinical practice will be discussed.

The thesis was focused around four overarching research questions, which are listed in the following sections along with the key findings for each research question.

The research questions were addressed with a meta-analytic approach (research question 1) and quantitative analyses based on cross-sectional data from a sample of 65 PwPD (research questions 2 – 4), 50 caregivers of PwPD (research questions 3 and 4), and 43 healthy controls (research question 4). PwPD completed an assessment covering executive functions, awareness, QoL, and health status, and caregivers rated the executive functioning of PwPD and their own level of burden associated with caring for a PwPD. Healthy controls completed assessments of executive functions and awareness.

7.2 Summary of the findings

Research question 1. What pattern of executive impairment can be identified from the research literature on EF in people with early stage PD without dementia, and what are the critical issues for improving consistency in this field?

There is a wealth of research examining EF in PD, but studies have produced mixed findings. In Chapter 2 the literature on EF in PD was systematically reviewed and results from a homogeneous group of studies were synthesized in a series of meta-analyses. The complexity of the literature was demonstrated in that the EF concept was operationalised in terms of 30 abilities and tested by 60 measures, frequently without a clearly-articulated theoretical framework. Such difficulties associated with defining and assessing cognitive constructs are frequently listed in theoretical discussions of EF (Chan et al., 2008; Rabbitt, 1997) and cognition in general (Cohen, 2000). The review indicated that methodological challenges in defining and assessing EF may have a substantial impact on the clarity of research evidence in PD.

Despite these challenges, the results of the meta-analyses were surprisingly consistent, as they indicated that in all five tests of EF included in the analyses PwPD performed significantly worse than healthy controls. The study demonstrated the potential of a meta-analytic approach in clarifying complex literature in areas such as EF in PD. The approach has been employed previously in PD studies and has offered clarification for a number of research questions, for example with regard to the magnitude of cognitive decline (Muslimovic et al., 2007), effectiveness of exercise for PwPD (Goodwin, Richards, Taylor, Taylor, & Campbell, 2008), or associations between PD and cigarette smoking and coffee drinking (Hernán, Takkouche, Caamaño-Isorna, & Gestal-Otero, 2002). The consistent

results of the meta-analyses might be related to the fact that PwPD in the included studies were relatively similar with regard to severity of motor symptoms, depression level and global cognition. As these clinical characteristics may be related to performance on EF tests (Locascio, Corkin, & Growdon, 2003; Uekermann et al., 2003), the homogeneity in the included studies could possibly contribute to less variability in the data, allowing the group differences to emerge more prominently. Therefore, it seems that the clarity of the research evidence could be improved by better precision in describing study samples, and ideally by employing more rigorous inclusion criteria to facilitate higher homogeneity in the individual study groups.

While the consistency of the presented results might suggest impairment across the whole spectrum of EF, the meta-analyses synthesized only part of the existing evidence, as only five out of 60 measures of EF were included. There is no rationale for assuming that these five tests constitute a comprehensive assessment of EF. More importantly, the meta-analysis reported only small differences between PwPD and controls, and the clinical significance of the reported deficits on standard tests of EF is not clear (B. A. Wilson et al., 1997).

Research question 2. Which areas of EF are particularly problematic in early stage PD?

The study reported in Chapter 3 extended the results of the meta-analyses by specifying the areas which seem to be particularly problematic in early stage PD. Performance on the nine standard tests of EF was analyzed with a data-driven approach which identified two distinctive groups of EF tests, one consisting of attentional control tasks and the other consisting of abstract reasoning tasks. The study demonstrated that these two distinctive aspects of EF might be differentially affected in early PD, with PwPD showing more

impairment on tasks requiring attentional control than on tasks requiring abstract reasoning. These findings supplement the results of the meta-analyses reported in Chapter 2, as most of the EF tests on which impairments were identified seem to rely predominantly on efficient attentional control. The results are also in line with the current understanding of the neuronal basis of EF and the neuropathology underlying EF impairment in PD, as attentional control is identified as closely related to the function of prefrontal cortex and the striatum, which is thought to be compromised in PD (Bonelli & Cummings, 2007; Dauer & Przedborski, 2003; E. K. Miller & Cohen, 2001). It has also been reported that deficits in attentional control in PD may be determined by COMT genotype (Williams-Gray et al., 2009).

The significance of the impairment on attentional control tests needs to be interpreted in the context of the frequency of clinically significant deficits. In the group of PwPD who screened positive for EF deficits, a large proportion (55%) performed within the normal range on all nine tests of EF. Of the remainder, around 30% had a single impaired score. Impaired performance was most frequent on the Trail Making (TM) test; 18.2% of PwPD performed at 1.5 SDs below the mean on the TM test (33% when not controlling for motor impairment), whereas there were no abnormal scores on the Proverb test. Only 15% of PwPD had impaired performance on two or more tests. It should be noted that these are not prevalence rates, as the analysis was based on a subgroup of a convenience sample (52% of the total sample of PwPD), but it demonstrated which areas of EF are particularly problematic in early stage PD.

The results of Chapter 3 may inform test selection for neuropsychological assessment of EF in PD. To date there is no formal recommendation with regard to which

standard tests of EF are most sensitive to executive impairment in PD. The recently published diagnostic criteria for PD-MCI (Litvan et al., 2012) included examples of tests that might be used in PD, but the list is not based on evidence from PD studies. The results suggest that among the nine tasks comprising the D-KEFS, the switching conditions of the Trail Making, Color-Word Interference, and verbal fluency tests are most useful for identifying executive deficits in PD (Delis et al., 2001). This is in line with Muslimovic et al. (2005), who reported that the Trail Making test is the most frequently impaired test of EF in PwPD, and clearly discriminates between PwPD and controls.

Research question 3. How do EF deficits affect quality of life and health status for the PwPD, and the caregiver stress associated with caring for PwPD?

The study reported in Chapter 4 explored how QoL and health status in PwPD, and caregiver burden, are influenced by EF deficits. Previous studies have identified a number of factors impacting on quality of life and subjective health status in PwPD. Quality of life in PwPD and caregiver burden in PD are typically considered in terms of health and motor impairment, but there is increasing evidence that non-motor difficulties may also have a significant impact on quality of life in PwPD and caregiver burden (Den Oudsten et al., 2007a; Hely et al., 2005; Martinez-Martin et al., 2005; Soh et al., 2011). Relatively little attention has been given specifically to EF in this respect. The study presented in Chapter 4 contributed to our understanding of the complex variety of factors influencing well-being in PD by reporting the potential role of EF-related behavioural problems. The regression analyses showed that behavioural problems related to executive functioning, as assessed by the BRIEF-A questionnaire, may contribute to QoL and health status in PwPD, and add to burden for caregivers of PwPD. Similar associations between EF-related behavioural difficulties and

well-being in patients and caregivers were observed in people with Alzheimer's disease (AD) (Bonney et al., 2007). It was also reported that EF-related behavioural difficulties may negatively impact on functional abilities in AD (Boyle et al., 2003; Norton, Malloy, & Salloway, 2001). Better understanding of factors influencing well-being in PwPD will make it possible to develop and implement appropriate interventions, enhancing provision of person-centred care for people diagnosed with PD and their families.

Research question 4. How accurate are PwPD in assessing their overall executive functioning and their performance in a given task?

The objective of the study reported in Chapter 5 was to explore whether PwPD can accurately appraise their own executive deficits. This is an important question, as the inability to adequately assess one's own limitations may have negative implications for PwPD and their caregivers. Awareness has been extensively studied in the area of dementia (Bettcher et al., 2008; Clare, 2004; Clare et al., 2010; Graham et al., 2005), but there is limited evidence with regard to PD, and the existing studies focus on the evaluative judgement level only (Clare, Marková, et al., 2011).

The study presented in Chapter 5 employed a comprehensive methodology to provide information about the multifaceted concept of awareness. Awareness was evaluated at two levels: the evaluative judgment level and the performance monitoring level (Clare, 2004). The evaluative judgment level of awareness was assessed with a discrepancy score approach. This approach, which has not been previously employed in PD studies, indicates not only whether self- and informant ratings are similar, but also whether the scope of differences is similar across the study groups. PwPD with executive deficits and PwPD with normal EF expressed similar levels of accuracy to healthy controls, although self-

ratings by PwPD tended to be more negative than informant ratings in all three groups. This pattern is different form the one observed in Alzheimer's disease (AD), where patients tend to overestimate their memory functioning, and rate themselves more positively than they are rated by their caregivers (Clare et al., 2010). People with traumatic brain injury (TBI) also tend to report less impairment than their families and clinicians, particularly with regard to cognitive and behavioural abilities, and to a lesser extent with regard to physical functioning (Sherer et al., 1998). In AD, discrepancies in the appraisal of memory functioning were reported to increase stress in caregivers and impact on the quality of the caregiving relationship (Aalten et al., 2005; Nelis et al., 2011). In PD, despite the different direction of the discrepancies, a lower level of agreement between self- and informant rating was related to higher levels of caregiver burden, as observed in Alzheimer's disease (Nelis et al., 2011). Better understanding of the association between differences in appraising executive functioning and stress in caregivers could possibly lead to improvements in supporting PwPD and their caregivers, and further studies are needed to explore this relationship.

To assess awareness at the performance monitoring level, the accuracy ratio for self-evaluation *versus* objective test performance was calculated and compared across the study groups. The results showed that PwPD with executive impairments were less accurate than PwPD without executive impairments and controls. Decreased awareness at the performance monitoring level was observed in people with AD, who overestimated performance on a memory test (Clare et al., 2010), and in people with brain injury, who acknowledged a smaller proportion of errors than healthy controls in a naturalistic tasks (Hart, Giovannetti, Montgomery, & Schwartz, 1998). The results presented in Chapter 5 suggest that PwPD who have executive deficits may lack the ability to recognise their

limitations while performing specific tasks, which may have implications for their functional abilities. Lower awareness in dementia was found to be associated with older age, less anxiety and lower general cognition (Clare, Whitaker, et al., 2011), and inaccurate appraisal of behavioural limitations in people with TBI may be related to cognitive and emotional disturbances (Prigatano, Altman, & O'brien, 1990). The mechanisms underlying inaccurate performance monitoring in PD require further investigation.

7.3 Methodological considerations

Researching EF is associated with a number of challenges that might have impacted on the presented studies, and these potential limitations should be considered when interpreting the results of this thesis.

While numerous definitions and tests of EF are available, there is no consensus about a comprehensive theory of EF that can provide a point of reference for test selection and interpretation in clinical studies (Salthouse, 2005). The interpretation of EF tests is further complicated by the fact that performance on these tests might be influenced by non-executive cognitive functions also involved in test performance. To improve reliability of test interpretation in the present study, the participant group included only PwPD who performed within the normal range on a screening test of general cognition, and employed measures that involve minimum motor control. Nevertheless, the potential role of non-executive deficits in EF performance needs to be acknowledged.

The heterogeneous pathology of PD is associated with numerous motor and non-motor symptoms which may also influence performance on EF tests in a number of ways (Colman et al., 2009; Kobayakawa et al., 2008). For example, test performance involves

motor control and speech, which are known to be affected by PD pathology. There are also non-motor symptoms of PD that could affect test results, for example apathy, depression, fatigue, and sleep deprivation (Locascio et al., 2003). It was not possible to fully control for all potential confounds, but to minimize their impact only PwPD in the mild to moderate stages of PD with no clinically significant depression were included, and the assessment was completed during the 'on medication' phase. Nevertheless, the possible impact of PD-related factors needs to be considered when interpreting results of this thesis.

Time-efficient tools for identifying PwPD with potential EF deficits are important in clinical practice. In the studies presented here, PwPD were screened with the Frontal Assessment Battery (FAB), which is reported to have good psychometric properties and is commonly used in research and clinical practice (Lima et al., 2008). However, only a small proportion of PwPD identified by FAB as having EF deficits had abnormal scores on a detailed assessment of EF, while some PwPD who scored above the cut-off on the screening task had abnormal scores on the TM and Color-Word Interference tests. This suggests that the FAB might be sensitive to only one specific profile of executive deficits, while PwPD with other types of EF deficits not captured by FAB were not included in the study presented in Chapter 3. It would therefore be important to investigate in a future study whether the same pattern is evident in a larger group of PwPD not screened for EF deficits.

Interestingly, only the behavioural ratings of EF-related difficulties (BRIEF-A), and not the standard tests of EF (TM test and Color-Word Interference test), made a significant contribution to the regression models of quality of life, health status in PwPD, and caregiver burden. One possible explanation for the differential contribution of EF measures relates to differences in the level of ecological validity. Standard tests of EF are known to have low

ecological validity, as it is questionable to what extent difficulties in drawing a line connecting numbers and letters in ascending order, while alternating between numbers and letters, translates into everyday life (Burgess et al., 1998; Manchester et al., 2004; Rabin et al., 2006; Roth et al., 2005). It is also argued that the structured nature of their administration removes some executive demands and makes them insensitive to some key aspects of EF, such as coping with novelty or organizing and prioritizing tasks (Manchester et al., 2004; B. A. Wilson et al., 1997). Behavioural ratings of EF focus specifically on the aspects of EF that are relevant for everyday functioning, and are therefore likely to be more directly related to well-being. Another interpretation is that the BRIEF-A and standard tests of EF assess different constructs (Toplak, West, & Stanovich, 2013), and that it is the aspect of EF assessed by the BRIEF-A that seems relevant for well-being in PD. The aspect of EF assessed by standard tests of EF seems not to be relevant to well-being, at least not at the level of severity observed in the current study (B. A. Wilson et al., 1997). This argument relates to the ongoing discussion about whether EF is a one executive ability or a group of related executive abilities (Miyake et al., 2000; Stuss & Alexander, 2007). To date, there seems to be no agreement with regard to what abilities should be considered as 'executive' (Edelstyn et al., 2007). Definitions of EF frequently identify successful, socially acceptable goal-oriented behaviour as the key contribution of EF (Burgess & Alderman, 2004; Lezak, 2004). Goal-oriented behaviour might mean overall efficiency in identifying appropriate goals, maintaining motivation and employing appropriate strategies to achieve these goals within a complex social context. This seems to be a broad definition of EF that encompasses motivation, personality, and other non-cognitive abilities (Brown & Pluck, 2000), potentially captured by the BRIEF-A. However, goal-oriented behaviour might also have a substantially different meaning, as it could be interpreted as the ability to manage specific task demands

according to clearly-stated rules in the well-defined context of a testing situation (Ardila, 2008; Stuss & Alexander, 2000). This seems to be the understanding of EF most commonly employed in the PD literature and assessed by the standard tests of EF. However, the behavioural aspect of EF might also need to be assessed to provide a more comprehensive picture of the executive impairment in PD.

Scaled scores on standard tests of EF facilitate the interpretation of test performance in terms of impairment, as they provide an indication of how likely it is that a given score will be observed in a healthy, age-matched population. However, caution is needed when such scaled scores are used for determining executive impairment, as there seems to be no agreement with regard to what constitute a comprehensive assessment of EF, and how many impaired scores are required to conclude that the person has an executive impairment (Ingraham & Aiken, 1996; Liepelt-Scarfone et al., 2011). In the study reported in Chapter 3, 45% of the assessed PwPD had clinically significant impairment on at least one out of nine tests (1.5 SD below mean), but only 15% of PwPD had more than one impaired score. The rates of executive impairment in PD reported in the literature vary from 9% to 50% (Caviness et al., 2007; Foltynie et al., 2004; McKinlay et al., 2009) and the inconsistency may reflect the differences in criteria used.

It should be noted that as PwPD included in the present study were volunteers, there might be under-representation of PwPD with poorer health or who are otherwise overwhelmed by the experience of PD (Bootsma-van der Wiel et al., 2002). The fact that all participants were offered home visits might possibly reduce the impact of poor health on the decision to participate, but nevertheless some PwPD who feel less confident in their cognitive abilities might be less likely to participate in a research project exploring cognition

and well-being in PD. Additionally, in the study presented in Chapter 3, three out of 40 participants identified as having possible EF deficits experienced marked fatigue and completed only first part of the study. This possible recruitment bias could result in these studies reporting a lower level of deficits and distress than is actually present in people diagnosed with PD.

7.4 Directions for future research

The studies presented in this thesis have contributed to our understanding of EF in early stage PD. The findings also raise some further questions and suggest directions for future research.

Establishing the clinical significance of the observed deficits should be an important objective of studies investigating executive functioning in PD, as this seems to be the key information needed to adequately educate and support people who are diagnosed with PD. To establish the clinical significance of EF deficits in PD, future studies need to explore the mechanism of the association between EF-related behavioural problems and subjectively perceived quality of life and health status, and investigate how EF deficits documented by standard tests of EF translate into everyday functioning. Future research should integrate the caregiver's perspective to offer a more comprehensive picture of executive functioning in PD. The caregiver's perspective is particularly relevant in the context of awareness, as it seems that PwPD may not always accurately acknowledge some difficulties in specific tasks. Future studies could explore the potential consequences of inaccurate self-appraisal for everyday functioning, and examine strategies to prevent possible excess disability associated with this problem.

In contrast to the limited guidelines for formal neuropsychological assessment in PD, cognitive screening in PD has attracted considerable attention. Several PD-specific scales are available (Kalbe et al., 2008; Mahieux et al., 1995; Marinus, Visser, Verwey, et al., 2003; Pagonabarraga et al., 2008), some generic measures have been validated for use in PD (Athey et al., 2005; Llebaria et al., 2008; Reyes et al., 2009), and a number of reviews of the available measures have been published (Barone et al., 2011; Chou et al., 2010; Kulisevsky & Pagonabarraga, 2009). The Frontal Assessment Battery (FAB, Dubois et al., 2000) is one of the few scales developed specifically for screening abilities related to frontal lobe functions (Kulisevsky & Pagonabarraga, 2009). The scale has been validated for use in PD studies (Lima et al., 2008); however, future studies might need to more carefully evaluate how the FAB relates to standard tests of EF sensitive to PD-specific deficits, and establish the discriminative properties of the FAB in screening for EF deficits in PD.

The meta-analytic approach proved useful in evaluating the complex literature on EF in PD, and future meta-analytic studies may bring further benefits in the area of understanding cognitive change in PD. This approach is, however, less helpful with regard to evaluating studies employing elaborate experimental paradigms and less frequently used tests, as evidence from such studies cannot be easily synthesized in a meta-analysis. Future studies need to employ more precision in defining executive functions and in selecting and interpreting measures of EF. It might also be beneficial if a formal recommendation of measures sensitive to EF deficits in PD is proposed. Likewise, developing a theoretical framework of EF in PD might help with organizing existing evidence and thus guide future studies.

There is extensive evidence of executive problems in PD, but the personal experience of living with executive deficits seems to be mostly overlooked. Questionnaire-based studies document the complaints of PwPD but do not fully explain the nature of these or the consequences for everyday life. A qualitative approach might prove particularly useful in exploring the subjective experience of PwPD. It could help to clarify the nature of the association between EF-related behavioural problems and the well-being of PwPD and their caregivers, and provide an explanation for the associations and effects observed in quantitative studies. A qualitative approach could help to facilitate better understanding of how PwPD with low scores on standard tests of EF function in their everyday life and could lead to identification of potentially helpful intervention approaches. An in-depth analysis of the general experience of living with PD has been achieved in a small number of interview studies (Bramley & Eatough, 2005; Haahr, Kirkevold, Hall, & Ostergaard, 2010; Marr, 1991), but to date there is no qualitative study focusing specifically on cognitive problems or on the group of PwPD who have cognitive deficits.

7.5 Practical implications of the study findings

Assessment of EF in PD requires careful planning to allow meaningful interpretation of test results. For example, there should be minimum involvement of motor components or the impact of motor function should be controlled in a baseline condition. Neuropsychological assessment should include tests requiring attentional control as these seem to represent the main area of difficulty in EF in early PD. The assessment should also include measures of behavioural aspects of EF, as such ratings provide relevant information about functioning that is otherwise not obtained from standard neuropsychological testing. Employing standard criteria for PD-MCI may assist in more consistent reports of the prevalence rates.

It is widely acknowledged that PD is associated with non-motor as well as motor symptoms (Chaudhuri et al., 2005), and that non-motor complications significantly impact on quality of life in PD (Hely et al., 2005). However, treatment for PD focuses on motor disability, while non-motor disturbances are frequently overlooked and rarely addressed in routine healthcare (Brown et al., 2011). This thesis suggests that EF-related behavioural difficulties might have implications for everyday life in PD and might need to be addressed with rehabilitative techniques, as these are likely to assist in maintaining quality of life in PD.

When considering EF in people diagnosed with PD, the caregiver perspective should be included as this brings unique information relevant for health-related aspects of QoL in PwPD and is particularly important for understanding the burden associated with caring for PwPD. Caregivers' opinions seem particularly relevant in the context of awareness of difficulties. It seems that despite being relatively critical of their own EF when making overall judgements, some PwPD with executive deficits may fail to appreciate the severity of their difficulties when performing specific tasks. Inaccuracies in appraising their own abilities may have consequences for everyday functioning and also impact on caregivers of PwPD, and such inaccuracies need to be considered when assessing functional abilities in PD.

Litvan et al. (2012) emphasise that recognizing cognitive deficits is important because it facilitates early detection of PwPD who are at risk for developing dementia and opens the possibility of offering them appropriate interventions at the pre-dementia stage. So far, it is not clear what pattern of cognitive impairment predicts dementia and whether EF is predictive of dementia in PD; some studies have found EF deficits to be predictive of dementia (Janvin, Aarsland, & Larsen, 2005; Levy et al., 2002), but other studies have not

(Williams-Gray et al., 2009). The results presented in Chapter 4 suggest that even relatively mild executive deficits might be sufficient to negatively impact on PwPD and caregivers, and developing appropriate strategies to help alleviate the impact of these deficits on everyday life may offer an opportunity to improve quality of life, whether or not these deficits will develop into dementia later on.

7.6 Conclusions

Parkinson's disease is a common neurodegenerative disease associated with a plethora of motor and non-motor symptoms, including cognitive decline. Despite substantial research activity in the area, the impact of cognitive decline on the daily lives of people with PD is largely unknown. The results presented in this thesis contributed new knowledge in the context of executive functioning in early stage PD and may lead to greater clarity in future studies on EF in PD.

The reported relationship between executive functioning and well-being in PwPD and caregivers suggests the need for specific rehabilitative interventions, and the findings on awareness of executive functioning in PwPD have practical implications for planning such interventions. Policy guidelines recommend person-centred care as the priority for high quality healthcare, and specify that services need to be arranged around the specific individual needs of the care recipients (Department of Health, 2001; Institute of Medicine, 2001; Van der Eijk et al., 2011). The findings of this thesis can help to improve understanding of the aspects of EF that are most problematic for people diagnosed with PD and the specific factors affecting the subjective quality of life in PD, and may aid development of a PD-tailored protocol for neuropsychological assessment and specific rehabilitative interventions.

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Appendices

Appendix A. Ethical Approval

NHS

Pwyllgor Moeseg Ymchwil Gogledd Cymru (Y Orllewin)
North Wales Research Ethics Committee (West)

Betsi Cadwaladr University Health Board
Ysbyty Gwynedd
Clinical Academic Office
Bangor, Gwynedd
LL57 2PW

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PRIVATE & CONFIDENTIAL
Miss A Kudlicka
PhD Student
Bangor University
School of Psychology
Bangor, Gwynedd
LL57 2AS

21 May 2010

Dear Mrs Kudlicka

Study Title: **Executive functions in people with Parkinson's disease: a comprehensive evaluation**
REC reference number: **10/WNo01/21**
Protocol number: **1**

The Research Ethics Committee reviewed the above application at the meeting held on 20 May 2010. Thank you for attending to discuss the study.

Ethical opinion

Scientific design and conduct of the study:
The Committee concluded that the research design and the proposed analysis were deemed suitable for answering the research question. The Committee queried inconsistencies in the sample size proposed. The CI clarified that the sample size for screening will range from 35 -60. No further ethical issues were raised.

Suitability of the applicant and facilities; community considerations:
The Committee concluded that the Chief Investigator is sufficiently qualified to carry out the project. The local facilities and arrangements are suitable. No further ethical issues were raised.

Anticipated benefits/risks for research participants:
The Committee discussed the anticipated benefits and potential risks to participants.
The Committee queried the procedure to deal with disclosures of malpractice or abuse and the requirement to break confidentiality.
The Committee requested that this is written explicitly in the PIS for participants (both clients and carers) and explicit consent sought. No further ethical issues were raised.

Care and protection of research participants (welfare and dignity):
The Committee was satisfied that the welfare and dignity of potential participants has been taken into account in a professional manner. No further ethical issues were raised

Adequacy and completeness of Participant Information:
The Committee agreed that generally the language used is clear and understandable and all the procedures described in the protocol have been addressed in the Information Sheet, but felt that some minor corrections are needed: No further ethical issues were raised.

Informed Consent process:
The Committee noted that written informed consent is taken as part of a process, with participants having sufficient time to consider the information and an opportunity to ask questions. The Committee queried whether the consent will be free and unchallenged as the clinician will seek consent. The CI clarified that the research team will take consent and the involvement of the clinician will be for identification purposes only. No other ethical issues were raised.

Data protection and participant's confidentiality:
The Committee discussed where and for how long will data be stored, and clarified who will have access to the data. No further ethical issues were raised.

General comments/ missing information/ typographical errors/ application errors:
No ethical issues were raised

Members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Sponsors are not required to notify the Committee of approvals from host organisations.

The Committee requested that the procedure to deal with disclosures of malpractice or abuse and the requirement to break confidentiality is written explicitly in the PIS for participants (both clients and carers) and explicit consent sought.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents
The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
REC application	48801/118507/1/622	10 May 2010
Protocol	1	10 May 2010
Referees or other scientific critique report		22 April 2010
Participant Information Sheet: participants	1	10 May 2010
Participant Information Sheet: informants	1	10 May 2010
Participant Consent Form: participants	1	10 May 2010
Participant Consent Form: informants	1	10 May 2010
GP/Consultant Information Sheets	1	10 May 2010

Interview Schedules/Topic Guides	1	10 May 2010
List (description) of measures/questionnaires	1	10 May 2010
CV Chief Investigator (Mrs A Kudlicka)		07 May 2010
CV Co-Investigator (Dr J V Hindle)		06 May 2010
CV Academic Supervisor (Prof L Clare)		07 May 2010
Evidence of insurance or indemnity	UMAL	01 August 2009

Membership of the Committee
The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review
Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/WNo01/21 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp **Mr David Owen**
Chair

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers"

Copy to: *Sponsor's Representative: Prof Oliver Turnbull, Bangor University*
R&D office for BCUHB - West

North West Wales Research Ethics Committee

Attendance at Committee meeting on 20 May 2010

Committee Members

Name	*Profession*	*Capacity*	*Present*
Dr. Swapna Alexander	Consultant Physician	Expert	Yes
Mr. John Kevan Blomeley	Teacher (retired)	Lay +	Yes
Mrs. Rebecca Burns	Research Nurse (deputy to Mrs. Chester)	Expert	No
Mrs. Kathryn Chester	Research Nurse	Expert	Yes
Dr. Christine Clark	Consultant Obstetrician & Gynaecologist	Expert	No
Dr. Michael Cronin	Consultant Paediatrician (deputy to Dr. Clark)	Expert	Yes
Dr. Derek James Crawford	Consultant Surgeon (Vice-Chairman)	Expert	No
Mrs. Gwen Dale-Jones	PA (retired)	Lay +	Yes
Mr. Hywel Lloyd Davies	Solicitor (Alternate Vice-Chairman)	Lay +	Yes
Mr. Henry Alan Owen Hughes	Pharmacy Professional Services Lead	Expert	Yes
Dr. Mike C Jackson	Consultant Clinical Psychologist	Expert	No
Mr. Clive Robert Jenkins	Consultant GCP Auditor	Lay	Yes
Ms. Gillian Jones	Information Governance Manager	Lay	Yes
Dr. Mark Lord	Consultant Pathologist	Expert	No
Mrs. Mair Martin	Pharmacist (deputy to Mr. Hughes)	Expert	No
Mr. David Owen	Retired Chief Constable (Chairman)	Lay +	Yes
Mr. Paramasivam Sathyamoorthy	Consultant Orthopaedic Surgeon	Expert	No
Dr. Thanthullu Vasu	Consultant Anaesthetist	Expert	Yes
Mr. Christopher John Whitaker	Statistician	Lay	No
Dr. Philip Wayman White	General Practitioner	Expert	Yes

In attendance

Name	*Position (or reason for attending)*
Miss Angela Filippi	Assistant Coordinator

North West Wales Research Ethics Committee
LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	10/WNo01/21	**Issue number:**	2	**Date of issue:**	21 May 2010
Chief Investigator:	Mrs Aleksandra Kudlicka				
Full title of study:	Executive functions in people with Parkinson's disease: a comprehensive evaluation				

This study was given a favourable ethical opinion by North West Wales Research Ethics Committee on [##SF1ClockStopDate##]. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* (1)
Professor L Clare	Professor of Clinical Psychology	Bangor University	North Wales West REC	21/05/2010	

Approved by the Chair on behalf of the REC:

..... (Signature of Chair/Co-ordinator)
(delete as applicable)

A. FILIPPI ..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

Appendix B. Participant Information Sheet

Ysgol Seicoleg
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Fax: (01248) 382599
e-mail: pspa16@bangor.ac.uk
www.psychology.bangor.ac.uk

PARTICIPANT INFORMATION SHEET

Memory, concentration and planning in Parkinson's disease

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and talk to others about the study if you wish. Please ask us if there is anything that is not clear or if you would like further information. Take your time to decide whether you wish to take part.
Thank you for reading this information sheet.

What is the purpose of this study?
Some people with Parkinson's disease (PD), who have problems with walking, stability or precise movements due to PD, also complain about their memory and concentration. Little is known about these problems in PD. In our study, we aim to find out about non-physical difficulties caused by PD. For example, we want to know how common these difficulties are and whether they affect the everyday life of persons with PD. We will also talk to participants to find out what kind of help they might find useful.

Why have I been invited?
You have been invited because you were diagnosed with Parkinson's disease and are attending Movement Disorders clinic. We are looking for 65 people to take part in this study.

Do I have to take part?
You do not have to take part. It is up to you to decide. If you decide to take part in the study, we will ask you to sign a consent form. You can keep this information sheet and please remember you will be free to withdraw from the study at any time without giving a reason. A decision not to take part, or to withdraw from the study, will not affect the standard of care you receive in any way.

What do I need to do if I take part?
We will arrange a meeting for time and place that are convenient for you and that will not disrupt your normal activities. You may take part in the study at Bangor University or at your own home. It might be a good idea to meet during the time when you feel your medication is working well. We will ask you to fill out a number of questionnaires (for example, about your well-being, everyday functioning, mood) and perform some tasks (for example, to remember a list of words, to try to solve a puzzle, or explain how you understand a proverb). We will also ask you to tell us how you cope with your chores and activities in terms of remembering, concentration and planning - we would like to audio-record our conversation for further transcription and analysis. Your partner (or another relative or friend) will also be asked to complete some questionnaires. The study is in two parts. Initially, we would meet with you on one occasion. This visit should last no more than one and a half hours. After this visit, we may ask you to take part in the second stage. This would involve two further visits, each lasting no more than one and a half hours. Taking part in the study does not require any other changes to your routine.

What are the possible risks of taking part?
We do not anticipate that there are any risks to people taking part in this research. You may find some of the tasks a little tiring or frustrating.

What are the possible benefits of taking part?
We do not think you will benefit directly from taking part in this study, although you may find it enjoyable and stimulating to complete the tasks. Also, the results of this research may help improve care for people who have Parkinson's disease in the future.

Will my taking part in the study be kept confidential?
Yes. In normal circumstances all information collected about you during the study will be kept confidential. All data will be stored securely and separately from any of your personal details. Only the researchers involved in the study will have access to this data. However, if the researcher observes or hears something that causes very serious concern about your well-being, it may be necessary to share this information with other professionals. The researcher would make every effort to first inform you of the need to share this information.
Also, the researcher will ask your permission to inform your GP that you are taking part in the study.

What will happen if I don't want to carry on with the study?
You may withdraw from the study at any time without giving a reason and this will not affect the standard of care you receive in any way. We may need to use the data collected before you decide to withdraw.

What if there is a problem?
We do not consider that taking part in the study may cause any risk to you and there are no special compensation arrangements if you are harmed by taking part in the study. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay your legal costs.

If you have a concern about any aspect of this study, you should speak to the researchers and we will do our best to answer your questions and resolve any concerns. If you remain unhappy and wish to complain formally, you can do this through the School of Psychology. The contact details are given below.

Who is organising and funding the research?
The research is being funded by the School of Psychology, Bangor University, and the 125th Anniversary Scholarship award. The project is being led by Mrs Aleksandra Kudlicka (PhD student) and supervised by Professor Linda Clare, a clinical psychologist who works at Bangor University, and Dr John Hindle, Consultant Physician in the Movement Disorders Clinic, Llandudno Hospital.

What will happen to the results of the research?
We will publish the results of the study in scientific journals. All information about participants will be anonymous, so you will not be identifiable in any publication. We can inform you of the findings of the study if you wish.

Who has reviewed the study?
All research in the NHS is analysed by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being and dignity. This study has been reviewed and granted approval by the North West Wales Research Ethics Committee.

Who can I contact for further information?
For more information about this research, please contact:
Mrs Aleksandra Kudlicka
School of Psychology, Bangor University, Bangor, Gwynedd, LL57 2AS
Tel: 01248 383621
Email: pspa16@bangor.ac.uk

Professor Linda Clare
School of Psychology, Bangor University, Bangor, Gwynedd, LL57 2AS
Tel: 01248 388178
Email: l.clare@bangor.ac.uk

Dr John Hindle
Llandudno Hospital, Hospital Road, Llandudno, Conwy, LL30 1LB
Tel: 01492862366
Email: j.v.hindle@nww-tr.wales.nhs.uk

If you have any complaints about the conduct of this study you can contact:
Mr Hefin Francis, School Manager
School of Psychology, Bangor University, Bangor, Gwynedd, LL57 2AS.
Tel: 01248 388339
Email: h.francis@bangor.ac.uk

Thank you for considering taking part in this research study!

Appendix C. Participant Consent Form

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www.psychology.bangor.ac.uk

PARTICIPANT CONSENT FORM

Title of Project: **Memory, concentration and planning in Parkinson's disease**

Name of Researcher: Aleksandra Kudlicka

Patient Identification Number for the study: ☐

	Please initial boxes
1. I confirm that I have read and understand the information sheet (Version 1. 10/05/2010) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I agree to provide some information in the form of an interview with researcher if required, and agree to this being tape-recorded.	☐
4. I agree to my GP being informed of my participation in the study.	☐
5. I understand that the researcher may need to inform other professionals if she observes or hears something that causes very serious concern about my well-being or that of my relative/friend. The researcher would make every effort to first inform me of the need to share this information.	☐
6. I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

Appendix D. Informant Information Sheet

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www.psychology.bangor.ac.uk

INFORMANT INFORMATION SHEET

Memory, concentration and planning in Parkinson's disease

We have invited your partner/another relative/friend to take part in a research study. To gain the full picture of his/her situation we also need to talk to someone that knows him/her very well. For that reason we would like to invite you to take part in the research study as well.

Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and talk to others about the study if you wish. Please, ask us if there is anything that is not clear or if you would like further information. Take your time to decide whether you wish to take part. Thank you for reading this information sheet.

What is the purpose of this study?
Some people with Parkinson's' disease (PD), who have problems with walking, stability or precise movements due to PD, also complain about their memory and concentration. Little is known about these problems in PD. In our study, we aim to find out about non-physical difficulties caused by PD. For example, we want to know how common these difficulties are and whether they affect the everyday life of persons with PD. We will also talk to participants to find out what kind of help they might find useful.

Why have I been invited?
You have been invited because your partner/relative/friend was diagnosed with Parkinson's disease and is attending the Movement Disorders clinic, and has agreed to take part in our study. We are looking for 65 people with Parkinson's disease to take part in this study.

Do I have to take part?
You do not have to take part. It is up to you to decide. If you decide to take part in the study, we will ask you to sign a consent form. You can keep this information sheet and please remember you will be free to withdraw from the study at any time without giving a reason. A decision not to take part, or to withdraw from the study, will not affect the standard of care your partner/relative/friend receives in any way.

What do I need to do if I take part?
We will arrange a meeting time and place that are convenient for you and that will not disrupt your normal activities. You may take part in the study at Bangor University or at your own home. We will ask you to fill out some questionnaires about your well-being and your relative/friend's well-being, everyday functioning, mood and how s/he copes with her/his chores and activities in terms of remembering, concentration and planning. It will take normally up to 30 minutes and can be completed during the meeting with your relative/friend. Taking part in the study does not require any other changes to your routine.

What are the possible risks of taking part?
We do not anticipate that there are any risks to people taking part in this research.

What are the possible benefits of taking part?
We do not think you will benefit directly from taking part in this study. However, the results of this research may help improve care for people who have Parkinson's disease in the future.

Will my taking part in the study be kept confidential?
Yes. In normal circumstances all information collected about you during the study will be kept confidential. All data will be stored securely and separately from any of your personal details. Only the researchers involved in the study will have access to this data. However, if the researcher observes or hears something that causes very serious concern about your well-being or that of your relative/friend, it may be necessary to share this information with other professionals. The researcher would make every effort to first inform you of the need to share this information.

What will happen if I don't want to carry on with the study?
You may withdraw from the study at any time without giving a reason and this will not affect the standard of care you receive in any way. We may need to use the data collected before you decided to withdraw.

What if there is a problem?
We do not consider that taking part in the study may cause any risk to you and there are no special compensation arrangements if you are harmed by taking part in the study. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay your legal costs.

If you have a concern about any aspect of this study, you should speak to the researchers and we will do our best to answer your questions and resolve any concerns. If you remain unhappy and wish to complain formally, you can do this through the School of Psychology. The contact details are given below.

Who is organising and funding the research?
The research is being funded by the School of Psychology, Bangor University, and the 125th Anniversary Scholarship award. The project is being led by Mrs Aleksandra Kudlicka (PhD student) and supervised by Professor Linda Clare, a clinical psychologist who works at Bangor University, and Dr John Hindle, Consultant Physician in the Movement Disorders Clinic, Llandudno Hospital.

What will happen to the results of the research?
We will publish the results of the study in scientific journals. All information about participants will be anonymous, so you will not be identifiable in any publication. We can inform you of the findings of the study if you wish.

Who has reviewed the study?
All research in the NHS is analysed by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being and dignity. This study has been reviewed and granted approval by the North West Wales Research Ethics Committee.

Who can I contact for further information?
For more information about this research, please contact:
Mrs Aleksandra Kudlicka
School of Psychology, Bangor University, Bangor, Gwynedd, LL57 2AS.
Tel: 01248 383621
Email: pspa16@bangor.ac.uk

Professor Linda Clare
School of Psychology, Bangor University, Bangor, Gwynedd, LL57 2AS
Tel: 01248 388178
Email: l.clare@bangor.ac.uk

Dr John Hindle
Llandudno Hospital, Hospital Road, Llandudno, Conwy, LL30 1LB
Tel: 01492862366
Email: j.v.hindle@nww-tr.wales.nhs.uk

If you have any complaints about the conduct of this study you can contact:
Mr Hefin Francis, School Manager
School of Psychology, Bangor University, Bangor, Gwynedd, LL57 2AS.
Tel: 01248 388339
Email: h.francis@bangor.ac.uk

Thank you for considering taking part in this research study!

Appendix E. Informant Consent Form

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	Please initial boxes
1. I confirm that I have read and understand the information sheet (Version 1. 10/05/2010) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without medical care or legal rights of my partner/relative/friend being affected.	
3. I agree to provide some information in the form of an interview with researcher if required, and agree to this being tape-recorded.	
4. I understand that the researcher may need to inform other professionals if she observes or hears something that causes very serious concern about my well-being or that of my relative/friend. The researcher would make every effort to first inform me of the need to share this information.	
5. I agree to take part in the above study.	

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

Appendix F. A structured form used to review articles considered for the literature review

Title, author, year of publication:			
Inclusion criteria:	Yes	No	Not clear
1. The main aim of the study was to investigate EF in PD: *EF itself or its components; relationship between EF and x; analysis of deficits (e.g. EF) underlying x.*			
2. The severity of PD in patients included was mild to moderate (stage I-III H&Y)			
3. Patients were not diagnosed with: dementia			
depression			
no surgical intervention, brain injuries, other relevant conditions			
4. Reliable criteria for diagnosis of PD:			

Issues considered		**Information given/not given/details**	**Controls**
Patients:	Sample size		
	Mean age (SD)		
	Mean education level (SD)		
	Premorbid intelligence		
Illness:	Severity of symptoms H&Y stage		
	Type/dose of medic.		
	Duration		
	Hallucinations		
	Laterality		
	Symptoms type		
	Tested during On/Off		
Aim of the study			
Object/s of investigation (as directly stated by author/s) Measured (not impaired/inconclusive)[+] Impaired [–] lower then controls [*]			
Global cognition Memory Verbal ability Visuoperceptual functions/visuoconstructive skills Global EXECUTIVE FUNCTION (Working memory) (Attention) Set-maintenance Set-shifting/inhibition Cognitive/processing speed Reaction time Mental flexibility Verbal fluency			
Problem solving Reasoning Strategy generation Planning Decision making			
Abstract thinking SAS Mental effort Central executive processes			

Measures used (not impaired/inconclusive)[+] Impaired [–] lower then controls [*]
FAB Stroop Test Part A Part B Part C (interference) Trail Making Test A, B, B/A Fluency tasks – letters, category, alternating COWAT (verbal fluency) (attention and processing speed) Digit span forward & backward Digit Ordering Test PASAT (mental flexibility and reasoning) Wisconsin Card Sorting Test WAIS Similarities Raven Progressive Matrices Odd Man Out Test MDRS Concept formation subscale Word relations judgment (planning, decision making) Tower of London etc. Iowa Gambling Test, Game of Dice Task Other
Results/Conclusions
EF conceptualisation Not existing – random test without justification Random test/s with some justification Discussion of tests choice, unjustified generalization about EF Directly stated dimension of EF without generalization about EF EF discussed and attempt to use comprehensive assessment of EF *Other:*
Quality of the study / Comments

Appendix G. Detailed summary of studies examined at the final stage of the literature search and excluded from the review after in-depth analysis of content

Authors (year)	**Summary**	**Participants** n (men), mean age, years (SD or range, as reported)	**PD characteristics** Diagnosis based on; H&Y stage; Depression, PD type, Laterality, Hallucinations, Medication, Tested on/off, $M_{PD\ duration}$	**EF components and measures** List of EF components (as specified by authors, but also other relevant abilities that were tested) and measures of EF that were used	**Reasons for exclusion**
Amboni, Cozzolino, Longo, Picillo, and Barone (2008)	Authors compared executive functioning in two groups of PwPD, with and without freezing of gait. PwPD with freezing of gait performed significantly worse on most cognitive tests.	28 PwPD No control group *Demographic data available only for the PwPD subgroups.*	Diagnosis basis: UKPDSBB H&Y stage: < 2.5 Dementia: no Depression: no Medication: details given Tested on/off: on $M_{PD\ duration}$ = <10 years	**Cognitive functions:** Phonemic Fluency Tasks, Frontal Assessment Battery (FAB), the Ten Point Clock-Test, the Stroop Test *No indication given of which tests are intended to measure EF.*	No control group.
Auriacombe et al. (1993)	Authors examined verbal fluency deficits in PwPD and suggested that deficits in verbal fluency may be related to lexical retrieval impairment.	Experiment 1: 25 PwPD 62.32 (11.08) 19 Controls, 50.00 (12.55) Experiment 2: 18 PwPD, 11 Controls	H&Y stage: I-II Dementia: no Medication: details given Tested on/off: on $M_{PD\ duration}$ = 7.74 (5.15) years	Phonemic and Semantic Fluency Tasks, Design Fluency, Category Drawing. Rey Auditory Verbal Learning Test (RAVLT) *It was not discussed which tests are supposed to measure EF.*	The study examined verbal fluency in terms of language abilities not EF. Depression not assessed.
Bialystok et al. (2008)	Authors compared performance on two concurrent tasks in PwPD, older controls and young controls. PwPD used a different strategy to controls, possibly reflecting reduced flexibility in switching between tasks, but it was beneficial for performance on the primary task. PwPD scored better than older and young controls on some of performance indices.	17 PwPD (9 men) 68.5 (6.0) 15 older controls (5 men) 70.4 (4.4) 15 young controls (5 men) 20.9 (2.7)	H&Y stage: I-III (not complete) Dementia: no (not complete) Medication: details given Tested on/off: on $M_{PD\ duration}$ = 5.1 (2.6)	**Switching:** Experimental paradigm (the breakfast task) **Short-term verbal memory:** Digit Span Forward **WM:** Alpha Span	Depression not assessed. Incomplete information about general cognition and PD severity. Experimental paradigm.
Brown, Soliveri, and Jahanshahi (1998)	Authors examined how EF contribute to performance on the Random Number Generation Test (RNG). Overall performance on the RNG was comparable in PwPD and controls.	16 PwPD 61.7 (6.1) 8 controls 58.5 (9.1)	H&Y stage: I-III Tested on/off: half in 'off', half in 'on' $M_{PD\ duration}$ = 5.8 (4.0)	Random Number Generation Test (RNG) Visuomotor Tracking Task *Authors discussed what abilities may be involved in performance on the above task*.	No information about general cognition or depression level.

Cameron, Watanabe, Pari, and Munoz (2010)	Authors investigated switching between pro-saccade eye movements (automatic) and anti-saccade eye movements (suppressing automatic eye movement). PwPD had greater difficulty than controls in switching to anti-saccade eye movement, but where quicker to switch back to the pro-saccade eye movement.	12 PwPD (8 men) 60.3 12 controls (5 men) 59.9	H&Y stage: I-III Dementia: no Medication: details given Tested on/off: on	**Switching between pro-saccade and anti-saccade eye movements:** Experimental paradigm	No direct assessment of EF. Experimental paradigm. Depression not assessed.
Crucian et al. (2007)	Authors investigated response inhibition in PwPD. Results suggested defective response inhibition in PwPD, possibly related to the laterality of the PD symptoms. There was no difference between 'on' and 'off' medication performance. No differences were found on the fluency and anti-saccade tasks.	17 PwPD (9 men) 66.06 (12.04) 30 controls 63.9 (10.97)	H&Y stage: I-III Dementia: no Tested on/off: on and off separately $M_{PD\ duration}$ = 8.87 (6.25) years	**Response inhibition**: Crossed Response Inhibition experimental paradigm* **Frontal-cognitive bedside tests**: COWAT, The Anti-saccade Task (experimental paradigm)	Depression not assessed. Experimental paradigm.
Dalrymple-Alford et al. (1994)	Authors investigated whether PD pathology influences central executive. Both groups performed comparably in the single-task condition; PwPD scored significantly lower than controls in the dual task condition. Authors interpreted this as evidence for impaired central executive in PwPD.	8 PwPD 65.6 (3.0) 8 controls 62.4 (2.1)	H&Y stage: I-III Dementia: no Depression: elevated scores Laterality: details given Medication: details given $M_{PD\ duration}$ = 4.4 (1.3) years	**Central executive:** Dual task paradigm* (tracking task and digit span forward) **Categorisation and behavioural regulation:** WCST, Phonemic Fluency*	Depression level significantly higher in PwPD than in controls. Experimental paradigm.
Donovan, Siegert, McDowall, and Abernethy (1999)	Authors investigated word generation strategies in the fluency tasks (clustering and switching). PwPD performed worse than controls on both fluency tasks, and there were some differences in the strategy use.	13 PwPD (9 men) 68.15 (45-85) 11 Controls (3 men) 63.81 (46-81)	H&Y stage: I-III Dementia: no $M_{PD\ duration}$ = 0-18 (median 6) years	Phonemic and Semantic Fluency Tasks (COWAT)*, Animal Naming Task from the Boston Diagnostic Aphasia Examination	The study examined verbal fluency in terms of language abilities, not EF. Incomplete information about depression level.
Drag, Bieliauskas, Kaszniak, Bohnen, and Glisky (2009)	Authors investigated source memory, in relation to various tests related to frontal functioning. The EF composite score (and only digit span backward individually) was significantly lower in PwPD than in controls.	24 PwPD 69.04 (7.42) 24 controls 68.67 (8.34)	H&Y stage: I-III Dementia: no Depression: mild to moderate depression in 7 PwPD Tested on/off: on/off separately	**Source memory:** Experimental paradigm **Tests of frontal functioning**: Verbal Fluency FAS (total words), mWCST (categories achieved), Digit Span Backward*, WMS-III Mental Control, WAIS-T Mental Arithmetic	Experimental paradigm. The study included participants with elevated depression scores.

Elgh et al. (2009)	Authors aimed to describe the pattern of cognitive functioning in early stage PD. In the tests listed as EF measures only one out of eight performance indices of WCTS indicated significant difference (PwPD<controls), after adjusting for age, gender, education and psychomotor function.	88 PwPD (49 men) 68.1 (9.3) 30 controls (16 men) 68.2 (6.6.)	Diagnosis basis: Gibb et al. 1988 H&Y stage: newly diagnosed Dementia: no Depression: yes, 14 PwPD Medication: 2 patients on low dose of dopamine, others without medication	**EF**: WCST*, Mental Control (WMS-III) **Working memory:** Digit Span Forward and Backwards **Attention:** TMT A* and B* **Verbal function:** Phonemic and Semantic* Fluency (COWAT), Boston Naming Test, *Authors discussed what abilities were assessed with what tests. Here only the relevant categories are reported.*	The study included 14 PwPD with elevated depression scores.
Fales, Vanek, and Knowlton (2006)	Authors compared backward inhibition (an automatic mechanism observed when switching between tasks) in PwPD and controls. Out of the 25 performance indices drawn from the five EF tests only two were significantly lower in PwPD than in controls.	21 PwPD (13 men) 66.9 (8.2) 25 controls (13 men) 68.8 (9.6)	H&Y stage: I-III Dementia: no Depression: no Medication: details given Tested on/off: optimally medicated $M_{PD\ duration}$ = 5.8 years (3.5)	**Backward inhibition**: Task-Switching Test (Experimental paradigm) **EF:** WCST (non-perseverative errors*), Stroop Test, Colour Trail test, ToL (time to first move*), Verbal and Semantic Fluency Tests	The focus of the study was a non-EF automatic process involved in set-shifting. Experimental paradigm.
N. Fournet, Moreaud, Roulin, Naegele, and Pellat (1996)	The study investigated whether attentional deficits in PwPD are related to impairment in central executive. PwPD had significantly shorter spans, but the interference did not affect them more than controls, which does not support the hypothesis of impaired central executive.	15 PwPD (9 men) 66.1 (8.2) 15 controls 66.6 (11.5)	H&Y stage: I-III Dementia: no Medication: details given $M_{PD\ duration}$ = 8.0 years (4.8)	**Working memory and central executive specifically:** Experimental paradigm (verbal, visual, spatial spans with two conditions of articulatory suppression: repeating phoneme 'da' and counting upward in threes)	Depression not assessed. Experimental paradigm.
Graceffa, Carlesimo, Peppe, and Caltagirone (1999)	Authors investigated verbal working memory in relation to the articulatory loop and central executive. PwPD performed similar to controls on articulatory loop task, but their performance decreased significantly more than in controls when concurrent task was added, suggesting deficits in the central executive.	12 PwPD 65.2 (48-82) 12 controls 65.6 (41-82)	H&Y stage: I-III Dementia: no PD type: rigid-akinetic Laterality: bilateral Medication: details given Tested on/off: on	**Articulatory loop and central executive:** Word Span (Brizzolara et al. 1993) and Brown-Peterson Paradigm	Depression not assessed. Experimental paradigms.
Hausdorff et al. (2006)	Authors examined EF and attention in PD and elderly fallers. PwPD had significantly lower EF index score then control group.	30 PwPD (70% men) 71.3 (7.8) 25 controls (66% men)70.0 (6.1) 18 fallers (33% men) 77.1 (4.9)	Diagnosis basis: Gelb et al., 1999) H&Y stage: II-III Dementia: no	Go-NoGo Response Inhibition Test, Verbal Memory, Stroop Interference Test (no-interference condition*), Non-Verbal Memory, Finger Tapping, Catch Game, Staged Information Processing Speed Test; EF index score* *No indication was given of which measures were included in the EF index score.*	The main interest of the study was the group of elderly fallers and not PwPD. Depression not assessed.

Y.-H. Hsieh, Chen, Wang, and Lai (2008)	Authors examined what contributes to impaired performance on the Stroop test. Results suggested that slower motor responses and greater interference effects in PwPD were important contributors.	27 PD PwPD (17 men) 63.10 (10.49) 27 controls (14 men) 63.48 (9.15)	Diagnosis based on: two or more clinical signs of PD H&Y stage: I-III Dementia: cognitive status indicated by normal performance in the word list generation and digit span $M_{PD\ duration}$= 3.34 (2.33) years	**Inhibitory control, WM updating:** Stroop Test (color naming*, word reading*, colour-word naming*, decision time, interference score*)	Cognitive status was not assessed formally. Depression not assessed.
Inzelberg et al. (1996)	Authors investigated performance on motor and cognitive switching tasks in PwPD and controls. Both mental and motor switching was impaired in PwPD in comparison to controls, but there was no significant correlation between them.	9 PwPD (6 men) 74 (8) 7 controls (4 men) 74 (9)	H&Y stage: II-III Dementia: PwPD described as non-demented but there is no further details Tested on/off: off	**Mental switching:** Modified WCTS * **Motor switching:** Experimental paradigm* (upper limb reaching toward a visual target)	Results of cognitive screening/tests were not reported. Experimental paradigm. Depression not assessed.
Inzelberg et al. (2001)	Authors investigated the relationship between motor and cognitive switching in PwPD. Both mental and motor switching were impaired in PwPD but not correlated.	8 PwPD (5 men) 74 (9) 6 controls (3 men) 73 (9)	H&Y stage: II-III Dementia: no Tested on/off: off	**Mental switching:** Modified WCTS **Motor switching:** Experimental paradigm* (upper limb reaching toward a visual target)	Depression not assessed. Experimental paradigm.
Kemps, Szmalec, Vandierendonck, and Crevits (2005)	Authors investigated how central executive contributes to performance on a visuospatial task.	15 PwPD (7 men) 67.20 (4.39) 15 controls 7 men) 67.8 (4.44)	H&Y stage: I-III Dementia: no Depression: no Medication: details given Tested on/off: on $M_{PD\ duration}$ = 11.93 (8.30)	**Visuo-spatial abilities**: Corsi Blocks* **Concurrent visuo-spatial sketch pad task:** Spatial Tapping (experimental paradigm) **Central executive task:** Random Interval Repetition Task (experimental paradigm)	Experimental paradigm. EF was not the main focus of the study. Depression and cognitive status not assessed
Kim, Cheon, Park, Kim, and Jo (2009)	Authors investigated the frequency and pattern of cognitive impairment in PwPD; 40% of patients showed impairment in at least one of 5 assessed cognitive domains, with memory commonly being impaired.	141 PwPD No control group. *Demographic data available only for the PwPD subgroups.*	Diagnosis basis: UKPDSBB Dementia: no Depression: no PD type: proportions of tremor/akinetic-rigid given Medication: details given	**EF:** Phonemic Controlled Oral Word Association Test **Attention:** Digit Span Forward The *study included a number of neuropsychological tests. Here only the relevant cognitive domains are reported.*	Test results only given for the PwPD subgroups. No control group. No exact H&Y stage values.

Lewis, Cools, et al. (2003)	Authors investigated several aspects of WM in two PwPD groups: PwPD with good performance on the Tower of London (ToL) test and PwPD with poor performance on ToL. PwPD with poor ToL performance had impaired performance on the verbal memory tasks requiring information manipulation.	41 PwPD 24 controls (8 men) 65.3 (8.2) *Demographic data available only for the PwPD subgroups.*	Diagnosis basis: UKPDSBB H&Y stage: I-III Dementia: no Medication: details given	**EF:** ToL **Verbal WM:** Experimental paradigm **Neuropsychological testing:** Verbal and Categorical Fluency, Pattern and Spatial Recognition Memory Tests (CANTAB); Motor Latency (CANTAB Motor Screening)	Test results only given for the PwPD subgroups. Incomplete control data. PwPD with elevated depression scores included.
Lewis, Slabosz, Robbins, Barker, and Owen (2005)	Authors investigated different aspects of working memory in PwPD 'on' and 'off' dopaminergic medication. L-dopa seemed to improve accuracy and response time, but not attentional set-shifting.	20 PwPD 70.2 (6.0) 19 controls in WM paradigm 68.3 (7.0) 21 controls in set-shifting paradigm 68.2 (8.0)	Diagnosis basis: UKPDSBB H&Y stage: I-III Dementia: no Depression: no Medication: details given	**WM** (maintenance, retrieval and manipulation of information**):** Experimental paradigm **Attentional set-shifting:** Experimental paradigm	EF was not the main focus of the study. Experimental paradigms.
McDonald, Brown, and Gorell (1996)	Authors examined two hypotheses of slower reaction times on the lexical decision task in PwPD: semantic deficit and set-shifting deficit. PwPD did not differ from controls in language tests, but scored significantly lower on the WCST test.	28 PwPD (18 men) 63.68 (7.73) 28 controls (18 men) 64.18 (5.75)	H&Y stage: 0.5 – 2.5 Dementia: no Depression: depression level significantly higher in PwPD than controls Medication: details given $M_{PD\ duration}$ = 66 month (4-160)	**Lexical Decision Task:** Experimental paradigm (making word/nonword judgments about target letter strings) **Tendency to perseverate:** WCST* **Semantic processing**: Shipley-Hartford Vocabulary Test, Boston Naming Test, Spelling Test	EF was not the main focus of the study. Depression level significantly higher in PwPD than in controls
Monetta and Pell (2007)	Authors investigated potential correlates of impaired metaphor comprehension in PwPD. Performance on neuropsychological tests was compared in PwPD with good *vs*. poor metaphor comprehension, and controls. Results suggested less efficient processing of metaphors in PwPD, possibly related to deficits in WM.	17 PwPD 66.4 (11.6) 17 controls 67.4 (9.8)	Diagnosis basis: motor criteria H&Y stage: mild to moderate, but no H&Y stage given Dementia: no Depression: yes Laterality: details given Medication: details given Tested on/off: on	**Metaphor comprehension:** Experimental paradigm **EF/frontal:** Digit Span Forward, Verbal Working Memory Span, Colour Trail Making Test, Verbal Fluency Test, ToL, Warrington Recognition Memory Test (faces and words), the Benton Phoneme Discrimination and Face Recognition Subtests	Experimental paradigm. Tests' results only for the PwPD subgroups. Depression level significantly higher in PwPD.
Ozer et al. (2007)	Authors investigated relationship between several disease characteristics and cognitive functioning in two groups of PD patients: with and without visual hallucinations (VH). PwPD with VH scored significantly lower than PwPD without VH group on the Stroop test, semantic fluency and clock drawing, but not in 'alternating category' fluency or WCST (category).	63 PwPD No control group *Demographic data available only for the PwPD subgroups.*	Diagnosis basis: UKPDSBB H&Y stage: I-II Dementia: no Hallucinations: yes, see groups Medication: details given Tested on/off: on	**Frontal functions**: Stroop Test, WCST, Categorical Verbal Fluency, Clock Drawing. The *study included a number of neuropsychological tests. Here only the relevant cognitive domains are reported.*	Test results only given for the PwPD subgroups. No control group. Depression not assessed.

Possin, Filoteo, Song, and Salmon (2009)	Authors examined performance of PwPD on the Inhibition of Return task with and without cues. PwPD exhibited impaired performance on the task without cues, but not when cues were provided.	18 PwPD (11 men) 67.0 (8.3) 18 controls (9 men) 69.4 (8.2)	Diagnosis basis: 2 of 3 cardinal symptoms H&Y stage: I-III Dementia: no Depression: no Laterality: details given Medication: details given Tested on/off: on $M_{PD\ duration}$ = 5.4 (3.8) years	Inhibition of Return Task: Experimental paradigm	No EF measure. Inhibition and attention discussed in terms of involuntary processes. Experimental paradigm
Raskin, Sliwinski, and Borod (1992)	Authors investigated semantic and phonemic clustering in verbal fluency tasks. PwPD produced more semantic clusters in the semantic retrieval task.	25 PwPD (12 men) 65.9 (10.2) 22 Controls (10 men) 62.0 (9.6)	H&Y stage: I-III Dementia: no PD type: details given	**Semantic and phonemic clustering in letter retrieval:** Phonemic Fluency (COWAT) **Semantic* and phonemic clustering in semantic retrieval:** Semantic Fluency (Animal Naming from the Boston Diagnostic Aphasia Examination)	Only the linguistic aspects of verbal fluency tasks were considered. Depression not assessed.
Raskin, Borod, and Tweedy (1992)	Authors examined shifting and spatial-orientation abilities in PwPD and controls. PwPD performed poorer than controls on the majority of the set-shifting tests.	20 PwPD (10 men) 64.60 (10.29) 20 controls (8 men) 62.60 (10.98)	H&Y stage: I-III Dementia: no Medication: details given Tested on/off: on	**Set-shifting functions:** COWAT (alternating*), Uses of Objects Test*, Digits Forwards and Backwards (difference), Competing Program*, Go/No-Go, Motor Programs I*, Motor Programs II* The *study included a number of spatial-orientation tests not reported here.*	Depression not assessed.
Rogers et al. (1998)	Authors compared, PwPD, people with frontal lobe damage and controls with regard to the efficiency of executive control, understood as efficient switching between two simple tasks. Switching abilities appeared as relatively preserved in PwPD.	12 PwPD (6 men) 59.2 (1.8) 12 controls (5 men) 58.5 1.8 *Data from people with frontal lobe damage are not included here.*	H&Y stage: I-II Medication: details given Tested on/off: $M_{PD\ duration}$ = 2.4 years (0.3)	**Executive control processes**: Task-Switching Task (Experimental paradigm, switching between digit and letter-naming) **Background neuropsychology:** Phonetic and Semantic Fluency, Spatial Working Memory Task, Recognition Memory (pattern, spatial*)	Depression and cognitive status not assessed. Experimental paradigm.
Santangelo et al. (2009)	Authors investigated correlations between cognitive functioning and pathological gambling in PwPD with and without pathological gambling. PwPD with pathological gambling performed significantly worse on a number of frontal lobe function tests.	30 PwPD No control group *Demographic data available only for the PwPD subgroups.*	Diagnosis basis: UKPDSBB Dementia: no Depression: yes Medication: details given Tested on/off: on	**EF:** Frontal Assessment Battery **Frontal lobe functions:** flexibility (WCST), WM (Corsi Blocks), logical abstract thinking (Raven's Coloured Progressive Matrices), spatial planning (Rey-Osterrieth Complex Figure, ROCF), set-shifting (TMT) **Memory:** ROCF, Rey Auditory Learning Test	PwPD with elevated depression scores included. No exact H&Y stage indicated. No control group.

Siri et al. (2009)	Authors compared PwPD with and without pathological gambling with regard to cognitive functioning. PwPD with pathological gambling performed better than PwPD without pathological gambling on several cognitive tests, but their caregivers reported more behavioural disturbances.	63 PwPD No control group. *Demographic data available only for the PwPD subgroups.*	Diagnosis basis: UKPDSBB Medication: details given Tested on/off: on	**EF:** Phonemic and Semantic Fluency, Raven's Coloured Progressive Matrices Sets, Frontal Assessment Battery **Short term memory:** Rey Auditory Verbal Learning Test **Attention:** attentive matrices **Behavioural disturbances:** Neuropsychiatric Inventory (NPI)	No exact H&Y stage indicated. No exact MMSE scores. Authors mentioned using a depression screening tool, but no values were reported. No control group.
Sobreira et al. (2008)	Authors analysed relationships between various tests of EF in PwPD.	35 PwPD 63.1 (12.4)	Diagnosis basis: Gelb at al. 1999 H&Y stage: <III Dementia: yes, MMSE 18-29 Depression: no Tested on/off: on	Attention, Initiation/Perseveration, and Conceptualisation subscales of Mattis Dementia Rating Scale, SCOPA-COG, WCST, FAB, Digit Span Backward, Verbal Fluency. *Abilities assessed by each test were described in detail.*	PwPD with mild dementia were included. No control group.
Tamura, Kikuchi, Otsuki, Kitagawa, and Tashiro (2003)	Authors aimed to investigate the differential contribution of attentional set-shifting and attention resources to performance on WM tests. PwPD scored poorer than controls on several tasks of WM and attention. Performance on tasks requiring set-shifting was not specifically analysed.	24 patients (15 men) 60.9 (9.72) 24 controls (11 men) 61.7 (9.58)	H&Y stage: I-III Dementia: no Medication: details given Tested on/off: on $M_{PD\ duration}$ = 6.00 years (5.98)	**Verbal memory:** Digits Forward, Digits Backward*, Five Times Rehearsal, Mental Calculation (WAIS-R)*, Delayed Recall of Words **Visual memory:** Forward and Backward Visual Memory Span Test (WMS-R) **Attention:** Kana Pick-Out Test, TMT A, B*, A-B*	None of the tests were specified as measuring EF or set-shifting. Depression not assessed.
Rachel Tomer, Aharon-Peretz, and Tsitrinbaum (2007)	Authors assessed whether symptoms asymmetry (left/right onset of PD) is related to spontaneous and reactive flexibility in PwPD.	35 PwPD (21 men) 12 controls 59.5 (8.4) *Demographic data available only for the PwPD subgroups.*	Diagnosis basis: UKPDSBB H&Y stage: I-III Dementia: no Depression: yes, 50% of PwPD PD type: details given Laterality: yes, see groups Medication: details given	**Spontaneous flexibility:** Alternate Uses Test **Reactive flexibility:** Intradimensional/ Extradimensional Attentional Set-Shifting Task from CANTAB	Test results only given for the PwPD subgroups. PwPD with elevated depression scores included.
R. S. Wilson, Gilley, Tanner, and Goetz (1992)	Authors investigated dissociation between the visuospatial and executive functions. PwPD showed deficits only on the ideational fluency tasks, while deficits on spatial orientation tasks seem to be related to age and verbal intelligence rather than PD.	10 younger PwPD (4 men) 53.6 (7.7) 7 young controls (2 men) 46.4 (7.7) 10 older PwPD (4 men) 68.9 (5.3) 8 older controls (3 men) 69.3 (6.3)	Diagnosis basis: 2 of 3 cardinal PD symptoms H&Y stage: I-III Dementia: no Hallucinations: no	**EF aspects: ideational fluency** (Topics Test, Things Categories Test); **flexibility of use (**Making Groups, Different Uses) **Visuospatial:** spatial orientation (Card Rotations Test, Cube Comparison Test) **Verbal comprehension:** Extended Range Vocabulary	Depression not assessed.

van Spaendonck, Berger, Horstink, and Buytenhuijs (1996)	Authors investigated the relationship between EF (verbal fluency and cognitive shifting) and several PD characteristics. Cognitive shifting was correlated with motor symptoms (rigidity), while there were no such correlations with fluency tasks.	45 PwPD (23 men) 57.4 (10.5) 33 controls 57.4 (8.7)	Diagnosis basis: 2 of 3 cardinal symptoms H&Y stage: newly diagnosed Medication: no anticholinergic drugs, 34 de novo patients $M_{PD\ duration}$= 5.8 (3.7)	**EF: fluency** (Semantic and Phonemic); **cognitive shifting** (WCST, Animal Sorting Test, Spatial Sorting Test) **Reference tests: intelligence** (WAIS-R: Vocabulary, Similarities, Picture Competition, Block Design), **memory** (RAVL), **attention** (Stroop Test parts B & C)	No formal comparison of PwPD and control group. PwPD with elevated depression scores included.
Zamarian et al. (2006)	Authors examined the role of EF in arithmetic abilities in PwPD. PwPD scored significantly lower than controls on all EF measures and one of WM tests (digit span backward). PwPD scored poorer than controls in only three out of over 30 measures reported.	15 PwPD (13 men) 66.1 (7.1) 28 controls (7 men) 63.1 (5.6)	H&Y stage: <III Dementia: no Medication: details given Tested on/off: no motor fluctuations $M_{PD\ duration}$= 5.3 (3.4)	**EF:** semantic and alternating fluency (Regensburger Wortflussigkeitstest, CERAD); Interference Naming (Nürnberger-Alters-Inventar); divided attention and cognitive flexibility (TMT-B); set shifting (Odd-Man-Out) **WM:** Digit Span Backward The *study included a number of neuropsychological tests. Here only the relevant cognitive domains are reported* **Arithmetic abilities:** Number Processing and Calculation Battery	Depression not assessed.
Zec et al. (1999)	Authors investigated semantic, phonemic and alternating fluency in PwPD. PwPD performed similar to controls in phonemic fluency tasks, scored lower then controls in 2 out of 3 semantic fluency trials, and were impaired in all 3 alternating trials.	45 PwPD (29 men) 66.4 (10.2) 45 controls (11 men) 63.1 (10.6)	H&Y stage: I-III, one PwPD = IV Dementia: no	Semantic Fluency (animals, boy's names, states) Phonemic Fluency (letters F, A, and S) Alternating Fluency (colours/occupations, animals/states, words beginning with C/P)	The study included PwPD in H&Y > III Depression not assessed.

* Significant difference between PwPD and controls; PwPD – people diagnosed with Parkinson's disease; UKPDSBB - UK PD Society Brain Bank; H&Y – Hoehn and Yahr, EF – Executive functions; WM – Working memory; WCST – Wisconsin Card Sorting Test, TMT AB - Trail Making Test A, B, ToL - Tower of London test

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Appendix H. Detailed summary of articles included in the systematic review.

Author (year)	Aim of the study	Participants n (men), mean age, years (SD or range, as reported)	PD characteristics Diagnosis based on; H&Y stage; Depression, PD type, Laterality, Hallucinations, Medication, Tested on/off, $M_{PD\ duration}$	EF components and measures List of EF components (as specified by authors, but also other relevant abilities that were tested) and measures of EF that were used (if it was not clear whether authors considered a test as an EF measure that measure was included (in italics), if clearly not related to EF it was omitted).
Studies focused on executive or frontal functions as a whole, selectively or in relation to other factors.				
Bondi et al. (1993)	To examine whether PwPD exhibit Frontal System Dysfunction, and whether this impairment may contribute to memory and visuoperceptual deficits. Frontal System Dysfunction was considered as a whole and more specific abilities were only mentioned.	19 PwPD (16 men), 67.32 (6.85) 19 controls (7 men), 69.26 (5.36)	H&Y stage: I-III Dementia: no Depression: no Tested on/off: on Median $_{PD\ duration}$ = 8 years (1-17)	**Frontal system tasks (composite score*):** Phonemic, and Semantic Fluency*, Modified WCST *, California Sorting Test*, Verbal Temporal Ordering*.
Colman et al. (2009)	To investigate the relationship between EF and language problems (verb production).	28 PwPD (16 men), 61.39 (8.8) 28 controls(16 men), 62.93 (9.04)	Diagnosis based on: UKPDSBB H&Y stage: I-III Dementia: no Depression: no Laterality: details given Medication: details given Tested on/off: on $M_{PD\ duration}$ = 6.04 years (4.55)	**Attention:** 3 subtests of Testbatterie zur Aufmerksamkeitsprufung (Sustained Visual*, Sustained Auditory and Divided Attention), **WM:** Digit Span Forward and Backward, **Cognitive set-switching:** TMT A and B + Odd Man Out (composite score*) **Inhibititory control:** Stroop Test **Verbal Fluency:** Phonemic, Semantic, and Action Fluency **Abstract structure processing:** Experimental paradigm
Dujardin et al. (2001)	To compare executive functioning and memory in sporadic and familial Parkinson's disease.	#12 sporadic PwPD (7 men), 65.92 (51-74) 12 familial PwPD (5 men), 63.42 (44-76) 12 controls (6 men), 59.25 (47-73)	Diagnosis based on: UKPDSBB H&Y stage: I-III Dementia: no Depression: no PD type: familial/sporadic Medication: details given $M_{PD\ duration}$ = 103/74 months	**Planning:** Verbal Fluency, Spatial Sequences Generation* **Resistance to interference:** Set shifting: WCST, Alternate Fluency*, Motor Sequences*, Brown-Peterson Paradigm* **Memory:** Immediate (Digit Span Forward and Backward, Spatial Span, Word Span); working memory (Decline Of Storage Abilities %) The *study included a number of long-term memory tests not reported here.*

Farina et al. (1994)	To investigate performance of PwPD in a task sensitive to impairment resulting from unilateral frontal cerebral excision.	22 PwPD (11 men), 52.86 (39-72) 19 controls (6 men), 53.42 (33-66)	H&Y stage: I-III Dementia: no Depression: no Medication: details given $M_{PD\ duration}$ = 57.7 months (12-132)	**Organization, planning and memory**: Classification* and Recall of Pictures
Farina et al. (2000)	To examine frontal functions (set-shifting) and explicit memory in early PD.	20 PwPD (13 men), 57.9 (8.3) 18 controls (10 men), 56.6 (6.4)	H&Y stage: I-II Dementia: no Depression: no Medication: details given $M_{PD\ duration}$=28 months (3-96)	**Abstract behavior and shifting ability:** WCTS (2*/4 variables) **Concept formation and free recall:** Test of Categorization and Recall (2*/5 variables) **Abstract non-verbal reasoning:** Ravens Progressive Matrices* **Short-term verbal memory and attention:** Digit Span **Short-term visuo-spatial memory and attention:** Corsi's Block-Tapping **Visuospatial long-term memory:** Corsi's Supra Span Tapping* **Verbal long-term memory:** Paired Associated Learning Test (Measures not discussed: Odd Man Out (1*/2 variables), Phonemic Fluency)
Uekermann et al. (2004)	To investigate executive functioning in relation to motor and affective symptoms in early PD.	20 PwPD (8 men), 55.9 20 controls (9 men), 53.2	H&Y stage: I-II Dementia: no Depression: controlled in the analysis Medication: details given Tested on/off: no fluctuations $M_{PD\ duration}$= 4.6 years (3.0)	**Initiation:** (Phonemic*, Semantic, Alternating Fluency) **Planning and problem solving:** Key Search, Six Elements* and Zoo Map Test (BADS, Behavioral Assessment of the Dysexecutive Syndrome) **Reasoning:** Temporal Judgment* and Cognitive Estimation task (BADS), **Inhibition:** Rule Shift Cards* (BADS), Hayling test* **Self-reported behavioral problems:** Dysexecutive Questionnaire (BADS)
Price and Shin (2009)	To clarify how PD pathology influences sequence learning and underlying processes, including EF.	12 mild PD patients (H&Y stage I) 71.9 (2.0) 10 moderate PD patients (H&Y stage II-III) 71.4 (1.4) 10 controls 70.5 (3.2)	H&Y stage: I-III Dementia: no Depression: no Medication: details given Tested on/off: on $M_{PD\ duration}$=4.0 (0.9)/9.7 (1.1) years	**Mental set-shifting:** Modified WCTS (perseverative errors) **Concept formation:** Modified WCST (number of categories) **Spontaneous cognitive flexibility:** Semantic Fluency (COWAT)* **Working memory:** CSpan Test

Price (2010)	To examine the contribution of EF to problem-solving abilities.	15 PwPD (10 men), 67.67 (1.42) 12 controls (8 men), 64.2 (1.67)	H&Y stage: I-III Dementia: no Depression: no Laterality: details given Medication: details given $M_{PD\ duration}$= 6.47 (1.2)	**Problem solving:** Anagram Task (baseline* and cued) **Executive functions:** Set shifting (WCST-64, perseverative errors), inhibitory control (Stroop Test - Interference, response time) **Semantic verbal fluency:** COWAT* **Working memory:** CSpan (total correctly recalled)
Zgaljardic et al. (2006)	To explore the pattern of executive impairment in PD patients based on the current understanding of frontostriatal circuits. Neuropsychological measures were assigned to three circuits: **the anterior cingulate cortex** (ACC), **the dorsolateral prefrontal cortex** (DLPFC), **and the orbitofrontal cortex** (OFC).	32 PwPD (19 men), 66.9 (8.1) 29 controls (15 men), 66.7 (5.7)	H&Y stage: I-III Dementia: no Depression: no Medication: details given	**ACC*** (response monitoring, inhibition, initiation, apathy): Apathy Scale, Initial Fluency, Stroop Test (interference index) **DLPFC*** (set-shifting, working memory, intrinsic response generation, and conditional associate learning): Category Fluency, Digit Span, Frontal Systems Behavior Scale (executive scale), Phonemic Fluency, Odd Man Out, Petrides Conditional Associate Learning – Criterion (no. trials), Petrides Conditional Associate Learning – Errors, Spatial Span, Verbal Fluency Switching Accuracy; **OFC** (disinhibition, decision-making, impulsivity, and perseveration, depression): Beck Depression Inventory, Frontal Systems Behavior Scale (disinhibition scale), Alternating Loops (no. errors), Twenty Questions Test (abstraction score), Total Questions (weighted score)
Studies investigating subcomponents of executive (or frontal) functions; selectively or in relation to other factors.				
Altgassen et al. (2007)	To explore four components of working memory (including the central executive) and clarify which of them contributes to the observed planning deficits in PD.	16 patients (11men), 61.1 (6.9) 16 controls (8 men), 62.6 (9.1)	H&Y stage: I-III Dementia: no Depression: no Laterality: details given Medication: details given, Tested on/off: no medication 12h prior to testing $M_{PD\ duration}$ = 4.81 (3.0)	**Planning:** ToL* **Working memory:** Phonological loop (Digit SpanForward), visuospatial sketchpad (Block Span Forward), episodic buffer (Logical Memory*), Central executive processes (N-back Task*)
Bouquet et al. (2003)	To investigate the nature of executive impairment in PD by testing abilities known to be involved in the Supervisory Attentional System (SAS): internal strategy generation and inhibition of unwanted responses.	20 PwPD (12 men), 66.1 (7.6) 20 controls (13 men), 63.5 (10.1)	Diagnosis basis: UKPDSBB H&Y stage: I-III Dementia: no Depression: no Tested on/off: on $M_{PD\ duration}$ =10.25 years (5.83)	**Internal strategy generation and inhibition of unwanted responses:** Hayling test*, * Phonemic*, Semantic*, and Alternating Fluency*, TMT
Bublak et al. (2002)	To explore working memory in PD by investigating how the level of demand influences performance in	14 PwPD (5 men), 55.1 (14.7) 14 controls 55.2 (14.7)	H&Y stage: I-III Dementia: no Depression: no	Digit Ordering Test, Working Memory Capacity Test, Response Time Test

	a task requiring the manipulation of a constant number of items. Working memory resources seem to diminish excessively with the increasing complexity of the task.		Medication: details given Tested on/off: on, 2-4h after the last dose of medication $M_{PD\ duration}$=47.3 months (50.0)	
Cools et al. (2001)	To assess set-shifting abilities while controlling for concept formation, rule learning, working memory and general cognitive slowing.	43 PwPD (31 men), 62.1 (1.2) 27 controls (18 men), 59.4 (1.8)	Diagnosis based on: UKPDBB criteria H&Y stage: I-III Depression: additional analysis with non-depressed only Medication: details provided Tested on/off: on $M_{PD\ duration}$= 6.9 years (7.2)	**Set-shifting**: Set-switching Task **Background assessment**: The One-Touch ToL Planning*, Verbal Fluency, Intra/Extra-Dimensional Set-Shifting Task* (CANTAB), Pattern* and Spatial Recognition Memory (CANTAB)
Cronin-Golomb et al. (1994)	To investigate whether problem solving deficits can be explained by set-shifting impairment only or whether there is a more complex underlying pathology.	15 non-medicated patients (14 men), 62.5 (44-73) 15 medicated patients (11 men), 63.9 (44-79) 15 controls (10 men), 63.9 (42-77)	H&Y stage: I-III Dementia: no Depression: no Laterality: details given Medication: details given Tested on/off: on $M_{PD\ duration}$ = 1.9 years (1-4)	**Problem solving**: Poisoned Food Problems* (set-shifting component), Hukok Logical Thinking Matrices Test, Mental Calculation; **Concept formation and comprehension**: WAIS-R Similarities, Concept Comprehension Test, Proverb Interpretation
Downes et al. (1993)	To examine the hypothesis that the primary deficit in PD is related to impaired internal control of attention.	20 PwPD (11 men), 60.05 (10.23) 14 controls (7 men), 60.0 (10.53)	Diagnosis basis: 2 of 3 cardinal symptoms H&Y stage: I-III Dementia: no Depression: no Medication: details given Median $_{PD\ duration}$ = 30 months (15-156)	**Set shifting and attention**: Verbal Fluency (2x single semantic/letter, 2x alternating semantic, 2x alternating letter, 2x alternating semantic/letter*)
Euteneuer et al. (2009)	To investigate decision-making and emotional processing in PD by examining performance on two gambling tasks; to assess cognitive functions in the area of EF.	21 PwPD (7 men), 67.60 (7.31) 23 controls (12 men), 64.4 (8.56)	H&Y stage: I-III Dementia: no Depression: no PD type: details given Medication: details given $M_{PD\ duration}$=85.7 months (72.70)	**EF and working memory**: Modified Card Sorting Test, Phonemic and Semantic Fluency*, (Digit Span Backward, DEMTect subtests (2* of 5 variables)) **Reasoning**: subtest of Leistungsprüfsystem (German intelligence scale) **Decision-making under risk**: Game of Dice Task* **Decision making under ambiguity**: Iowa Gambling Test; **ToM:** Reading the Mind in the Eyes

Gabrieli et al. (1996)	To examine the relationship between working memory and strategic memory in early stage unmedicated PwPD. Authors attempted to clarify the nature of WM performance in early unmedicated PD, in the verbal dimension in particular.	10 PwPD (6 men), 60.1 (7.5) 10 controls (2 men), 55.5 (9.7)	H&Y stage: I-II Dementia: no Depression: no Medication: unmedicated $M_{PD\ duration}$= 2.9 years (1.6)	**Working memory**: Verbal span*, arithmetic span* **Strategic memory:** self-ordering pointing*, temporal ordering*, word recall*
Gilbert et al. (2005)	To clarify the mechanism of working memory impairment in PD by investigating three possible causes: a limited storage capacity, an impaired executive component, and a reduction of psychomotor speed.	14 patients (5 men), 66.29 (11.08) 14 controls 65.79 (10.33)	H&Y stage: I-III Dementia: no Depression: no Medication: details given Tested on: on $M_{PD\ duration}$= 7.29 years (4.53)	**Executive tasks:** Alphabetical Recall* and Updating Memory Tasks **Storage Task:** Digit Span
S. Hsieh et al. (1995)	To investigate set-shifting aptitude using modified version of odd-man-out task. Authors compared reaction times for shift trials and non-shift trials, in cued and non-cued conditions.	12 PwPD (8 men), 64.8 (7.1) 12 controls (5 men), 61.1 (8.6)	H&Y stage: I-III Dementia: no Depression: no	**Set-shifting**: Odd Man Out *
Kehagia et al. (2009)	To investigate the effects of PD on mental control. Authors aimed to clarify how disease severity influences set-switching task performance, and to address problems of paradigm heterogeneity.	13 PwPD (H&Y stage I) (10 men), 62.2 (9.1) #11 H&Y stage II (7 men), 66.6 (8.5) 16 controls (10 men), 63.6 (8.3)	Diagnosis based on: UKPDBB H&Y stage: I and II Dementia: no Depression: no Tested on/off: on and off	**Background neuropsychological profile**: Phonemic Fluency, Spatial and Pattern (H&Y stage II group*) Recognition Memory **Switching**: Set-switching task (H&Y stage II group*)
Kliegel et al. (2005)	To examine prospective memory/memory for intentions and self-initiated implementation in PD.	16 PwPD (11 men), 61.2 (6.9) 16 controls (11 men), 62.6 (9.1)	H&Y stage: I-II Dementia: no Depression: no Medication: details given Tested on/off: off $M_{PD\ duration}$=4.81 (3.00)	**Prospective memory** (formation, retention, initiation and execution of intention): Prospective Memory Task (planning phase*) **Divided attention:** Tests of Attention Battery **Short-term memory span:** Digit Span Forward **Working memory*:** Operation Span Measure **Inhibition:** Stroop Test*

Kobayakawa et al. (2008)	To clarify the pattern of decision-making in gambling task.	34 PwPD (12 men), 69.9 (8.9) 22 controls (13 men), 67.6 (6.9)	H&Y stage: I-III Dementia: no Depression: no Medication: details given Tested on/off: on $M_{PD\ duration}$=6.4 (3.4)	**Decision making**: Iowa Gambling Task* **EF**: WCTS **Short-term memory and attentional ability:** Digit Span **Emotional arousal:** Skin Conductance Responses*
McKinlay, Grace, et al. (2008)	To explore planning abilities in PD by systematic manipulation of ToL test parameters: search depth, sub-goal moves and goal hierarchy. There was no evidence for general planning difficulties in PwPD when compared to controls. When the ambiguity of goal hierarchy increased (sub-goal sequence was less predictable) PwPD performed worse than controls.	30 PwPD 65.77 (6.6); 30 controls 66.43 (5.3)	H&Y stage: I-III Dementia: no Depression: no Tested on/off: on $M_{PD\ duration}$ = 7.3 (4.6)	**Planning**: ToL
Mimura et al. (2006)	To examine decision-making in PwPD and its relationship to the ability to infer mental states of other people and to executive functions.	13 PwPD (5 men), 68.9 (7) 40 controls (age-matched)	H&Y stage: II-III Dementia: no Depression: controlled in analysis Tested on/off: on	**Set-shifting:** WCTS (2* of 3 variables) **Planning:** Maze-tracing of WISC-R*, Inhibition: Stroop test*, VF phonemic* and semantic **Decision making**: Iowa Gambling Test * **Mind-reading**: Reading the mind in the eyes test*
R. Tomer et al. (2002)	To examine relationship between motor impairment and cognitive flexibility.	28 PwPD (18 men), 66.4 (9.5) 19 controls (10 men), 67.1 (9.1)	H&Y stage: newly diagnosed Dementia: no Depression: controlled in analyses PD type: details given Medication: unmedicated	**Reactive flexibility** (set-shifting): WCST (3* of 4 variables) **Spontaneous flexibility** (ideas generation): Alternate uses*
Witt et al. (2006)	To examine the effects of foreknowledge on task switching performance. Authors controlled for the influence of age and tested the relationship between task switching and performance on the WCTS.	20 PwPD (14 men), 59.25 (8.58) 20 older controls (12 men), 59.00 (5.70) 20 young controls (12 men), 25.90 (2.57)	Diagnosis based on: UKPDBB H&Y stage: I-III Dementia: no Depression: no Medication: details given Tested on/off: on $M_{PD\ duration}$ = 3.25 years (4.40)	**EF:** Stroop test* (reading time and reading error only), VF* (semantic, phonemic), WCTS* **Switching abilities** in the predictable (cued) and unpredictable conditions: Task-switching Test*

Studies focused on the overall cognition with executive or frontal functions clearly distinguished.				
Muslimovic et al. (2005)	To describe the pattern of cognitive impairment in newly diagnosed PD patients. EF were specifically addressed.	115 PwPD (61 men), 66.2 (10.1) 70 controls (37 men), 63.7 (7.30)	H&Y stage: I-III Dementia: no Depression: HADS-D Medication: details given $M_{PD\ duration}$ = 18.8 (10.7) months	**EF*:** Modified WCST (number of categories achieved, errors, perseverative errors); Semantic Fluency, WAIS-III Similarities; ToL-Drexel Test (problems solved in minimum number of moves) **Attention:** Digit Span Forward and Backward*; TMT-B*, Stroop Test (interference)
Studies investigating executive/frontal functioning, but with two or more of the following weaknesses: 1) background theories of executive/frontal domains were not discussed; 2) subcomponents of EF/frontal functions were not distinguished; 3) It was not clear which tests were intended to measure which subcomponents.				
Cooper et al. (1991)	To assess cognitive functions in a homogeneous group of early untreated PwPD.	60 PwPD (31 men) 59.8 (37.3-77.6) 37 controls (20 men), 59.6 (40.2-76.1)	Diagnosis based on: PD Society criteria H&Y stage: newly diagnosed Dementia: no Depression: depressed analyzed separately Medication: never treated $M_{PD\ duration}$ = 15.75 months (3-48)	**Frontal tasks:** WCST (1*/9), Picture Arrangement (WAIS); **Cognitive sequencing and working memory:** Digit Ordering* **Memory:** Digit Span Forward and Backward*, Rey-Osterreith and Taylor Figures, Brown-Peterson Paradigm; **Language:** Semantic and Alternating Fluency*
Costa et al. (2008)	To clarify the relationship between prospective memory and EF. Almost 50% of patients were impaired in digit span tasks and almost 40% showed impairment in card sorting task. No formal group comparison for particular tests.	23 PwPD (12 men), 63.5 (10.0) 25 controls (12 men), 65.0 (7.7)	Diagnosis based on: 2 of 3 cardinal symptoms and good response to levodopa H&Y stage: I-III Dementia: no Depression: no Medication: levodopa Tested on/off: on $M_{PD\ duration}$ = 7.69 (8.5) years	**EF:** Modified Card Sorting Test, Phonological Fluency **Short-term and working memory:** Digit Span Forward and Backward, Corsi Test Forward and Backward **Prospective memory:** Prospective Memory Task
Edelstyn et al. (2007)	To investigate a number of cognitive abilities, including executive functions. In depth analysis of recognition memory and its components/ underlying processes, including role of EF in organization of material during encoding and retrieval.	17 PwPD (11 men), 65.4 (8.9) 17 controls (9 men), 64.5 (7.4)	H&Y stage: II-III Dementia: no Depression: no Hallucinations: no Medication: details given Tested on/off: on $M_{PD\ duration}$ = 7.7 years (8.6)	**EF** (fluid intelligence): Matrix Reasoning*, the Hayling* and Brixton* Tests

Pagonabarraga et al. (2007)	To examine relationship between decision-making (limbic function) and cognitive functions (including EF).	35 PwPD (22 men), 67.2 (8.0) (19 stable and 16 fluctuating) 31 controls (16 men), 70.2 (10)	H&Y stage: I-III Dementia: no Depression: no Medication: details given Tested on/off: on $M_{PD\ duration}$ = 8.4 years (5)	**Attention and executive prefrontal function:** Digit Span Forward and Backward, Stroop Test **Limbic function:** Iowa Gambling Test* **Global cognition:** MMSE, Mattis Dementia Rating Scale, VF Phonemic and Semantic Fluency
Saltzman et al. (2000)	To explore the possibility of acquired ToM impairment in PD and examine the relationship between ToM and EF.	11 PwPD (6 men), 70.98 (13.43) 8 older controls (3 men), 71.61 (9.42) 9 young controls (3 men), 20.87 (2.53)	Diagnosis based on: UKPDSBB H&Y stage: II-III Dementia: no Depression: no Medication: details given	**EF:** California Card Sorting Task* (correct sorts), VF* (phonemic), Five-Point Fluency task* (figural fluency) **Theory of mind:** (composite score*)
Woods and Tröster (2003)	To examine cognitive functioning of non-demented PwPD and compare data with 1-year follow up to determine cognitive risk factors for dementia.	18 PwPD (12 men), 69.39 (5.80) 18 controls (12 men), 68.76 (6.44)	Diagnosis based on: 3 cardinal PD features and positive response to levodopa H&Y stage: I-III Dementia: no Depression: no $M_{PD\ duration}$ = 5.50 (3.35)	**EF**: WCST (number of categories), Mattis Dementia Rating Scale (Conceptualization) **Language:** COWAT, Boston Naming Test

*PwPD significantly lower than controls; #PD group included in the meta-analyses; PwPD – people diagnosed with Parkinson's disease; DS - digit span, H&Y - Hoehn and Yahr, WCST - Wisconsin Card Sorting Test, VF - verbal fluency, TMT AB - Trail Making Test A, B, ToL - Tower of London Test, UKPDSBB - UK PD Society Brain Bank

Appendix I. Questions on Life Satisfaction Scale

Questions about your Satisfaction with Life

The following questions are about how satisfied you are with your life and individual areas of you life. You should also indicate how important individual areas of your life are (for example, your occupation or leisure activities) for your satisfaction and your well-being.

Please answer all of the questions, including those which do not seem to apply to you. For example, for the question about your "relationship with your partner" if you do not have a partner you can still indicate how important this would be to you and how satisfied you are with the current situation (without partner).

Do not be influenced by whether you feel good or bad now. Think about the last four weeks when answering the questions.

FIRST, PLEASE CHECK **HOW IMPORTANT** EACH INDIVIDUAL AREA OF LIFE IS FOR YOU.
BEFORE YOU BEGIN, PLEASE READ QUESTIONS 1-8 BELOW.

How important for you is (are) your…	Not important	Slightly important	Moderately important	Very important	Extremely important
1. friends/acquaintances	☐	☐	☐	☐	☐
2. leisure activities	☐	☐	☐	☐	☐
3. health	☐	☐	☐	☐	☐
4. income/financial security	☐	☐	☐	☐	☐
5. occupation/work	☐	☐	☐	☐	☐
6. living condition	☐	☐	☐	☐	☐
7. family life/ children	☐	☐	☐	☐	☐
8. relationship with your partner/sex life	☐	☐	☐	☐	☐

NOW PLEASE CHECK HOW SATISFIED YOU ARE WITH THESE INDIVIDUAL AREAS OF YOUR LIFE.

How satisfied are you with your…	Dissatisfied	Slightly dissatisfied	Slightly satisfied	Moderately satisfied	Very satisfied
1. friend/acquaintances	☐	☐	☐	☐	☐
2. leisure activities	☐	☐	☐	☐	☐
3. health	☐	☐	☐	☐	☐
4. income/financial security	☐	☐	☐	☐	☐
5. occupation/work	☐	☐	☐	☐	☐
6. living condition	☐	☐	☐	☐	☐
7. family life/ children	☐	☐	☐	☐	☐
8. relationship with your partner/sex life	☐	☐	☐	☐	☐

As shown below, the section about 'Health' is divided into various areas. Again, you should indicate how **important** the individual areas are to you, and how satisfied you are with them.

PLEASE ANSWER AL OF THE QUESTIONS. DO NOT BE INFLUENCED BY WHETHER YOU FEEL GOOD OR BAD NOW. THINK ABOUT THE LAST 4 WEEKS WHEN ANSWERING THE QUESTIONS.

How important for you is your…	Not important	Slightly important	Moderately important	Very important	Extremely important
1. physical condition	☐	☐	☐	☐	☐
2. ability to relax	☐	☐	☐	☐	☐
3. energy level/enjoyment of life	☐	☐	☐	☐	☐
4. ability to get around (for example walking, driving)	☐	☐	☐	☐	☐
5. ability to see and hear	☐	☐	☐	☐	☐
6. being free from anxiety	☐	☐	☐	☐	☐
7. being free from discomfort and pain	☐	☐	☐	☐	☐
8. not needing help/care	☐	☐	☐	☐	☐

Please now mark how satisfied you are with these individual areas.

How satisfied are you with your…	Dissatisfied	Slightly dissatisfied	Slightly satisfied	Moderately satisfied	Very satisfied
1. physical condition	☐	☐	☐	☐	☐
2. ability to relax	☐	☐	☐	☐	☐
3. energy level/enjoyment of life..	☐	☐	☐	☐	☐
4. ability to get around (for example walking, driving)	☐	☐	☐	☐	☐
5. ability to see and hear	☐	☐	☐	☐	☐
6. being free from anxiety …….	☐	☐	☐	☐	☐
7. being free from discomfort and pain	☐	☐	☐	☐	☐
8. not needing help/care	☐	☐	☐	☐	☐

The following aspects of health are worth considering particularly in people with movement disorder. As with the previous questions, please indicate how important the individual aspects are to you personally and how satisfied you have been with them.

Again, please answer all questions and think about how you have been feeling over the past 4 weeks and no how you feel at this precise moment.

FIRST, PLEASE CHECK HOW IMPORTANT EACH INDIVIDUAL ASPECT ID FOR YOUR HEALTH. BEFORE YOU BEGIN, PLEASE READ QUESTIONS 1-12 BELOW.

How important for you is (are)…	Not important	Slightly important	Moderately important	Very important	Extremely important
1. controllability/fluidity of movement	☐	☐	☐	☐	☐
2. absence of dizziness/steadiness when standing and walking ……	☐	☐	☐	☐	☐
3. hand dexterity throughout the day (e.g. when eating and writing)	☐	☐	☐	☐	☐
4. articulation/fluency of speech	☐	☐	☐	☐	☐
5. ability to swallow	☐	☐	☐	☐	☐
6. absence of bodily sensations…..	☐	☐	☐	☐	☐
7. bladder/intestinal function	☐	☐	☐	☐	☐
8. sexual excitability	☐	☐	☐	☐	☐
9. undisturbed sleep	☐	☐	☐	☐	☐
10. memory/clear thinking	☐	☐	☐	☐	☐
11. independence from help (e.g. when dressing and getting washed	☐	☐	☐	☐	☐
12. inconspicuousness of illness	☐	☐	☐	☐	☐

PLEASE NOW MARK HOW SATISFIED YOU ARE WITH THESE SAME ASPECTS.

How satisfied are you with …	Dissatisfied	Slightly dissatisfied	Slightly satisfied	Moderately satisfied	Very satisfied
1. controllability/fluidity of movement	☐	☐	☐	☐	☐
2. absence of dizziness/steadiness when standing and walking	☐	☐	☐	☐	☐
3. hand dexterity throughout the day (e.g. when eating and writing)	☐	☐	☐	☐	☐
4. articulation/fluency of speech	☐	☐	☐	☐	☐
5. ability to swallow	☐	☐	☐	☐	☐
6. absence of bodily sensation	☐	☐	☐	☐	☐
7. bladder/intestinal function	☐	☐	☐	☐	☐
8. sexual excitability	☐	☐	☐	☐	☐
9. undisturbed sleep	☐	☐	☐	☐	☐
10. memory/clear thinking	☐	☐	☐	☐	☐
11. independence from help (e.g. when dressing and getting washed)	☐	☐	☐	☐	☐
12. inconspicuousness of illness	☐	☐	☐	☐	☐

Appendix J. Caregiver Burden Inventory

Caregiver Burden Inventory

For each item circle a number in the columns to the right that represent how often the statement describes your feelings.

0 never
1 rarely
2 sometimes
3 quite frequently
4 nearly always

1	He/she needs my help to perform many daily tasks.	0	1	2	3	4
2	He/she is dependent on me.	0	1	2	3	4
3	I have to watch him/her constantly.	0	1	2	3	4
4	I have to help him/her with many basic functions.	0	1	2	3	4
5	I don't have a minute's break from his/her chores.	0	1	2	3	4
6	I feel that I am missing out on life.	0	1	2	3	4
7	I wish I could escape from this situation.	0	1	2	3	4
8	My social life has suffered.	0	1	2	3	4
9	I feel emotionally drained due to caring for him/her.	0	1	2	3	4
10	I expected that things would be different at this point in my life	0	1	2	3	4
11	I'm not getting enough sleep.	0	1	2	3	4
12	My health has suffered.	0	1	2	3	4
13	Caregiving has made me physically sick.	0	1	2	3	4
14	I'm physically tired.	0	1	2	3	4
15	I don't get along with other family members as well as I used to.	0	1	2	3	4
16	My caregiving efforts aren't appreciated by others in my family.	0	1	2	3	4
17	I've had problems with my marriage (or other significant relationship).	0	1	2	3	4
18	I don't get along as well as I used to with others.	0	1	2	3	4
19	I feel resentful of other relatives who could but do not help.	0	1	2	3	4
20	I feel embarrassed over his/her behavior.	0	1	2	3	4
21	I feel ashamed of him/her.	0	1	2	3	4
22	I resent him/her.	0	1	2	3	4
23	I feel uncomfortable when I have friends over.	0	1	2	3	4
24	I feel angry about my interactions with him/her.	0	1	2	3	4

Appendix K. Geriatric Depression Scale (GDS-15)

GDS

Instructions: Choose the best answer for how you felt over the past week.

1	Are you basically satisfied with your life?	Yes / No
2	Have you dropped many of your activities and interests?	Yes / No
3	Do you feel that your life is empty?	Yes / No
4	Do you often get bored?	Yes / No
5	Are you in good spirits most of the time?	Yes / No
6	Are you afraid that something bad is going to happen to you?	Yes / No
7	Do you feel happy most of the time?	Yes / No
8	Do you often feel helpless?	Yes / No
9	Do you prefer to stay at home, rather than going out and doing new things?	Yes / No
10	Do you feel you have more problems with memory than most?	Yes / No
11	Do you think it is wonderful to be alive now?	Yes / No
12	Do you feel pretty worthless the way you are now?	Yes / No
13	Do you feel full of energy?	Yes / No
14	Do you feel that your situation is hopeless?	Yes / No
15	Do you think that most people are better off than you are?	Yes / No

Appendix L. Performance Rating

Performance Rating Scoring Sheet

Prediction and post-diction

Before: '*How well do you think you will do this task*?' Choose from the list below
(Ask AFTER the practice task, present the show card)
After: 'How well do you think you did this task?' Choose from the list below
(Ask immediately AFTER the completing the task, present the show card)

Trail Making Test						
		Very Poor	Poor	Alright	Good	Very Good
TMT 1 – Scanning	Before	0	1	2	3	4
	After	0	1	2	3	4
TMT 2 – Numbers	Before	0	1	2	3	4
	After	0	1	2	3	4
TMT 3 – Letters	Before	0	1	2	3	4
	After	0	1	2	3	4
TMT 4 – Switching	Before	0	1	2	3	4
	After	0	1	2	3	4
TMT 5 –Speed	Before	0	1	2	3	4
	After	0	1	2	3	4
Colour-Word Interference						
		Very Poor	Poor	Alright	Good	Very Good
CWI 1 – Naming	Before	0	1	2	3	4
	After	0	1	2	3	4
CWI 2 – Reading	Before	0	1	2	3	4
	After	0	1	2	3	4
CWI 3 – Inhibition	Before	0	1	2	3	4
	After	0	1	2	3	4
CWI 4 – Switching	Before	0	1	2	3	4
	After	0	1	2	3	4

 Very Good

 Good

 Alright

 Poor

 Very Poor