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Executive dysfunction in Parkinson's disease: A review

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Executive dysfunction can be present from the early stages of Parkinson's disease (PD). It is characterized by deficits in internal control of attention, set shifting, planning, inhibitory control, dual task performance, and on a range of decision-making and social cognition tasks. Treatment with dopaminergic medication has variable effects on executive deficits, improving some, leaving some unchanged, and worsening others. In this review, we start by defining the specific nature of executive dysfunction in PD and describe suitable neuropsychological tests. We then discuss how executive deficits relate to pathology in specific territories of the basal ganglia, consider the impact of dopaminergic treatment on executive function (EF) in this context, and review the changes in EFs with disease progression. In later sections, we summarize correlates of executive dysfunction in PD with motor performance (e.g., postural instability, freezing of gait) and a variety of psychiatric (e.g., depression, apathy) and other clinical symptoms, and finally discuss the implications of these for the patients' daily life.

Idiopathic Parkinson's disease (PD) is one of the most common neurodegenerative disorders, affecting about 1–3% of the population older than 65 years (de Rijk et al., 2000). The prime characteristic of PD is degeneration of dopaminergic neurons in the substantia nigra pars compacta, which results in a drastic reduction in dopamine in the basal ganglia, particularly the posterior putamen in the early stages of the disease (Kish, Shannak, & Hornykiewicz, 1988). As the disease progresses, this degeneration extends to the anterior striatum/caudate, limbic nuclei, and neocortical regions (Kalaitzakis & Pearce, 2009). The associated symptoms are mainly motor, particularly bradykinesia and akinesia (slowness and poverty of movement), muscular rigidity, resting tremor, and posture and gait problems – together with a host of non-motor symptoms, which include the impairment of cognition.

The neuropsychological deficits in PD range from mild executive dysfunction in the early stages to mild cognitive impairment (MCI) and dementia in the later stages. In newly diagnosed untreated patients with PD, cognitive impairment has been reported in 18% (Aarsland et al., 2009) or 36% (Foltynie, Brayne, Robbins, & Barker, 2004) of incident cohorts. With disease progression, many patients show features of MCI (Aarsland et al.,

*Correspondence should be addressed to Marjan Jahanshahi, Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology, The National Hospital for Neurology & Neurosurgery, 33 Queen Square, London WC1N 3BG, UK (e-mail: m.jahanshahi@ucl.ac.uk).

2009), which has a mean prevalence of 27% (range 19–38%) (Litvan *et al.*, 2011). The diagnostic criteria for MCI in PD have been recently outlined by a task force of the Movement Disorder Society (MDS) (Litvan *et al.*, 2012). MCI can include executive dysfunction and impairment of attention and working memory (WM), as well as deficits confined to language, memory, or visuospatial domains. MCI is a predictor of dementia in PD, which in the long term develops in up to 80% of patients (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sørensen, 2003; Aarsland, Tandberg, Larsen, & Cummings, 1996; Hely, Reid, Adena, Halliday, & Morris, 2008). The diagnostic criteria for dementia in PD have also been outlined by an MDS task force (Emre *et al.*, 2007). Impairment of executive functions (EFs), particularly word fluency (WF), has been found to be a predictor of later development of dementia (Janvin, Aarsland, & Larsen, 2005; Levy, Jacobs, *et al.*, 2002; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007).

In this review, we focus on executive dysfunction, which can be present from the early stages of PD (Elgh *et al.*, 2009; Foltynie *et al.*, 2004). We start by defining EF and tests suitable for its assessment in PD. We then outline the specific nature of executive dysfunction in this disorder, consider the clinical features of the illness that influence or are related to executive dysfunction. We then review the changes in EF with progression of PD, and discuss the impact of dopaminergic treatment of PD on different EF and end by considering implications of executive dysfunction for daily life of patients.

What are executive functions?

Executive function refers to a set of cognitive processes that control goal-directed behaviours from goal formulation and intention formation to successful execution and processing of the outcome. Two models relevant to the conceptualization of EF are the supervisory attentional system (SAS) of Norman and Shallice (1986) and Baddeley and Hitch's (1974) multicomponent model of WM. According to the SAS model, routine actions are performed automatically and overseen by 'contention schedulers'. These are low-level control units, several of which can operate in parallel. It is therefore possible to perform two or more routine tasks at the same time without conflict between different action schemes as long as performance remains entirely automatic and supervisory control is not required. Conversely, non-routine actions need conscious attentional control and supervision, and are coordinated by the SAS. In the Baddeley and Hitch (1974) model, the central executive is the quintessential component of WM responsible for the attentional, conscious 'executive' control and the allocation of cognitive resources. The central executive has limited capacity. There is a strong consensus that the role of the prefrontal cortex is largely analogous to the 'central executive' or the SAS while the role of the basal ganglia has been equated with that of the 'contention schedulers', concerned with automatic control of action (Miller & Cohen, 2001; Norman & Shallice, 1986).

More recently, this concept of automatic versus controlled processing has undergone neuroanatomical refinement in relation to the pathophysiology of PD (Redgrave *et al.*, 2010). The dopaminergic neurons in the posterior putamen, which are severely affected in PD, are particularly relevant for the execution of automatic behaviours. Therefore, it has been suggested that PD patients compensate by relying on non-routine action control mediated by the relatively preserved rostromedial striatum. In accordance with previous concepts, due to basal ganglia dysfunction, PD patients need to exert cortical executive control even for routine tasks, which healthy individuals perform automatically. This

over-reliance on a 'goal-directed' mode of action control to compensate for a deficient automatic 'habit' system taxes executive and attentional processes in PD.

Given that a host of cognitive processes is essential for the control of goal-directed behaviours, many definitions of EF have been provided and a variety of cognitive processes have been subsumed under the term EF. Executive processes have been defined and classified according to different schemes. Lezak (1995) conceptualized EF as having four main components: volition, planning, purposive action, and effective performance. Definitions of EF have been expanded by others to include choice of strategies, switching to adjust to changing circumstances, and monitoring of task progression (Burgess & Alderman, 2004). Further component processes of EF noted by different researchers are concept formation, sequencing of complex actions, and cognitive flexibility (Anderson, Northam, Hendy, & Wrenall, 2001; Lafleche & Albert, 1995) while allocation of attention is implicitly included (Anderson *et al.*, 2001; Lezak, 1995; Norman & Shallice, 1986). Recently, the concept of EF has been even further expanded to include more general aspects of the control of behaviour such as emotional regulation, theory of mind (ToM), decision-making and risk taking, insight, and metacognition (i.e., knowledge and beliefs about our own cognitive processes and capacities) (Godefroy *et al.*, 2010).

In general, EFs are relevant to optimal functioning in daily life (Godefroy *et al.*, 2010). As shown in Table 1, Godefroy and the Group for the study of EFs (2010) have proposed criteria for the dysexecutive syndrome, which include behavioural disorders (e.g., apathy, hyperactivity, distractibility, stereotyped and perseverative behaviour, and environmental dependency) as well as cognitive deficits (response inhibition, rule deduction and generation, maintenance and shifting of set, information generation). For the clinical diagnosis of the dysexecutive syndrome, three or more domains must be impaired. As Table 1 in conjunction with the following sections shows, this is often the case for patients with PD. Although comorbidities such as apathy are a feature of PD and relevant to the consideration of the dysexecutive syndrome in the disorder, here our focus will be on cognitive executive deficits.

Assessment of executive function in PD

A list of standardized tests commonly used for the neuropsychological assessment of EF in PD is presented in Table 2. These include the Wisconsin Card Sorting Test (WCST), the Stroop, Trail Making Test (TMT), WF, Digit Span backwards (DIGSP-BW), Tower of London (ToL), the Hayling test, and Random Number Generation (RNG).

Executive dysfunction in PD has also been assessed with other tests. The Frontal Assessment Battery (FAB; Bugalho & Vale, 2011; Dubois, Slachevsky, Litvan, & Pillon, 2000) is a brief 6-item test of EF, which can be administered at the bedside. The Scales for Outcomes of Parkinson's Disease – Cognition (SCOPA-COG; Marinus *et al.*, 2003) is an assessment tool specifically developed for patients with PD to examine a range of cognitive functions including EF.

Several of the tests listed in Table 2 (e.g., ToL, Stroop) have been adapted for computerized administration. One computerized test used in the assessment of EF in PD is the intra-dimensional and extra-dimensional (ID/ED) set shifting test of the Cambridge Neuropsychological Test Automated Battery (CANTAB). This test was designed to decompose the component processes of the WCST such as discrimination learning, shifting to respond to another case of the same rule (same dimension), or shifting to a different rule (different dimension).

Table 1. Criteria for the behavioral and cognitive dysexecutive syndrome (Godefroy *et al.*, 2010)

Behavioural disorders	Cognitive disorders
Highly suggestive	
Global hypoactivity with apathy and/or abulia	Response inhibition
Global hyperactivity with distractability and/or psychomotor instability	Rules deduction and generation
Stereotyped and perseverative behaviour	Maintenance and shifting of sets
Environmental dependency (imitation and utilization behaviour)	Information generation (fluency tasks)
Supportive deficits and developing areas	
Disorders of emotional control (apathy, euphoria, moria (witzelsucht)[a], emotional lability)	Planning
Disorders of social behaviour	Response initiation and sustained alertness
Disorders of sexual, eating, and urinary behaviour	Coordination of dual tasks
Spontaneous confabulation, reduplicative paramnesia	Episodic memory strategic processes (retrieval and memory selection)
Anosognosia, anosodiaphoria	Theory of mind and metacognitive processes

Note. Highly suggestive: Impairment demonstrated in at least two studies showing a significant relation between the impairment and the lesion of the frontal subcortical network (typically comparison between anterior and posterior lesions).

Supportive deficits and developing areas: Impairment demonstrated in a group (or subgroup) of patients compared with healthy controls or controversial results across studies or limited number of studies.

To be considered as dysexecutive, the disorder should not be more readily explained by perceptuo-motor, psychiatric (depression, manic state, or obsessive–compulsive disorder), or other cognitive (language, memory, visuospatial) disturbances.

Table reproduced, with permission, from Godefroy *et al.* (2010).

[a]Fatuous affect, silliness combined with general indifference.

Solely relying on standard clinical or computerized tests to assess EF has recently come under scrutiny. Individual patients often perform well in a clinical or laboratory setting, but demonstrate disorganized behaviour at home in a less structured environment (Godefroy *et al.*, 2010). As a result, there has been a move towards the development of more naturalistic tests of EF such as the Six Elements Test (Shallice & Burgess, 1991) incorporated in the Behavioural Assessment of Dysexecutive Syndrome battery (Wilson, Alderman, Burgess, Emslie, & Evans, 1996). Another related approach has been to use patient reports of their cognitive problems together with ecologically valid and naturalistic tests of EF. In conjunction with measures of activities of daily living (ADL), these are particularly valuable for the management of problems in daily life. Godefroy *et al.* (2010) compared the levels of autonomy and functioning in daily life of PD patients with several ADL measures with scores from standard cognitive tests of EF (e.g., WF, Stroop, WCST, TMT), the patients' rates of behavioural-clinical dysexecutive syndrome (42%) and cognitive dysexecutive syndrome (39%) were similar.

Table 2. Tests of executive function used in neuropsychological assessment and the main processes involved in each test

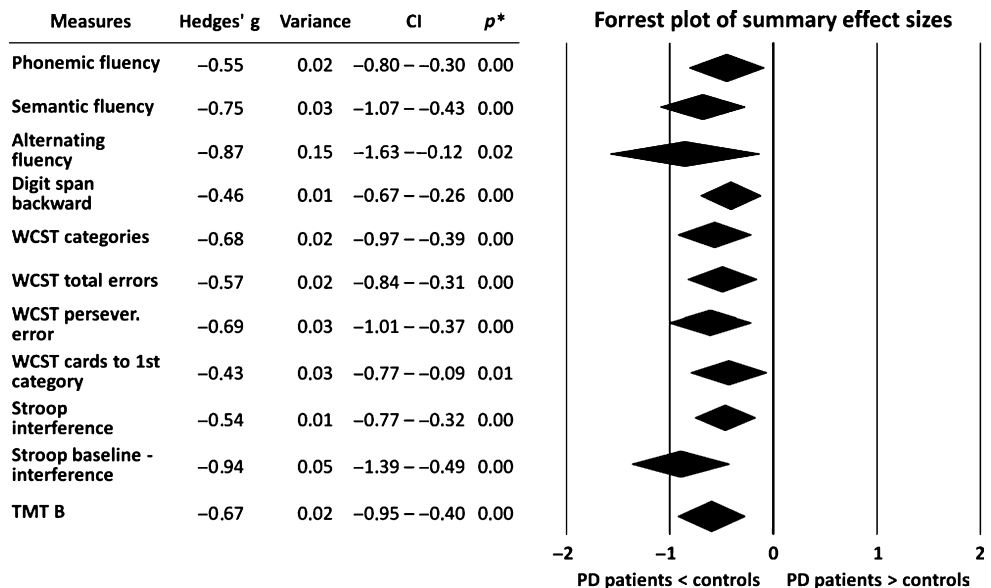| Test	Description	Processes involved
Wisconsin Card Sorting Test (WCST, various versions) and other card sorting tests	The WCST (Nelson, 1976) uses cards with geometrical figures that differ in one or more dimensions (shape, colour, number). Participants are presented with the cards one by one and have to sort these (i.e., discover a 'rule') by matching each to one of four stimulus cards differing in the same dimensions, with the rule changing after a fixed number of correct sorts. There are other versions with slightly different instructions. The main scores are the number of categories correctly sorted and the number of perseverative and non-perseverative errors	Set maintenance Set shifting Concept formation Rule use Inhibition Use of feedback
Stroop	The Stroop (Stroop, 1935) requires participants to name the colour of ink of colour words printed in incongruent ink as fast and accurately as possible, and in a control task to name the colour of ink of coloured rectangles as fast and accurately as possible. The time taken to complete each test and self-corrected and uncorrected errors are recorded. The difference of the two completion times of the interference and control tasks provides a measure of the Stroop effect	Conflict resolution Response inhibition Response generation
Trail Making Test (TMT)	In the simplest form of the TMT (Reitan, 1958), participants are asked to use a pencil to trace, as fast and accurately as possible, a sequence of numbers (Part A: 1-2-3-4, etc.) or alternating letters and numbers (Part B: A-1-B-2, etc.) that are presented on a sheet. Completion time for each version is recorded and the difference between the two completion times is an index of set shifting	Behavioural regulation Response initiation Response inhibition Set shifting/cognitive flexibility
Word fluency (WF)	For WF (Benton, 1968) participants produce as many words as they can think of beginning with a particular letter (phonemic) or belonging to a particular category, e.g., fruit (semantic), for 60s each, while avoiding proper nouns, numbers, and repetitions of the same word or word root (phonemic version). The number of correct words generated and repetition and set loss errors are recorded	Response generation Set maintenance Response inhibition Switching between clusters Monitoring

Continued

Table 2. (*Continued*)

Test	Description	Processes involved
Digit Span backwards (DIGSP-BW)	The DIGSP-BW (Wechsler & Stone, 1987) requires participants to repeat sequences of numbers of increasing length (2–9 items) in the reverse order of presentation by the examiner. The score is the number of correct items achieved and a scaled score can be derived using normative data	Holding information in working memory (WM) Manipulating of information in WM
Tower of London (ToL) and other tower tests	The ToL (Owen *et al.*, 1992) requires participants to move coloured balls across different-sized pegs to match a target configuration. They must always move just one ball at a time, while trying to make the minimal number of moves. The score is the number of moves. There are similar tower tasks with slightly different designs	Planning Inhibition Rule application
Hayling Sentence Completion Task (Hayling)	The Hayling (Burgess, 1997) involves completion of incomplete sentences read aloud and has two parts. In the initiation part, participants first complete each sentence as fast as possible with a highly associated missing word that makes the sentence meaningful. In the inhibition part, the sentence has to be completed with a word completely unconnected with the meaning of the sentence. The completion times are recorded and the degree to which the words generated in the inhibition section are related to the meaning of the sentence is determined and scored as A or B type errors	Response initiation Response inhibition
Random Generation of Numbers (RNG)	For RNG (Spatt & Goldenberg, 1993), participants are provided with a response set, e.g., numbers 1–9, and instructed to produce random sequences of numbers in pace with an external stimulus. The items produced are analysed for several forms of bias (e.g., counting bias, repetition bias, random generation index, etc.)	Response generation Response inhibition Monitoring Strategy shifting

The nature of executive dysfunction in PD

Executive dysfunction is perhaps the best defined cognitive impairment in PD. Early studies showed that relative to age-matched healthy controls, PD patients had deficits on 'classical' executive tests such as the WCST (Cooper *et al.*, 1992; Gotham, Brown, & Marsden, 1988; Lees & Smith, 1983; Taylor, Saint-Cyr, & Lang, 1986), Stroop (Gotham *et al.*, 1988; Taylor *et al.*, 1986), TMT (Gotham *et al.*, 1988; Taylor *et al.*, 1986), WF (Cooper *et al.*, 1992; Gotham *et al.*, 1988; Herrera, Cuetos, & Ribacoba, 2012; Taylor *et al.*, 1986), and the Tower of Toronto planning task (Saint-Cyr, Taylor, & Lang, 1988; Taylor & Saint-Cyr, 1995). These findings have been replicated in numerous later studies (e.g., Bouquet, Bonnaud, & Gil, 2003; Dujardin, Defebvre, Krystkowiak, Blond, & Destée, 2001; Foltynie *et al.*, 2004; Muslimovic, Schmand, Speelman, & de Haan, 2007; Uekermann *et al.*, 2004). In fact, a recent meta-analysis (Kudlicka, Clare, & Hindle, 2011) combined data of 33 studies on EF in early-stage (Hoehn & Yahr I–III) non-demented and unmedicated PD, based on standard neuropsychological tests. The results of this meta-analysis confirmed that patients with PD show significant impairment in WF tasks (semantic, phonemic, and alternating), DIGSP-BW, TMT, and various measures of the WCST and the Stroop (Figure 1). The effect size was very similar across the various measures of EF, with alternating WF and the Stroop being slightly more affected than the other measures. Below, we review some of the most common deficits of EF in PD reported in the literature.

Internal control of attention

In general, cognitive deficits become more prominent when patients have to rely on internal control of attention than when cues are available to guide their attention (Brown

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

Forrest plot of summary effect sizes

−2   −1   0   1   2

PD patients < controls   PD patients > controls

Figure 1. The results of a meta-analysis of performance on common tests of executive function in Parkinson's disease, showing the effect sizes relative to healthy controls. Figure reproduced, with permission, from Kudlicka *et al.* (2011). Hedges' g = corrected mean weighted effect size; CI = 95% confidence interval; WCST = Wisconsin Card Sorting Test; TMT B = Trail Making Test, part B. *Two-tailed test.

& Marsden, 1988a,b). Brown and Marsden (1988a) compared patients with PD and healthy controls when they performed either a cued choice reaction time task or the WCST. In the reaction time task, each trial contained an external cue indicating how the stimulus was to be processed. In contrast, on the WCST, there was no cue to indicate which of the three stimulus attributes was currently relevant. Therefore, only on the WCST participants had to focus attention on one attribute by means of some form of self-directed or 'internal' control. Patients with PD performed differentially worse than healthy controls on the WCST, but not the reaction time task, suggesting that they have problems with internal control of attention. These findings were confirmed in a subsequent experiment in which patients with PD were tested on two different versions of a computerized Stroop test in which the relevant stimulus attribute was either cued before each trial, or participants had to remember which attribute was currently relevant for making a response. PD patients but not controls performed differentially worse on the version without cues, which required internal attentional control (Brown & Marsden, 1988b). Similarly, on a modified version of the Odd Man Out test, patients with PD were impaired on shifting attention on the task with internal cues, but were normal on the tasks with external cues (Hsieh, Lee, & Tai, 1995).

According to the theoretical concepts of Norman and Shallice (1986) and Baddeley and Hitch (1974) discussed above, internal control of attention is essential for performance of non-routine tasks in daily life. Consequently, patients with PD encounter problems with tasks that require effortful processing (Weingartner, Burns, Diebel, & Le Witt, 1984) and self-directed formation of strategies (Taylor *et al.*, 1986). The speed of performance can further affect the level of functioning in PD. While pacing stimuli at slow rates can be utilized by the patients and improve performance on various tasks (Brown & Marsden, 1991; Dirnberger, Frith, & Jahanshahi, 2005), at fast rates keeping the pace becomes demanding in itself and necessitates extra executive control, which leads then to differentially poorer performance in PD.

There is also evidence that patients with PD have deficits in internal control of actions (Georgiou *et al.*, 1993, 1994; Jahanshahi *et al.*, 1995). For example, while PD patients relative to matched healthy controls show under-activation of the putamen, the dorsolateral prefrontal cortex, and supplementary motor area during self-initiated actions, the patterns of brain activation did not differ between the groups for externally triggered actions (Jahanshahi *et al.*, 1995).

The effects of dopaminergic medication on internal control of attention and action – mainly investigated with a range of reaction time tasks – are inconsistent, suggesting that medication improves overall speed of movement execution, but can have differential effects on the higher cognitive processes involved (see Jahanshahi, 2003 for a review).

Set shifting

Set shifting refers to the ability to switch rapidly between different response sets (Anderson, 2002). Early studies used the WCST and the TMT to demonstrate that patients with PD had problems with set shifting (Taylor & Saint-Cyr, 1995). In classical tests such as the WCST, several types of attentional shifting are involved. Later studies used more refined tasks such as the ID/ED shift test from the CANTAB battery to characterize the mechanisms underlying the patients' deficits (e.g., Robbins, 2007). Initial studies reported impaired set shifting in medicated and non-medicated PD patients on the computerized ID/ED shift test, the mechanisms of which were further clarified in subsequent studies (Cools, Barker, Sahakian, & Robbins, 2001; Owen *et al.*, 1993).

Although patients with frontal lesions were worse than controls in their ability to shift attention *away from* a previously relevant stimulus dimension, medicated patients with PD were worse at shifting attention *to* a previously irrelevant dimension; non-medicated patients with PD were impaired in *both* conditions (Owen *et al.*, 1993). Subsequently, Cools, Rogers, Barker, and Robbins (2009) demonstrated that the deficit shown by medicated PD patients is modulated by the salience of stimuli and does not reflect a problem with shifting *per se*, but rather disproportionate control by bottom-up attention to a salient dimension. The work of the Cambridge group and other groups on set shifting has also been important in identifying changes in EF with progression of PD and the influence of heterogeneity outlined below (Miah, Dubbelink, Stoffers, Deijen, & Berendse, 2012; Williams-Gray, Hampshire, Barker, & Owen, 2008).

Deficits in task switching for unmedicated patients with PD have also been reported for a digit comparison task in which participants had to compare the magnitude or shape of two visually presented digits (Fimm, Bartl, Zimmermann, & Wallesch, 1994). In contrast, a deficit in set shifting was not observed, regardless of medication status, when PD patients had to switch between the spatial and lexigraphic dimension in a letter search/identification task (Rowe *et al.*, 2008). The absence of negative feedback in this task was considered as a possible explanation of these findings.

Planning

Planning is the ability to identify and organize the steps and elements (e.g., skills or stimuli) needed to formulate and carry out an intention and achieve a goal (Lezak, 1995). It is a multi-faceted EF involving conceptual activity, impulse control, and sustained attention (Lezak, 1995). The ToL task and very similar versions such as the Tower of Toronto or Tower of Hanoi are among the most established tests of planning. PD patients were shown to have deficits in planning on the Tower of Toronto task (Saint-Cyr *et al.*, 1988). Owen, Doyon, Dagher, Sadikot, and Evans (1998), Owen *et al.* (1992) later conducted a number of studies in patients with PD with a CANTAB-modified ToL task (controlling for speed of movement initiation and execution and allowing a distinction between initial and subsequent thinking times) in which they examined patients at different stages of PD, on and off dopaminergic medication, and compared their performance to that of healthy controls as well as patients with frontal lesions (Table 3). Never medicated *de novo* patients with mild symptoms were not impaired on any of the measures, whereas medicated patients with mild or severe motor symptoms had longer latencies ('initial thinking times') to initiate correct responses and those with severe PD also had reduced accuracy. In contrast, for patients with frontal lesions, 'initial thinking times' were not significantly altered and were most similar to the controls, whereas their 'subsequent thinking times' were altered and their accuracy was reduced. The latter result was confirmed in a study using the Tower of Hanoi test (Pascual-Sedano *et al.*, 2008). Subsequently, in an imaging study, Lewis, Dove, Robbins, Barker, and Owen (2003) examined sub-samples of PD patients with normal and impaired planning on a ToL task and found that those who performed normally had prefrontal and striatal activation comparable to controls, whereas PD patients who were impaired on the ToL showed decreased activation of the prefrontal cortex and the striatum.

De Vito *et al.* (2012) 'encouraged [participants] to produce temporally and contextually specific events and to vividly imagine novel and plausible future episodes, given their current plans'. Medicated patients with PD had difficulties imagining possible future 'real life' scenarios, which was associated with poor scores

Table 3. Pattern of impairment on Tower of London (ToL) test in patients with non-medicated Parkinson's disease, patients with medicated mild or severe Parkinson's disease, and patients with lesions of the frontal lobe. Modified from Owen *et al.* (1992)

Task	Non-medicated Parkinson's disease (mild)	Medicated Parkinson's disease (mild)	Medicated Parkinson's disease (severe)	Frontal lobe lesions
Minimum move solutions	Ok	Ok	Impaired	Impaired
Initial thinking time	Ok	Impaired	Impaired	Ok
Subsequent thinking time	Ok	Ok	Ok	Impaired

on the FAB. Problems with planning in PD may also partly explain the patients' failure on tasks of 'prospective memory' – remembering to do something in the future, such as to keep an appointment or pick up groceries at the market (Altgassen, Zollig, Kopp, Mackinlay, & Kliegel, 2007).

In line with theoretical concepts of EF (Baddeley & Hitch, 1974; Norman & Shallice, 1986), it is possible that the deficits on these planning tasks partly relate to their reliance on an internal locus of attention and action control. As noted above, patients with PD are maximally impaired on tasks where they have to rely on self-generated strategies for planning and organizing behaviour, while their performance may be improved by externally provided plans and cues (Brown & Marsden, 1988a,b).

A recent review of prospective memory in PD (Kliegel, Altgassen, Hering, & Rose, 2011) suggested that for time-based tasks without external stimuli, patients are particularly impaired in planning (intention formation) and action initiation, whereas performance on tasks involving external stimuli (i.e., focal cues) is generally better. However, prospective memory on a time-based paradigm requiring three independent actions (writing own name on a sheet of paper, telling the examiner to turn on the computer, replacing the telephone receiver) after 10-min delays was largely restored to normal levels under dopaminergic medication (Costa *et al.*, 2008).

Inhibitory control and conflict resolution

A number of computerized tasks such as the Simon task, the Eriksen Flanker task, go/no go reaction times (RT), and stop signal tasks have been used to examine specific components of EF, inhibitory control over prepotent responses, and conflict resolution. Inhibitory control of automatic responses requires conscious supervision by the central executive (Baddeley & Hitch, 1974) and inhibition of prepotent habitual responses was one of the situations considered to engage the SAS by Norman and Shallice (1986). The results of these studies have shown that PD patients perform worse than healthy controls and have problems with the inhibition of prepotent responses and conflict resolution. On go/no go reaction time tasks, PD patients showed differentially greater impairment relative to controls with increased complexity of the decision (Cooper, Sagar, Tidswell, & Jordan, 1994). On the Simon task, interference during the incongruent trials was greater in PD patients who also made more errors than matched controls (Praamstra & Plat, 2001; Wylie, Ridderinkhof, Bashore, & van den Wildenberg, 2010). On the Eriksen Flanker task, PD patients showed greater interference effects from the incongruent flanker stimuli (Wylie *et al.*, 2009a), particularly when performing the task under speed instructions (Wylie *et al.*, 2009b). Relative to age-matched controls, PD patients have prolonged stop signal RTs on the standard task (Gauggel, Rieger, & Feghoff, 2004), as well as on a more

demanding conditional stop signal task (Obeso, Wilkinson, Casabona, *et al.*, 2011). Furthermore, in the latter study, PD patients also had greater difficulty in suppressing prepotent or habitual responses on the Stroop, Hayling and RNG, which suggested the existence of a generalized inhibitory deficit across motor and cognitive domains in PD (Obeso, Wilkinson, Casabona, *et al.*, 2011). Levodopa medication did not influence the speed of stopping on this task (Obeso, Wilkinson, & Jahanshahi, 2011).

More recently, Favre, Ballanger, Thobois, Broussolle, and Boulinguez (2013) investigated bradykinesia in PD in terms of release of proactive inhibitory control in warned and unwarned simple reaction time tasks and also examined the effect of dopaminergic medication and deep brain stimulation (DBS) of the subthalamic nucleus (STN). Relative to controls, the PD patients were impaired in releasing proactive inhibition when this was internally driven, which was considered responsible for their slowness in movement initiation. Although RT were generally improved by dopaminergic medication, medication status did not influence the internal control of proactive inhibition. In contrast, STN DBS had no global effect on RTs, but restored the voluntary release of proactive inhibition.

Dual task performance

Patients with PD are generally impaired in the concurrent performance of two tasks, which requires additional executive control. Given the patients' limited capacity to perform even single routine actions, the extra demands of supervisory control associated with the execution of the secondary task can exceed the capacity of their already overloaded central executive or SAS (Baddeley & Hitch, 1974; Norman & Shallice, 1986). Consequently, a severe impairment on such 'dual task' performance has been demonstrated in PD in experimental studies in the motor (Benecke, Rothwell, Dick, Day, & Marsden, 1986; Brown, Jahanshahi, & Marsden, 1993) and cognitive domains (Brown & Marsden, 1991; Brown, Soliveri, & Jahanshahi, 1998). For example, performance of a computerized version of the Stroop together with a secondary task was differentially worse in patients with PD than controls, and patients performed worse when this secondary task made additional executive demands (i.e., RNG) than when it was less resource-demanding (i.e., tapping) (Brown & Marsden, 1991). Similarly, on paced RNG or random letter generation, patients with PD not only showed greater serial bias in their responses than healthy controls, but this bias became differentially greater when the random generation task was performed concurrently with a secondary manual tracking or card sorting task (Brown *et al.*, 1998; Robertson, Hazlewood, & Rawson, 1996; Spatt & Goldenberg, 1993).

The patients' impairment in dual tasking is relevant to daily life, given that even rather simple tasks such as walking, which healthy people can perform automatically, require attentional control in patients with PD. Such a patient may therefore 'stop walking when talking'. In fact, a recent study in PD showed that 12% of the variance in interference of a dual task on walking speed was explained by reduced EF as measured by the Brixton test (a visuospatial sequencing task with rule changes), in conjunction with motor deficit (UPDRS-III). This indicates that automaticity of performance under complex walking conditions is multi-dimensionally determined (Rochester *et al.*, 2008).

Decision-making

Decision-making is the ability to choose between two or more alternative behaviours that need consideration among the available options according to the potential outcomes and

the motivational drive and goals of the individual. It involves the consideration of different options according to their relative value and advantages and disadvantages. The tasks used to study decision-making can be divided into two main categories (Brand, Labudda, & Markowitsch, 2006). In decision-making under risk, the participants are aware of the exact probabilities of different outcomes, whereas in decision-making under uncertainty, they decide without knowing what the probabilities of certain outcomes are. The latter, therefore, involves learning by trial and error, whereas in principle, this essential information is always available for decision-making under risk.

The Iowa gambling task (IGT) was designed to examine decision-making under ambiguity. Participants are asked to choose cards out of four different decks. Each card is associated with either an advantageous outcome (monetary gain) or a disadvantageous outcome (monetary loss). Initially, participants are unaware that two of the decks are 'advantageous' – cards selected from these decks are on average associated with either small monetary rewards or even smaller losses – whereas the other two decks are 'disadvantageous' – cards selected from these decks are associated with either large rewards or even larger losses. Repeated selection of cards from the 'advantageous' decks will result in overall profit, whereas repeated selection of cards from the 'disadvantageous' decks will result in a net loss over time. The results for patients with PD are not clear (Poletti, Cavedini, & Bonuccelli, 2011). Five studies with non-demented unmedicated or medicated PD patients found no significant impairments on the IGT (Czernecki *et al.*, 2002; Euteneuer *et al.*, 2009; Mimura, Oeda, & Kawamura, 2006; Poletti *et al.*, 2010; Thiel *et al.*, 2003), whereas three studies showed that PD patients selected more cards from disadvantageous decks than healthy controls (Kobayakawa, Koyama, Mimura, & Kawamura, 2008; Pagonabarraga *et al.*, 2007; Perretta, Pari, & Beninger, 2005). Several studies found no significant effect of dopaminergic medication on the IGT in PD (Czernecki *et al.*, 2002; Kobayakawa *et al.*, 2008; Perretta *et al.*, 2005).

The Cambridge gambling task (CGT) examines decision-making under risk. Participants are presented with a row of red or blue boxes (initially, five red/five blue) and informed that a single token has been placed under one box. Participants are then asked to bet on whether the token sits under a red or blue box. In subsequent trials, the proportion of red and blue boxes changes. On every trial, the participants are thus fully aware of the risk associated with a red or blue bet, and are expected to adjust their betting behaviour accordingly. Cools, Barker, Sahakian, and Robbins (2003) demonstrated that patients with PD are impaired on this task particularly when 'on' dopaminergic medication, exhibiting abnormal betting behaviour that might be associated with impulsivity and/or delay aversion, whereas Delazer *et al.* (2009) found a similar sample of PD patients not impaired. The Game of Dice task also examines decision-making under risk. Patients with PD are impaired on this task when unmedicated (Brand *et al.*, 2004) as well as when tested on dopaminergic medication (Euteneuer *et al.*, 2009).

Despite some similarities between the various gambling tasks, it is important to note that the tasks employed involve different processes and have different functional anatomical correlates. Decision-making under uncertainty on the IGT engages orbito-frontal areas (Seguin, Arseneault, & Tremblay, 2007), whereas decision-making under risk as in the CGT involves activation of the dorsolateral prefrontal cortex. Accordingly, these decision-making tasks are mediated by different basal ganglia-prefrontal circuits. This may explain possible differences in the effects and side-effects of dopaminergic medication on these different forms of decision-making task in PD. In clinical practice, however, only patients under dopaminergic medication (mostly with a dopamine agonist) appear vulnerable to develop pathological gambling (Djamshidian, Cardoso, Grosset, Bowden–

Jones, & Lees, 2011). Besides dopamine agonist therapy, a recent review found that lower scores on the DIGSP-BW, impulsive traits, and depression are associated with impulse control disorder in PD (Poletti & Bonuccelli, 2012).

Social cognition and theory of mind

Theory of mind is the ability to attribute mental states to oneself and others and to understand that others have beliefs, desires, and intentions different from one's own. Executive processes are relevant to social interaction and social cognition, including ToM. With the expansion of the definition of EF to encompass social cognition and ToM, a more recent body of work has examined these aspects of functioning in PD. Saltzman, Strauss, Hunter, and Archibald (2000) were the first to examine ToM and other EFs in 11 non-demented patients with PD. Compared with healthy controls, the patients were impaired on several ToM tasks (failure to predict other's beliefs in false belief story; failure to successfully conceal own actions from others) and also on standard measures of EF (WF and design fluency). The moderate positive correlations between ToM and the standard tests of EF suggest some overlap but also distinct processes being tapped by these measures. Santangelo *et al.* (2012) reported that 33 non-demented and non-depressed medicated patients with early PD performed worse than healthy controls on cognitive and affective ToM tests (Emotion Attribution Task vs. Advanced Test of ToM). The patients' lower cognitive scores on the ToM tests were associated with lower scores in the FAB, whereas lower affective ToM scores correlated only with behavioural scales such as the Frontal Behavioral Inventory and Apathy Evaluation Scale, suggesting two distinct domains of ToM, which are both impaired in PD. These results confirmed that the patients had problems with deciphering the desires and intentions of others when these differed from their own (Santangelo *et al.*, 2012). The patients' deficits were not associated with the levodopa equivalent dose. In another study, patients with PD tested 'off' dopaminergic medication were also reported to have difficulties with deception and telling lies, a deficit related to prefrontal hypometabolism as revealed by PET imaging (Abe *et al.*, 2009).

Appreciation of humour, which also requires social cognition and ToM, is reduced in patients with PD. Thaler *et al.* (2012) compared 39 medicated patients with PD and healthy controls using short video clips, audio sketches, and cartoons and found that the patients' sense of humour was poorer. The difference between patients and controls was strongest when 'non-obvious' humorous content was displayed via cartoons (i.e., when deciphering emotional and cognitive content was more effortful). In the same study, the patients' specific ToM deficit was evident by low 'social' subscores in the Sense of Humor Questionnaire, whereas other subscores were less impaired. The subsample of patients with poorer appreciation of humour scored lower on the FAB.

In summary, there is evidence that patients with PD have deficits on a range of executive processes including internal control of attention, set shifting, planning, inhibitory control, and conflict resolution. PD patients are also impaired on dual task performance and on a range of decision-making and social cognition tasks. These deficits in EF in PD could represent limitations of attentional resources or deficient allocation of resources (Brown & Marsden, 1988a,b). Many of these deficits (e.g., in planning and control of attention) have been shown to be associated with dysfunction at the level of the basal ganglia as well as the prefrontal cortex. In relation to the theoretical models reviewed above, PD patients' deficits are therefore consistent with problems with contention scheduling (i.e., low-level automatic processing) as well as dysfunction of the

SAS or the central executive (i.e., high-level controlled processing) (Dujardin, Degreef, Rogelet, Defebvre, & Destée, 1999).

Dopamine and executive function: The dopamine overdose hypothesis

In early PD, the loss of dopaminergic neurons in the striatum is not uniform and is greatest in the putamen and dorsal caudate (i.e., motor and dorsolateral circuits). The ventral striatum is relatively spared (Kish *et al.*, 1988), so that functions of the limbic and orbitofrontal circuits are mostly intact. According to the 'dopamine overdose' hypothesis, the observed cognitive deficits on medication are due to the fact that, while dopaminergic medication increases pathologically low dopamine levels in the putamen and dorsal striatum, it overstimulates the ventral striatum, which is not as severely dopamine depleted in the early stages of PD. This impairs the functioning of the circuits that pass through the 'overdosed' ventral striatum (Gotham *et al.*, 1988). Thus, a dose of dopaminergic medication which is sufficient to ameliorate symptoms associated with dysfunction of the motor and associative circuits can overdose the ventral striatum and impair the functions mediated by the limbic and orbitofrontal circuits (Gotham *et al.*, 1988), which then leads to adverse behavioural and cognitive consequences in specific EF tasks. The 'dopamine overdose' hypothesis explains the differential effects which dopaminergic medication can produce on motor versus specific cognitive functions, and can further explain why the effects of dopaminergic medication vary depending on the type of task, the specific executive processes involved, and the stage of illness in PD.

The 'dopamine overdose' hypothesis has some empirical support. Dopaminergic treatment of PD improves performance on EF tests mediated by the dorsolateral fronto-striatal circuit such as some deficits of planning and set shifting (Cools *et al.*, 2001; Gotham *et al.*, 1988; Lange *et al.*, 1992) but on medication patients become impaired on tasks mediated by the limbic and orbitofrontal circuits such as conditional associative learning (Gotham *et al.*, 1988), reversal learning (Swainson *et al.*, 2000), reward learning (Cools, Altamirano, & D'Esposito, 2006), probabilistic classification learning (Jahanshahi, Wilkinson, Gahir, Dharminda, & Lagnado, 2010), and risk-taking paradigms (Brand *et al.*, 2004; Cools *et al.*, 2001, 2003; Mimura *et al.*, 2006; Molina *et al.*, 2000; Voon & Fox, 2007). The effects of dopaminergic medication on social cognition seem complex, possibly because many neurotransmitters are involved and these processes are affected by dysfunction of cortical as well as mesolimbic structures (Thaler *et al.*, 2012).

Predictions made by the 'dopamine overdose' hypothesis have also been confirmed by a study specifically designed to test it. Miah *et al.* (2012) reported that 23 *de novo* PD patients were worse in their use of strategies on the CANTAB test of spatial WM than 55 medicated patients. In contrast, for the medicated patients, increasing doses of dopaminergic medication were associated with poorer performance on the CANTAB pattern recognition memory (PRM). These results suggest that while dopamine replacement therapy improved specific EFs (e.g., strategy use on the spatial WM task), it was associated with worsening of performance on a task mediated by the temporal lobes (PRM).

When considering the effects of dopaminergic medication on EF, the specific dopamine receptors which are activated appear to be important. While pergolide, a mixed D1/D2 agonist, did not produce any adverse effects on cognition, pramipexole, a mixed D2/D3 agonist, made WF and verbal memory worse (Brusa *et al.*, 2005). Dopaminergic overdose is also considered as a cause of pathological gambling as measured by the IGT, a problem only observed with dopamine agonists, but not with levodopa owing to the

different receptor profiles of these medications (Djamshidian *et al.*, 2011). In general, development of impulse control disorders such as pathological gambling, pathological shopping, hypersexuality, binge, and compulsive eating is often associated with dopaminergic medication, particularly dopamine agonists, in predisposed patients (Evans, Strafella, Weintraub, & Stacy, 2009; MacDonald & Monchi, 2011; Weintraub *et al.*, 2010). In future research, testing patients both off and on their dopamine medication while they perform various tests of EF will help ascertain whether medication is improving or impairing performance on specific tests.

Progression of PD and executive function

The studies listed in Table 4 have examined cognition, including EF, in cohorts of early and untreated PD. The rates of cognitive impairment across these studies range from 19% to 36%, with subjective complaints even higher at 59%, indicating that cognitive impairment including executive deficits are present from the early stages of the illness even before medication is introduced. Aarsland *et al.* (2009) tested a sample of 196 newly diagnosed, non-demented PD patients on the Serial Sevens from the Mini Mental State Examination (MMSE), semantic fluency, the Silhouettes and Cubes subtests from the Visual Object and Space Perception battery, and the Stroop. They found that even at the early stage of the illness shortly after diagnosis, PD patients had a twofold increased risk for MCI relative to a group of 201 healthy controls. In a more recent study, Miah *et al.* (2012) compared the performance of a group 23 *de novo* and 55 medicated PD patients with mild-to-moderate disease on five CANTAB subtests (strategy use in spatial WM, ToL, ID/ED set shifting, spatial short-term memory, PRM) and random generation of movements (a test analogous to RNG). The *de novo* patients were more impaired in strategy use on the spatial WM task than the medicated patients and healthy controls, but the group differences on the other four CANTAB tests were not significant. The generation of random sequences was impaired in both the *de novo* and medicated groups.

    Cross-sectional studies (Table 4) show that in parallel with the general progression of disease in PD, there is a gradual decline of EF. Worsening of the motor symptoms is associated with greater and more extensive cognitive impairment, including poorer EF. Progression of PD has a strong influence not only on the severity but also on the nature of executive deficits. For example, while attentional set shifting is impaired in all stages of PD irrespective of medication, deficits in EF as examined by the ToL are found for pre-planning in mild medicated PD and progress to the execution of these plans in severe medicated PD (Owen *et al.*, 1992). Similarly, while patients with mild medicated PD are impaired only on tests of spatial WM but not verbal or visual WM, all forms of WM are impaired in severe medicated PD, whereas unmedicated *de novo* patients with mild clinical symptoms are unimpaired on all three tasks (Owen, Iddon, Hodges, Summers, & Robbins, 1997).

    A number of longitudinal studies in PD have examined changes in cognition and EF over time. Foltynie *et al.* (2004) administered the National Adult Reading test, the MMSE, phonemic WF, the ToL and PRM from the CANTAB to 195 patients identified in an incident cohort of PD in Cambridgeshire, UK. Thirty-six per cent were classified as having cognitive impairment in the initial examination. In a follow-up study 3–5 years later, 79% of this sample was reassessed. Ten per cent of these had developed dementia, while 57% showed evidence of cognitive impairment, with fronto-striatal deficits being more common in the non-demented group. After correcting for age, tests involving posterior

Table 4. Studies of cognitive impairment in *de novo* and early Parkinson's disease

Study	Sample type	Sample size	Mean age (years)	Mean duration (months)	Assessments	Cognitive impairment (%)
Foltynie et al. (2004)	Population-based	159	70	30	MMSE, Neuropsych	36
Muslimovic et al. (2005)[a]	Clinic-based, newly diagnosed	115	66	19	MMSE, Neuropsych	24
Aarsland et al. (2009)[a]	Population-based, newly diagnosed, untreated	196	68	28	MMSE, Neuropsych	19
Elgh et al. (2009)[a]	Population-based, newly diagnosed, untreated	88	68	25	Neuropsych	30
Kandiah et al. (2009)	Clinic-based, newly diagnosed	106	61	Not provided	MMSE	31
Benoit-Leon et al. (2011)[a]	Population-based	46	78	23	MMSE, Neuropsych	59[b]

Note. Neuropsych = Neuropsychological assessment.
[a]Healthy control group included. [b]In contrast to all other studies, Benoit-Leon et al. report *subjective* cognitive impairment.

cortical areas, namely semantic WF and copying intersecting pentagons on the MMSE and non-tremor dominant phenotype at baseline were the predictors of global cognitive deficits at follow-up (Williams-Gray *et al.*, 2007). In a cohort of 115 consecutive patients with newly diagnosed PD, Muslimovic, Post, Speelman, and Schmand (2005) found that 24% were cognitively impaired, with deficits being most frequent on the measures of psychomotor speed, memory, and EF. In this study, age at disease onset emerged as a predictor of cognitive dysfunction in PD, and the patients who were cognitively impaired were older, more likely to be male gender, had later onset of disease, more severe PD, higher depression, and more severe axial symptoms and speech problems than the cognitively intact subgroup. At follow-up, 3 years later, among this newly diagnosed subgroup and another subgroup with established PD, 9% had dementia and 50% of the patients showed cognitive decline, with deterioration of psychomotor speed and attention and to a lesser extent memory and EF being characteristic of the patients who had been newly diagnosed at the time of the first assessment (Muslimovic, Post, Speelman, Haan, & Schmand, 2009). The investigators concluded that EF may not be the earliest primary cognitive domain to decline in PD. This was borne out by the results of a meta-analysis of 25 longitudinal studies on 901 initially non-demented PD patients (Muslimovic *et al.*, 2007), which showed that over 2.5 years, the magnitude of cognitive decline was small, with global cognitive ability, visuo-constructive skills, and memory, but not EF showing significant declines.

To summarize, different EFs are affected to different degrees and at different stages of PD. For example, attentional set shifting is compromised earlier than planning, and the decline in spatial WM is faster or more severe than for other forms of WM. The predictors for a more pronounced decline are male gender, older age, and later onset of disease. EFs are not used in isolation, but rely on other cognitive processes subserved by anatomical structures beyond the fronto-striatal circuits such as the temporal lobes (Kalaitzakis & Pearce, 2009; Owen *et al.*, 1997). The progressive executive and general cognitive decline in PD may reflect the increasing involvement of other non-dopaminergic neurotransmitter systems (Bassetti, 2011). This also explains why many of these late cognitive deficits do not respond well to dopaminergic medication, but improve with cholinergic medication (Schmitt, Farlow, Meng, Tekin, & Olin, 2010).

Clinical subtypes, heterogeneity of PD, and executive function

A number of PD subtypes have been recognized, which may modulate the severity of the dysexecutive syndrome. In relation to cognition, the 'motor and cognitive deficits' subtype (Graham & Sagar, 1999), 'older onset with cognitive impairment and rapid progression' (Post, Speelman, & de Haan, 2008; Schrag & Schott, 2006), and 'non-tremor dominant with cognitive impairment and psychopathology' (Reijnders, Ehrt, Lousberg, Aarsland, & Leentjens, 2009) are some of the subtypes empirically identified with cluster analysis. In another study using cluster analysis of demographic and clinical, motor, mood, and cognitive measures from 120 consecutive patients in the early stages of PD seen in a specialist clinic, Lewis, Slabosz, Robbins, Barker, and Owen (2005) identified four main subtypes: young onset, tremor dominant, non-tremor dominant with mild depression, and significant cognitive impairment particularly in measures of EF, and finally a group with rapid disease progression, but no cognitive impairment. Earlier, Lewis *et al.* (2003) had provided evidence for heterogeneity based on performance on tests of EF. PD patients with good versus poor performance on the ToL differed significantly in their ability to

manipulate information in WM, with only the latter group showing deficits relative to healthy controls. A later study in 103 drug-naive patients found no significant differences on the WCST, WF, and TMT between tremor dominant PD and the subtype with postural instability and gait disturbances (Domellof, Elgh, & Forsgren, 2011). However, of interest are the results of a recent meta-analysis of 27 cognitive studies (from 1989 to 2012), which found significant effect sizes on cognition measured by the MMSE for PD motor subtype and depression, with patients with non-tremor dominant motor symptoms or depression had more severe cognitive impairment (Tremblay, Achim, Macoir, & Monetta, 2013). As discussed below, the subtype of PD may modulate EF in conjunction with the laterality of motor symptoms.

Executive dysfunction, such as abnormal attentional set shifting in PD is further influenced by a val[158]met polymorphism, which commonly occurs in the catechol-O-methyltransferase (COMT) gene. On a modified version of the CANTAB ID/ED set shifting task, patients with high activity COMT genotypes (val/val) adopted the strategy of preferentially shifting attention within rather than between dimensions, whereas patients with low activity genotypes (met/met) did not adopt such a strategy, suggesting an inability to develop an attentional set (Williams-Gray *et al.*, 2008). Functional MRI revealed that such poor choice of strategies is associated with a significant under-activation in a fronto-parietal attentional network (Williams-Gray *et al.*, 2008).

Correlates of executive dysfunction in PD

Executive function has predictive value as a marker for later dementia in PD. In addition to higher current age, older age of onset, more severe motor symptoms, akineto-rigid subtype, experience of depression, and hallucinations, an impairment of WF is another predictor of subsequent development of dementia (Jacobs, Shuren, Bowers, & Heilman, 1995; Levy, Jacobs, *et al.*, 2002; Levy, Tang, *et al.*, 2002; Mahieux *et al.*, 1998). More recent studies with early PD have confirmed that the most important neuropsychological predictors of global cognitive decline (after correction for age) are semantic fluency and the ability to copy an intersecting pentagons figure from the MMSE (Williams-Gray *et al.*, 2007). As briefly described below, cognitive impairment and particularly executive dysfunction in PD are related to a number of motor and non-motor symptoms of the disorder.

Depression, apathy, hallucinations, and changes in personality

The severity of depression in PD has been found to be the single most important factor associated with the severity of cognitive impairment, including EF (Starkstein *et al.*, 1989). Negative effects of depression on EF seem to be strongest in patients with low level of education (Kummer *et al.*, 2009). Although across all executive and non-executive tests, cognitive performance is worse in depressed compared with non-depressed patients, the deficits in EF are among those particularly susceptible to depression (Stefanova *et al.*, 2006).

Independent of depression, apathy is another common symptom in PD associated with executive dysfunction (Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2009; Pluck & Brown, 2002; Zgaljardic *et al.*, 2007). The severity of apathy is significantly and negatively correlated with performance on tests of EF (Czernecki *et al.*, 2002), and apathy is a predictor of executive

dysfunction and dementia in PD (Dujardin *et al.*, 2009; Varanese, Perfetti, Ghilardi, & di Rocco, 2011). In a longitudinal study of 40 patients, Dujardin *et al.* (2009) reported that after a median period of 18 months, the rate of conversion into dementia was significantly higher for PD patients with apathy than those without. Similarly, in the non-demented group, the deterioration in cognitive performance, and particularly EF, over time was significantly greater in apathetic than in non-apathetic patients (Dujardin *et al.*, 2009). Apathy but not depression was associated with deficits in implementing efficient strategies during recall on the California Verbal Learning Test and on the WCST, and it was suggested that apathy is an early manifestation of the dysexecutive syndrome in PD (Varanese *et al.*, 2011). Factor analysis of a limited number of tests of EF (ToL, Stroop, TMT) in a sample of 46 PD patients showed that two factors, planning and inhibitory control, account for 75% of the variance of the scores. While poor planning was associated with severity of apathy, deficits in inhibitory control were correlated with the severity of PD motor symptoms (Weintraub *et al.*, 2005). Despite the methodological shortcomings of this study in terms of the limited number of tests of EF, the small sample size and limited patient to item ratio in the factor analysis, the results are interesting in revealing associations between the deficits in EF and the other PD-related motor and non-motor symptoms.

The other psychiatric problem that is associated with executive dysfunction in PD is visual hallucinations. A number of studies have documented that experience of visual hallucinations in PD was associated with impairment of EF (Barnes & Boubert, 2008; Imamura, Wada-Isoe, Kitayama, & Nakashima, 2008; Ozer *et al.*, 2007; Santangelo *et al.*, 2007; Shin *et al.*, 2012). Reduced EF in PD is also considered to be associated with changes in personality such as a decrease in spontaneity and a lack of concern for self-care (Zgaljardic *et al.*, 2006).

Association of executive function with postural instability and gait problems

There is evidence of an association among gait, falls, and cognition in PD. Postural instability in PD is associated with poorer performance on tests of attention and EF (Nocera *et al.*, 2010), and fallers perform worse on tests of attention than non-fallers (Allcock *et al.*, 2009). Even when 'on' dopaminergic medication, fallers had poorer EF (a composite measure of several tests) than non-fallers, while gait speed and coordination of fallers were worse than those of non-fallers, particularly under dual task conditions (verbal serial subtraction task) (Plotnik, Giladi, Dagan, & Hausdorff, 2011). In some studies, the allocation of attention during posture and gait tasks has been assessed using dual task procedures. These studies have shown that while healthy controls give attentional priority to posture and gait, PD patients are at higher risk of falls because they use a 'posture second' strategy (Bloem, Valkenburg, Slabbekoorn, & van Dijk, 2001). Increased stride variability increases the risk of falls in PD, and during dual tasking, stride variability is increased – which is again associated with reduced EF (Yogev *et al.*, 2005).

Freezing of gait (FoG) is a common, debilitating feature of PD (Rahman, Griffin, Quinn, & Jahanshahi, 2008). Although EF in patients with 'on' state FoG deteriorated in the course of a follow-up study over a period of 2 years, cognitive status of patients without 'on' state FoG remained unchanged (Amboni *et al.*, 2010). In a study of 'off' state walking at home under simple and complex (dual, dual cognitive, multi) conditions, Lord, Rochester, Hetherington, Allcock, and Burn (2010) established that gait deteriorated under complex conditions and that EF, together with attention, were among the most important factors

that determined resilience of walking against interference from cognitive tasks performed in parallel. The patients with impaired attention or EF showed increased interference under dual task and multi-task conditions. Together with motor function, attention and EF explained up to 66% of variance in gait interference. Vercruysse *et al.* (2012) subsequently confirmed in a multivariate regression model that EF as measured by the SCOPA-COG is a significant predictor of FoG.

On-state FoG is not responsive to levodopa and has been shown to be related to deficits in EF in PD (Amboni, Cozzolino, Longo, Picillo, & Barone, 2008). A subsequent 2-year follow-up study of 26 PD patients by the same group established that 'on' state FoG correlated with a faster progression of executive dysfunction. Thus, in early PD, better attention and EF can compensate for a loss of gait automaticity, but this is no longer an efficient strategy when the disease progresses and both attention and EF deteriorate too. These results emphasize the interrelation of motor and cognitive symptoms in PD. As noted below, effects in the opposite direction – of movement on EF – were also observed: moderate exercise (passive leg cycling) has been shown to improve EF as measured with the TMT (Ridgel, Kim, Fickes, Muller, & Alberts, 2011).

Olfaction and executive function

Both olfactory deficits and executive dysfunction are early and common symptoms of PD (Ponsen, Stoffers, Twisk, Wolters, & Berendse, 2009). When selected executive tests (a random generation motor task and the Corsi block span – a spatial test analogous to the digit span) and an olfaction test were compared for their predictive value over 5 years in a sample of 361 first-degree relatives of PD patients, only the test of olfaction was a significant predictor of subsequent development of PD (Ponsen *et al.*, 2009). Although some studies have found an association of olfaction deficits with impaired visual and verbal memory but not EF (Damholdt, Borghammer, Larsen, & Ostergaard, 2011), others have reported significant associations between olfactory deficits and impairment in EF (Parrao, Chana, Venegas, Behrens, & Aylwin, 2012). In the latter study, a subgroup with early PD (disease duration less than 1 year) was significantly impaired relative to matched controls on tests of olfaction as well as the DIGSP-BW, WCST categories correctly sorted, ToL, and phonemic WF.

Other factors associated with executive function in PD

In contrast to early reports (e.g., Tomer, Levin, & Weiner, 1993), a recent review concluded that the laterality of motor symptoms in PD has no influence on EF or other domains of cognitive functioning except visuospatial and language-related skills (Verreyt, Nys, Santens, & Vingerhoets, 2011). In confirmation of the laterality of motor symptoms influencing language-related performance, Obeso, Casabona, Bringas, Álvarez, and Jahanshahi (2012) found phonemic and semantic WF to be poorer in patients whose motor symptoms began on the right side of their body where the left hemispheric areas concerned with processing of motor and language function are presumably more severely affected than the homologous areas in the right hemisphere. Other studies have noted an association among the side of motor symptoms, PD motor subtype, and EF. Katzen, Levin, and Weiner (2006) examined 58 patients and reported that those with right onset tremor dominant PD scored better on the WCST and WF than left onset tremor dominant PD and the bradykinetic rigid subtype across the side of onset. Similarly, 18 patients of the tremor dominant or mixed subtype reported lesser

(ToM-relevant) alexithymic features compared with 24 patients of the subtype with postural instability and gait difficulty (Poletti, Frosini, *et al.*, 2011). However, these findings in small samples might be biased by other variables such as depression, as risk factors for depression in PD include akinetic-rigid presentation (Starkstein *et al.*, 1998), and patients with right-sided onset of tremor seem to have a lower risk of depressive symptoms than patients with other presentations (Dewey *et al.*, 2012). In 108 Patients 'on' dopaminergic medication, Williams *et al.* (2007) found that more severe right-sided motor symptoms predicted cognitive decline, although no separate measure of EF was included. The issue of laterality of motor symptoms and EF requires further investigation.

Rapid eye movement sleep behaviour disorder is common in PD, and sleep quality is generally compromised. Excessive daytime sleepiness is an early symptom (Boeve, 2007). In 35 non-demented PD patients, poor sleep (measured via wrist actigraphy) was associated with worse performance on tests of attention and EF (Stavitsky, Neargarder, Bogdanova, McNamara, & Cronin-Golomb, 2011).

A recent review of cognitive differences between male and female patients with PD (Miller & Cronin-Golomb, 2010) reported gender differences on a few EF tests (e.g., women superior on WF, men superior on tests with a spatial reasoning component). However, the underlying studies lacked proper control groups. As women generally perform better on verbal tasks while men do better on spatial tasks, conclusions about whether gender differences in EF in PD are above and beyond gender differences in the healthy adult population cannot be drawn.

Implications of impaired executive functions in PD in daily life

Executive processes are essential for goal-directed activities in daily life. Executive dysfunction in PD is therefore likely to affect a multitude of goal-directed behaviours. As a result, patients have difficulties with planning, organizational skills, concentration, and holding and manipulating information in WM while undertaking daily tasks (Bronnick *et al.*, 2006). As outlined above, it has been proposed that PD patients compensate for their inability to execute simple tasks such as walking in an automatic fashion by performing these ordinarily habitual movements in a goal-directed and controlled fashion (Redgrave *et al.*, 2010), which then overloads the executive system. This is supported by experimental evidence. For example, for walking, a motor secondary task (coin transference) and a cognitive secondary task (digit subtraction) led to the same degree of dual task interference – a decrease in cadence – in PD patients, whereas in healthy controls, cadence was not affected under dual task conditions (O'Shea, Morris, & Iansek, 2002).

Godefroy *et al.* (2010) have demonstrated that in PD, the rates of behavioural dysexecutive syndrome (42%) and cognitive dysexecutive syndrome (39%) are similar. Unfortunately, the predictive value of cognitive tests for behavioural dysexecutive symptoms was not examined, probably due to the small sample of patients (*n* = 45). Confirming this, PD patients who showed more severely impaired EF (e.g., FAB scores) reported more behavioural dysexecutive problems in daily life (Koerts, Tucha, *et al.*, 2011), although the discriminatory power was low (Dujardin *et al.*, 2010). It is of interest that the errors considered relevant to their daily life by the patients often related to attentional processes (being more distractable) and problems with memory retrieval (being unable to recall important details from the previous day) (Poliakoff & Smith-Spark,

2008). Similarly, Koerts, Beilen, Tucha, Leenders and Brouwer (2011) examined multi-tasking in PD and found that patients made less ambitious plans, and planned and executed these task mostly sequentially – in contrast to the parallel multi-tasking typically chosen by healthy participants.

Not only does medical treatment of PD modulate EF, but EF in turn can also affect the patients' compliance with their medical treatment. Even a subtle decline in EF, albeit still in the age-adjusted normal range of performance, was shown to deteriorate the patients' ability to manage their medication correctly (Manning *et al.*, 2012). Patients with poorer EF forgot to take their pills more often, or neglected to eat and drink at specific intervals after medication intake. This is even more remarkable considering that the general cognitive abilities of those patients who were unable to successfully schedule their own medication remained largely intact (Manning *et al.*, 2012).

Attentional deficits are acknowledged as another important cognitive symptom relevant to daily activities in PD. Bronnick *et al.* (2006) found that measures of attention from reaction time and vigilance tasks predicted the patients' ability to carry out activities in daily life, as rated by their caregiver. Other research has focussed on dual tasking in everyday situations. As outlined above, the concurrent performance of two or more attention-demanding tasks requires additional executive control. Patients with PD are impaired in such dual task performance, even more than healthy participants, given that even 'simple' tasks which healthy people can perform automatically often require a high level of attentional control in patients with PD (Rochester *et al.*, 2008).

Executive functions are relevant to driving. Safe driving requires a driver to perform multiple competing tasks and attend to a host of objects and ongoing events. Drivers with PD therefore tend to make more errors than healthy individuals (Grace *et al.*, 2005; Uc *et al.*, 2006). Although a majority of drivers with PD (67%) were safe drivers, those with neuropsychological impairment – reduced TMT – were more likely to be unsafe drivers than controls (Grace *et al.*, 2005). Dysexecutive symptoms in PD, such as poor TMT and Brixton scores, are associated with reduced tactical level driving performance such as speed adaptation and complex curve navigation (Stolwyk, Charlton, Triggs, Iansek, & Bradshaw, 2006). Apart from visuospatial abilities, the TMT score was the only independent predictor of at-fault safety errors in drivers with PD (Uc *et al.*, 2006).

Conclusions and future directions

Executive dysfunction in PD is characterized by deficits in internal control of attention, set shifting, planning, inhibition, conflict resolution, impairment in dual task performance, and on a range of decision-making and social cognition tasks. Executive deficits in PD are related to depression and apathy, postural instability, FoG, and other gait problems. (Amboni *et al.*, 2008; Lord *et al.*, 2010; Plotnik *et al.*, 2011). Medical treatment of the motor symptoms with dopaminergic medication has variable effects on executive deficits, improving some, leaving others unchanged, and worsening those mediated by the circuits through the ventral striatum, which are largely intact in early PD. Traditionally, the central concern of medical management in PD has been the treatment of motor symptoms. However, cognitive impairment, of which executive dysfunction is an important reflection, has a significant impact on the quality of life of the patients (Schrag, Jahanshahi, & Quinn, 2000) and carers (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999), and should therefore be considered in the clinical management of the disorder.

There is now some evidence that intensive training programmes can be effective for improving executive dysfunction in PD (Hindle, Petrelli, Clare, & Kalbe, 2013; Mohlman, Chazin, & Georgescu, 2011; Reuter, Mehnert, Sammer, Ochsner, & Engelhardt, 2012; Ridgel *et al.*, 2011). With the increasing focus on patients' active participation in their health care and the adoption of a self-management approach to chronic illness, such training for the improvement of executive dysfunction can be incorporated in future self-help guides for PD (Jahanshahi & Marsden 1998).

In accordance with current NIH goals for research in PD (NIH, 2013), future research on EF in PD should define risk factors for executive dysfunction, screen at-risk populations, and evaluate changes in EF with disease progression. Research should also develop neuroimaging and behavioural markers of executive dysfunction to better assess these non-motor symptoms, and should further elucidate the long-term effects of various pharmacological and surgical therapies and behavioural interventions such as occupational therapy, cognitive training, and exercise on EF in PD. While the 'dopamine overdose' hypothesis is supported by behavioural evidence from a number of studies on a range of tasks of EF, direct testing of the differential impact of dopamine replacement therapy on the different circuits implicated or spared in early PD using imaging and relevant EF tasks is necessary. Imaging could also clarify if the identified associations between executive dysfunction and symptoms such as apathy or FoG in PD are perhaps mediated by overlap in their neural substrates. The existing evidence from the handful of studies of cognitive training is promising and future randomized controlled studies could firmly establish if executive dysfunction can be improved through such training, and whether any benefits obtained are maintained in the long term in the patients' daily life situations and have an impact on their quality of life.

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