Psychologie

Serial prediction in Parkinson's disease: The contribution of motor loop dysfunction to cognitive impairment

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Klara Hagelweide, geb. Blume

aus Paderborn

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Dekan:	Prof. Dr. Guido Hertel
Erste Gutachterin:	Prof. Dr. Ricarda Schubotz
Zweite Gutachterin:	Prof. Dr. Karen Zentgraf
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ABSTRACT

Since its definition by Alexander and colleagues in 1986, the so-called motor loop was suggested to underlie the motor symptoms of Parkinson's disease (PD) patients, whereas cognitive deficits were supposed to result from dysfunctions in prefrontal loops or the mesolimbic dopaminergic pathway. However, according to recent studies, 15 to 36% of newly diagnosed PD patients suffer from mild cognitive impairment (MCI). In this early stage of the disease, the motor loop is by far most affected, manifesting in hypoactivity of the putamen and the supplementary motor area (SMA) and sometimes co-occurring compensatory hyperactivity of the lateral premotor cortex (PM) during motor tasks. In contrast to common assumptions about the exclusively motor character of premotor areas, they were shown to be involved in cognitive processing independent of motor output during the serial prediction task (SPT). Based on accumulating evidence that cognitive deficits in PD are related to motor impairment and motor loop dysfunction, the current work aimed to investigate if patients show a decline in serial prediction performance because of motor loop affection.

To this end, a behavioural study, a functional magnetic resonance imaging (fMRI) study and a positron emission tomography (PET) study were conducted with PD patients and age- and gender-matched healthy controls that performed the SPT. The participants were asked to attend to circles of different size that succeed each other according to a certain sequential pattern, and to indicate at the end of the trial if the order was violated. In each study two versions of the SPT were implemented that challenged processing within the SMA to a different degree. The SPT0 allows continuous tracking of presented stimuli, wherefore sequence learning can be based on ongoing sensory input. On the contrary, during the SPT+ gaps in sensory input complicate building an internal representation of the sequential structure. Because the acquisition and selection of sequences represented in the SMA builds on the ability of the putamen to control gating of cortical information, we hypothesised that PD patients would perform worse in serial prediction than healthy controls accompanied by hypoactivity in the putamen and SMA, especially after withdrawal of medication and in the SPT+ task. Furthermore, we expected that PM hyperactivity might work as a compensatory mechanism and restore performance to some extent, as found during motor tasks.

Supporting our hypotheses, PD patients performed worse or tended to perform worse than healthy controls in all three studies. The behavioural study revealed an interaction of task

version and medication status, i.e., PD patients' performance dropped after medication withdrawal especially in the SPT+ task, as expected. This pattern was not exactly replicated in the fMRI study, where patients without medication performed worse than with medication in both task versions. The SMA and putamen were found to be hypoactive compared to controls, as hypothesised, and the level of SMA activity predicted serial prediction performance of patients, especially in the SPT+. In addition, PM hyperactivity was found in the SPT+ compared to the SPT0 after medication withdrawal, probably indicating a compensatory mechanism, as the performance of patients was positively related to the individual PM activity level. In both the fMRI and the PET study, PM hyperactivity co-occurred with prefrontal hyperactivity. In the fMRI study, these activations were accompanied by sustained performance, whereas half of the patients in the PET study failed in the SPT+ so that the analysis had to be restricted to the SPT0. Here, hypoactivity in the putamen and hyperactivity of the PM were found, while the massive prefrontal overactivity probably marked inefficient cognitive strategies in this severely affected sample.

Taken together, the results confirm our assumption that motor loop dysfunction is related to cognitive deficits in learning and predicting sequential information in PD. Furthermore, hyperactivity of the PM and potentially the prefrontal cortex might be compensatory resources in cognitive tasks. These observations demonstrate that it is important to take the interaction of premotor and prefrontal dysfunction into account to better understand the neural underpinnings of cognitive difficulties and possible compensatory mechanisms in PD. As the premotor influence on cognitive impairment has so far been widely dismissed, this work accounts for this gap by refining former assumptions on neural underpinnings of MCI. Future studies should be mindful of concepts that overcome misconceptions of motor and cognitive functions as separated entities.

1 INTRODUCTION

Over two hundred years ago, in 1817, James Parkinson published six case observations of the neurological syndrome that later was termed after him. Based on his observations he defined the common characteristics of the disease as following:

> Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured. (Parkinson, 2002, p. 223)

Although the described motor symptoms are still key features of the disease's clinical assessment, today it is acknowledged that the senses and intellect, i.e., the sensory and cognitive abilities of patients respectively, are in fact impaired to some degree. Early noted by Ball in 1882, the association between Parkinson's disease (PD) and cognitive impairment was confirmed in the 1970s when general cognitive deficits of patients were found in a wide range of neuropsychological tasks (Lees & Brown, 1983). Since then, many studies proved subtle cognitive deficits of PD patients in attention, language and working memory tasks, visuospatial paradigms and memory recall. Recent studies estimate that a mild cognitive impairment is present in 15 to 36% of patients in early stages of the disorder (Aarsland et al., 2009; Elgh et al., 2009; Foltynie, Brayne, Robbins, & Barker, 2004; Muslimović, Post, Speelman, & Schmand, 2005; Poletti et al., 2012) and cognitive problems become more frequent and prominent with disease progression (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). A study that assessed the patients 15 to 18 years after diagnosis found that as much as 84% of the surviving patients suffered from cognitive decline in the late stages of the disease (Hely, Morris, Reid, & Trafficante, 2005).

Much knowledge about the pathology of the disease was gained in the last two hundred years, but unfortunately the neural correlates of cognitive impairment and their interactions with treatment are yet not fully understood. The cognitive difficulties of PD patients are heterogeneous and mirror the complexity of the disease which is caused by progressive cellular degeneration in subcortical and cortical networks and involves several neurotransmitter systems that interact with the employed treatments (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004; Kehagia, Barker, & Robbins, 2013; Rodriguez-Oroz et al., 2009). Despite the heterogeneity of underlying neural changes, cognitive deficits are mainly attributed to a dysfunction of prefrontal areas of the brain. A contribution of premotor areas to cognitive deficits is mostly overlooked, although these areas are deeply involved in pathological changes

in PD. Still often unrecognised, the lateral premotor cortex (PM) and the supplementary motor area (SMA) provide cognitive functions independent of motor implementation as demonstrated by the work of Schubotz and von Cramon (Schubotz, 2007; Schubotz & von Cramon, 2003). This thesis therefore poses a disregarded, but straightforward question: Does cognitive decline in PD partly depend on a dysfunction of premotor areas? To answer this question, we investigate if PD patients have difficulties in serial prediction, a cognitive task that depends on the premotor areas' engagement (Schubotz & von Cramon, 2003). This idea challenges the premature distinction between motor and cognitive dysfunction often made in studies of PD patients.

The theoretical background to this approach is described in the following in five main sections. First, PD will be characterised by giving an overview of motor and cognitive symptoms. To explain their neural underpinnings, the pathological changes on the level of the brain stem, the basal ganglia and the whole brain will be set out in the second section including a description of effective treatment approaches that normalise dysfunctional interactions within these systems. Third, studies of brain activity of PD patients during motor tasks will be presented to characterise motor dysfunction on the brain level and to understand the interaction of premotor areas in PD. The fourth section discusses the relation of motor dysfunction and cognitive impairment in PD patients complemented by a more general neuroscientific perspective on premotor functions and an introduction of the serial prediction task. Finally, the main research questions and hypotheses of this work are described in the fifth section. Afterwards, the research articles that examine these questions will be presented in the second main chapter followed by the third main chapter that concludes this work with a discussion of the studies' results and implications.

1.1 Clinical picture of Parkinson's disease

PD is the second most common neurodegenerative disorder in industrialised countries as it affects about 1% of people over 60 years of age (De Lau & Breteler, 2006). It is characterised by motor impairment, but also comprises cognitive decline and other non-motor symptoms including neuropsychiatric, gastrointestinal, sensory and autonomic problems and sleep disturbances (Chaudhuri, Healy, & Schapira, 2006) that have a high impact on the patients' quality-of-life (Antonini et al., 2012; Martinez-Martin, Rodriguez-Blazquez, Kurtis, Chaudhuri, & NMSS Validation Group, 2011). To address the question whether premotor dysfunctions contribute to the patient's cognitive impairments, this thesis focusses on motor and cognitive symptoms, each of which will be characterised in the following.

1.1.1 Motor symptoms

The motor syndrome of PD comprises bradykinesia, akinesia, muscle stiffness, postural imbalance and resting tremor, that is, an involuntary 4-6 Hz muscle activity of the limbs or the head at rest (Jankovic, 2008; Rodriguez-Oroz et al., 2009). *Bradykinesia* is characterised by a disability to quickly initiate and execute voluntary movements. Berardelli, Rothwell, Thompson and Hallett (2001) assume that movements are slowed because relevant muscles cannot be rapidly recruited and because the muscles' force is not appropriately scaled to the movement dynamics. During sequential motor tasks, patients show a progressive reduction in speed and amplitude that goes beyond an additive effect of slow single movements. Therefore, patients are especially affected during sequential movements ranging from repetitive simple movements to complex motor sequences. Bradykinesia is often complemented by akinesia, i.e., the poverty of automatic movements, such as reduced facial expressions and decreased stride length resulting in the characteristic shuffling gait of PD patients (Rodriguez-Oroz et al., 2009).

According to the UK Parkinson's disease Society Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992) the diagnosis of idiopathic PD is applicable if bradykinesia is present along with either resting tremor or muscle rigidity or postural imbalance. Circumscribed neurological causes of these symptoms must be excluded, whereas asymmetric symptom onset and a good response to dopaminergic medication help assuring the diagnosis. Depending on their predominant symptoms, patients can be classified into akinetic-rigid, tremor-dominant and a mixed subtype (Jankovic, 2008). Each of these subtypes have different clinical courses and prognoses. Typically, the first clinical symptoms emerge between 50 and 69 years of age (De Lau and Breteler, 2006; Hoehn and Yahr, 1998) with an earlier onset and milder course in the case of the tremor-dominant patients (Rajput, Voll, Rajput, Robinson, & Rajput, 2009). The disease progresses from unilateral and focal motor signs to severe motor disability in about 15 years (Rajput et al., 2009), leaving patients highly restricted in daily activities or bound to the wheelchair in its last stages (Hoehn and Yahr, 1998).

1.1.2 Cognitive symptoms

In parallel with motor degradation, cognitive symptoms typically expand from isolated shortcomings in one cognitive domain to more severe impairment of various cognitive functions (Hely et al., 2005; Williams-Gray et al., 2007). In the long term, about one third of PD patients develops a mild cognitive impairment (MCI), i.e., patients show mild to moderate deficits in at least one of the following domains: language, memory, attention, working

memory, executive or visuospatial functions (Litvan et al., 2012). Another half suffers from dementia which is characterised by a more comprehensive cognitive impairment that causes marked functional interference with daily living (Hely et al., 2005). Because some patient characteristics related to temporal lobe dysfunction increase the probability of a more rapid cognitive decline and thus dementia, MCI and dementia were proposed to be two distinct syndromes caused by different neural mechanisms (Kehagia et al., 2013; Williams-Gray et al., 2007). According to this assumption, dementia primarily depends on changes in the temporal cortex and is largely independent of the pathology of the motor and premotor areas. Because the aim of this work is to investigate the dependency of cognitive decline on the premotor areas, only MCI will be elaborated in the following.

MCI affects about one third of PD patients (Aarsland et al., 2010; Hely et al., 2005; Livtan et al., 2011; Williams-Gray et al., 2007) and is present in at least 15% of newly diagnosed and non-treated patients (Aarsland et al., 2009; Elgh et al., 2009; Foltynie et al., 2004; Muslimović et al., 2005; Poletti et al., 2012). It comprises minor deficits in various tasks including memory recall and visuospatial processing. However, the most profound deficits are typically found in verbal fluency, strategic planning, problem solving and response inhibition as well as maintaining and shifting attention (Kudlicka, Clare, & Hindle, 2011; Muslimović et al., 2005). Because all these tasks involve higher-order control of goal-directed behaviour, i.e., executive function, this pattern of deficits is also referred to as *dysexecutive syndrome* (e.g., Rodriguez-Oroz, 2009; Dirnberger & Jahanshahi, 2013).

The concept of executive function in a narrow sense refers to guiding behaviour towards a goal by preparing, selecting and inhibiting behavioural responses. In a broader reading, however, it comprises various aspects such as volition, decision making, forming and flexibly adjusting plans, sequencing of complex actions, switching between task goals, allocating attention to relevant features and manipulating information in working memory (Dirnberger & Jahanshahi, 2013). In PD patients, executive functions are typically measured by the Tower of London task (Shallice, 1982), the Wisconsin Card Sorting Test (Berg, 1948; Grant & Berg, 1948), the random number generation (Ginsburg & Karpiuk, 1994), the Trail Making Test (Reitan, 1958), the Stroop test (Golden & Freshwater, 1978), verbal fluency tests (e.g., Thurstone & Thurstone, 1943) or dual-task paradigms. The meta-analysis by Kudlicka and colleagues (2011) concluded that PD patients have difficulties in many of these tasks. For example, PD patients perform reliably worse than healthy controls in the Wisconsin Card Sorting Test that requires participants to flexibly shift between different sets of rules. Nevertheless, the authors point out that there are several issues with the concept of a

dysexecutive syndrome. On the theoretical side, there is no clarity which aspects do belong and do not belong to executive functions and how different subcomponents relate to each other and specific tests (see also Alvarez & Emory, 2006; Banich, 2009). On the empirical side, executive functions are not the only cognitive domains impaired in early stages of PD. As mentioned above, studies consistently found early visuospatial, verbal and mnemonic impairments of PD patients (Elgh et al., 2009; Muslimović, Schmand, Speelman, & De Haan, 2007; Watson & Leverenz, 2010; Zgaljardic et al., 2006). Furthermore, there is profound variability of cognitive deficits between and within patients: some domains may be unaffected in one patient that decline first in other patients (Lewis, Dove, Robbins, Barker, & Owen, 2003; Watson & Leverenz, 2010). From this perspective it may even be more appropriate to distinguish between different subtypes of MCI not yet described (Litvan et al., 2011).

In line with these concerns, the current thesis argues that the unifying notion of a dysexecutive syndrome or other one-dimensional concepts of MCI restrict a differentiated view on the neural causes of cognitive symptoms. Especially the contribution of motor and premotor areas to specific cognitive symptoms remains to be elucidated. Before describing dependencies of cognitive impairments on specific neural dysfunctions (see sections 1.3 and 1.4), the pathology of PD is clarified in the following section to give a general understanding of the neural underpinnings of the disease.

1.2 Neural pathological mechanisms

The main motor symptoms and MCI of PD patients can be attributed to aberrant information processing within the basal ganglia and associated cortical areas (Rodriguez-Oroz et al., 2009). The basal ganglia are a network of subcortical nuclei that comprise the striatum, the globus pallidus pars interna (GPi) and globus pallidus pars externa (GPe) in the telencephalon, the subthalamic nucleus (STN) in the diencephalon and the substantia nigra pars compacta and pars reticulata of the midbrain (Gerfen & Wilson, 1996; Mink, 1996). The striatum is the major input nucleus of the basal ganglia and consists of three structures, i.e., the putamen, the caudate nucleus and the ventral striatum. The basal ganglia's components and the thalamus, which relays information from the basal ganglia to the cortex, are depicted in Figure 1.

Other structures and pathological mechanisms also contribute to PD symptoms, for example cerebellar dysfunction (Wu & Hallett, 2013) suspected to contribute to resting tremor (Helmich, Janssen, Oyen, Bloem, & Toni, 2011), progressive Lewy body pathology in the cortex (Braak et al., 2004), and interactions of dopamine with other neurotransmitters such as

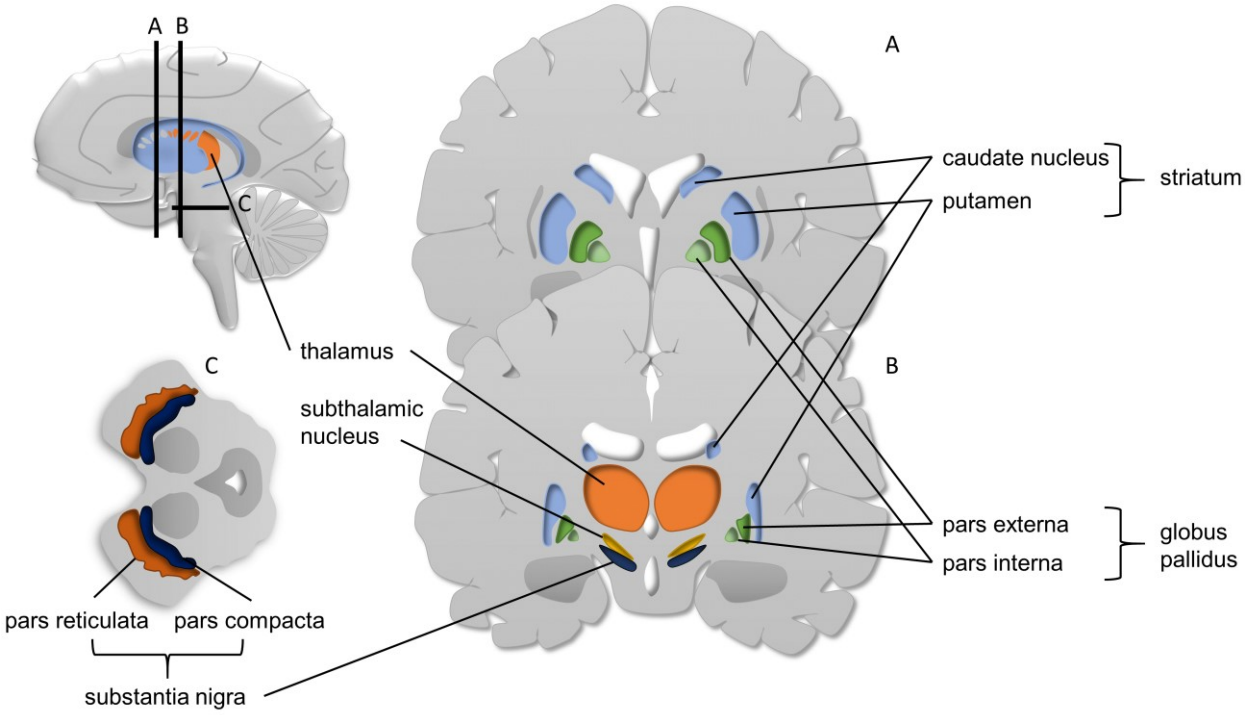

Figure 1: *Anatomic overview of the basal ganglia and the thalamus. A and B show coronal sections of the brain, C shows an axial section of the midbrain.*

glutamate, serotonin and acetylcholine. These and further pathological factors are beyond the scope of this work and therefore are not further described. The cascade of basal ganglia and cortical dysfunction originating from cell demise in the midbrain is outlined in the following.

1.2.1 Decline of the substantia nigra

Since Parkinson published his essay about two hundred years ago, great progress was made in unveiling the disorder's neural cause. In 1912 Lewy described cellular inclusions, which are now known as "Lewy bodies", in the brainstem, the basal ganglia and the thalamus of PD patients. Lewy bodies are characteristic of PD and linked to progressive neural loss in PD and other neurological diseases, although their exact role in neurodegeneration is yet unclear (Braak et al., 2004; Goedert, Spillantini, Del Tredici, & Braak, 2013). Tretiakoff in 1919 was the first who observed Lewy bodies in the substantia nigra of patients along with massive neural degeneration in this part of the brainstem (Parent & Parent, 2010). He assumed 'intimate relationships between the substantia nigra and Parkinson's disease. These relations are very likely that of a cause and its effects' (as cited in Parent & Parent, 2010, p. 317). Indeed, a few

years later the decline of neurons in the pars compacta of the substantia nigra was confirmed to be the most specific morphological change related to the disorder. Finally, the definition of the nigrostriatal dopaminergic pathway in the 1960s related the loss of neurons in the brainstem to reduced dopamine levels in the striatum of PD patients (Hornykiewicz, 2008), which is now well-established as the main pathological mechanism of the disorder.

The substantia nigra pars compacta predominantly contains dopamine producing neurons that project to the striatum (Moore, Bhatnagar, & Heller, 1971; Poirier & Sourkes, 1965). These neurons incrementally cease in the course of the disease and up to 98% of them are lost in late PD stages (Damier, Hirsch, Agid, & Graybiel, 1998). They are probably vulnerable to cell death because the metabolism of dopamine contributes to oxidative stress (Hwang, 2013), which together with mitochondrial impairment and protein mishandling leads to cell loss (Greenamyre & Hastings, 2004).

The first manifestations of PD begin when about 50% of nigral neurons are lost and consequently dopamine concentrations fall below 60–70% in the contralateral striatum (Kordower et al., 2013; Rodriguez-Oroz et al., 2009). The striatum is connected to the other basal ganglia structures via inner basal ganglia pathways which themselves are embedded in large-scale basal ganglia-cortical loops. Why dopamine is important for effective information processing in the basal ganglia and the cortex will be explained in detail in the following.

1.2.2 Disbalance of inner basal ganglia pathways

The striatum and the STN receive multiple cortical inputs which are processed via inner basal ganglia pathways and fed back to the cortex through the thalamus (Obeso, Marin, et al., 2008). Normal dopamine levels ensure effective information processing in these cortico-basal ganglia-thalamo-cortical loops by balancing the activity of several inner basal ganglia pathways that provide complementary processing of incoming information. Classical descriptions of the inner basal ganglia pathways only comprised the direct and the indirect pathway (Albin, Young, & Penney, 1989; DeLong, 1990; Gerfen & Wilson, 1998; Wichmann & DeLong, 1996), which were supplemented with the hyperdirect pathway and additional indirect pathways in more recent frameworks (Obeso, Marin, et al., 2008; Redgrave et al., 2010; Smith, Bevan, Shink, & Bolam, 1998). To give a rough overview of the complex dynamics in the basal ganglia only the interaction in the main pathways, i.e., the direct, the indirect and the hyperdirect pathway, will be described in the following (cf. Figure 2A; for a more complex model see Obeso, Marin, et al., 2008).

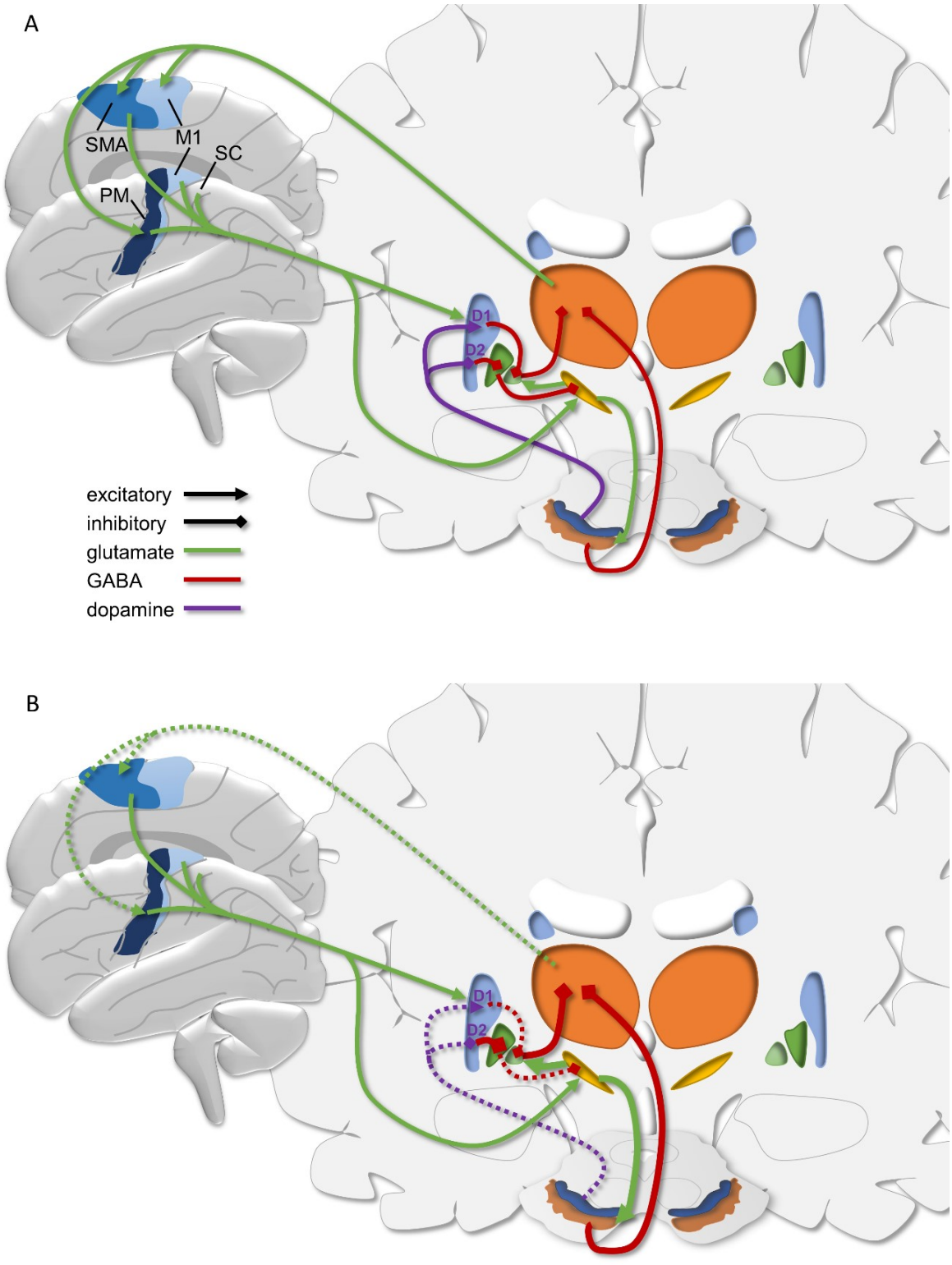

Figure 2: *Illustration of the main motor basal ganglia pathways. A: Inhibitory and excitatory connections in the basal ganglia and with the cortex. B: Pathological changes in Parkinson's disease: underactive and overactive connections are represented by dashed and thickened lines, respectively. GABA: gamma-amino-butyric-acid; M1: primary motor cortex; PM: lateral premotor cortex; SC: somatosensory cortex; SMA: supplementary motor area.*

The direct, the indirect and the hyperdirect pathways project to the substantia nigra pars reticulata and the GPi. These nuclei are the output structures of the basal ganglia and send tonic inhibitory signals to the thalamus and the brainstem. The output structures are fostered by activation of the indirect and hyperdirect pathway. In particular, the hyperdirect pathway receives direct cortical input to the STN which projects via excitatory connections to the output structures and therefore increases the level of inhibitory control over the thalamus and the brainstem. The indirect pathway receives striatal input that blocks activity in the GPe which inhibits the STN and the GPi. Therefore, activity of the indirect pathway intensifies activity in the output structures via disinhibition of both the STN and the GPi. In contrast, the inhibitory firing of the output structures is suppressed by activation of the direct pathway via inhibition of the GPi. Dopamine from the substantia nigra pars compacta facilitates the direct pathway via excitatory D1 receptors, whereas activity in the indirect pathway is decreased by inhibitory D2 receptors, thereby allowing pauses in the phasic inhibitory firing of the output structures (Gerfen & Wilson, 1998). Importantly, a specific neuronal population of the GPi is silenced by dopamine, thus not resulting in a general activation of the thalamus, but in a release of some thalamic neurons, while the remaining tonic inhibitory signalling of the GPi persists to suppress conflicting activity (Marsden & Obeso, 1994). Nambu (2008) suggests that the hyperdirect pathway inhibits large portions of thalamic neurons before neurons conveying a motor command are released via the direct pathway and finally inhibited again by the indirect pathway.

In the case of input from the motor cortex, the basal ganglia thus reinforce specific motor commands and inhibit opposing ones, allowing movements to run smoothly (Marsden & Obeso, 1994). Importantly, this does not indicate that the basal ganglia are indispensable to initiate and execute movements in general. They were rather found to enhance the automatic selection of the next action in a learned sequence of movements (Brotchie, Iansek, & Horne, 1991; Redgrave, Prescott, & Gurney, 1999; Seitz & Roland, 1992) or to facilitate motor learning (Turner & Desmurget, 2010). For example, phasic activity of pallidal neurons in monkeys was found to provide an internal cue which signalled the end of a movement component in a predictable sequence of movements (Brotchie et al., 1991). Building on this evidence and the neurochemical properties of basal ganglia neurons, Graybiel (1998) proposed that the basal ganglia help binding stimuli and motor responses together. If, for example, two movements regularly follow one another or if a movement is related to a specific external onset cue, the basal ganglia support associating both states. In other words, a movement and its predecessors can be chunked if they regularly occur in a specific temporal order. Subsequently, during the

execution of a learned sequence, the basal ganglia facilitate the fast and automatic retrieval of the second element as soon as the first evolves. According to this framework, the basal ganglia thus allow for implicit learning and automatic retrieval of movement sequences fostered by normal levels of striatal dopamine. Indeed, PD patients particularly suffer from impairments of related functions: they show difficulties to implicitly learn movement sequences (Clark, Lum, & Ullman, 2014; Siegert, Taylor, Weatherall, & Abernethy, 2006), to execute complex motor sequences compared to simple movements (Berardelli et al., 2001) and to move automatically compared to thoughtfully (Wu, Chan, & Hallett, 2010).

According to the classical nigrostriatal model of PD, these symptoms result from of underactivity in the direct pathway and overactivity in the indirect pathway caused by the dopaminergic deficit (Figure 2B). This rather simplistic model was expanded by newer frameworks that keep the assumption of a disbalance between activity in the direct versus indirect and hyperdirect pathways but take some additional features of the overwhelmingly complex dynamics of the basal ganglia into account (Graybiel, 2005; Nambu, Tachibana, Kaneda, Tokuno, & Takada, 2005; Redgrave et al., 2010). For instance, dopamine in the substantia nigra pars compacta projects not only to the striatum, but also to other basal ganglia nuclei and the cortex directly (Whone, Moore, Piccini, & Brooks, 2003). Moreover, basal ganglia output to the thalamus may not only be inhibitory, but also produce excitatory rebound spikes in the thalamus (Person & Perkel, 2005). Newer models emphasise the regulatory role of the GPe which is directly influenced by the direct pathway and possesses inhibitory back projections to the striatum (Obeso, Marin, et al., 2008; Redgrave et al., 2010). How the dysfunction of the inner basal ganglia pathways affects cortical activity will be described in the next section by introducing the cortico-basal ganglia-thalamo-cortical loops, which connect large proportions of the cortex to the basal ganglia.

1.2.3 Dysfunctional cortico-basal ganglia-thalamo-cortical loops

The cortical connections of the basal ganglia and the thalamus were gradually uncovered in the 1970s and 1980s by neural tracing methods and single cell recordings in animals (e.g., Schell & Strick, 1984; Selemon & Goldman-Rakic, 1985). Alexander, DeLong and Strick (1986) merged the findings in a framework proposing several segregated but similarly structured neuronal loops that connect the basal ganglia and the cortex (Figure 3A). According to this concept each loop receives input from a specific set of functionally related cortical areas. Their

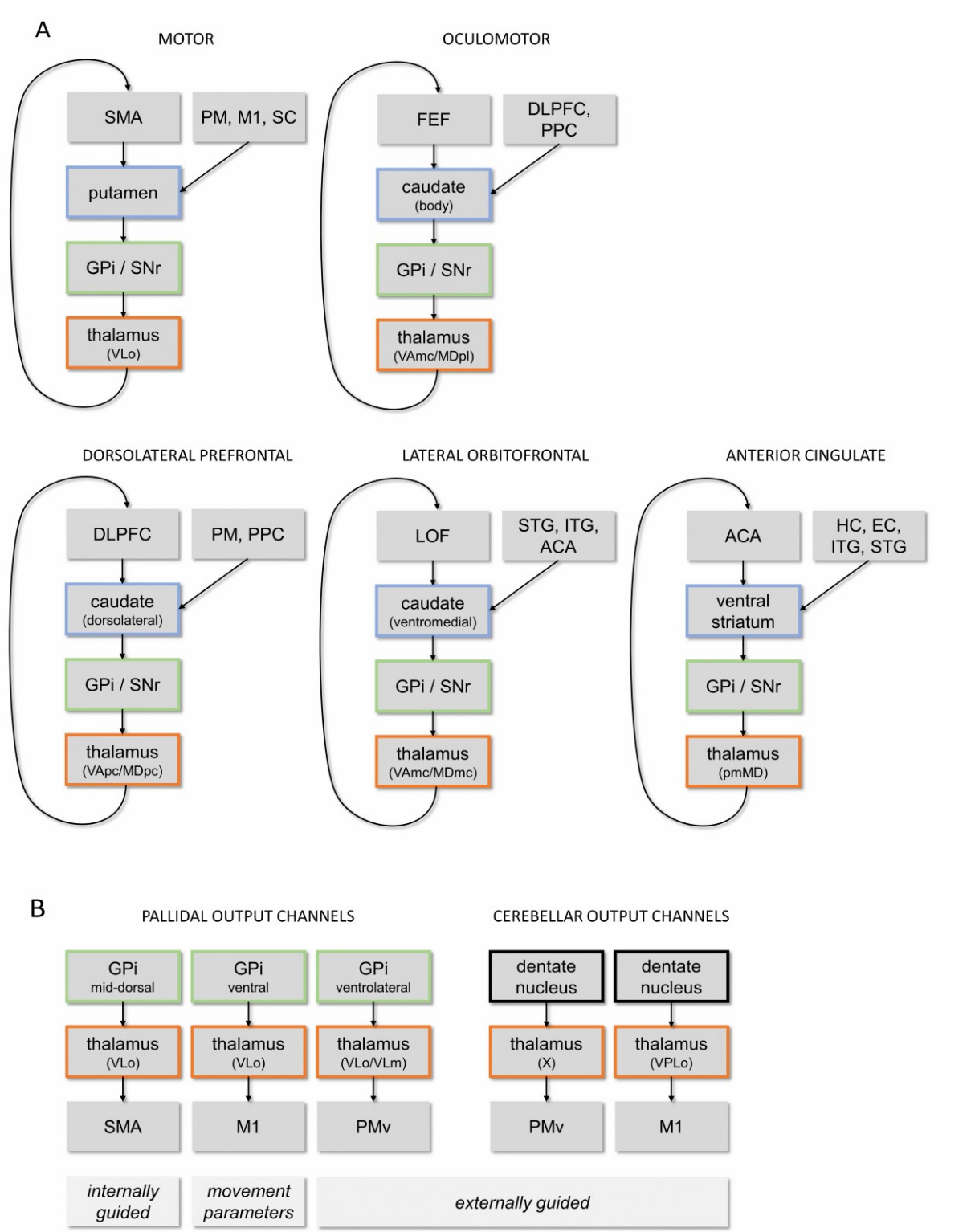

Figure 3: *Schematic illustration of pathways connecting the basal ganglia and the cortex. A: Five cortico-basal ganglia-thalamo cortical loops as proposed by Alexander et al., (1986) (modified from Alexander et al., 1986, p. 364). B: Pallidal and cerebellar connections to the motor and premotor cortex, the bottom row specifies if the pathway is primarily involved in adjusting movement parameters or performing internally or externally guided movements*

(modified from Middelton & Strick, 2000, p. 245). ACA: anterior cingulate area; DLFPC: dorsolateral prefrontal cortex; EC: entorhinal cortex; FEF: frontal eye fields; GPi: internal segment of globus pallidus; HC: hippocampal cortex; ITG: inferior temporal gyrus; LOF: lateral orbitofrontal cortex; M1: primary motor cortex; MDpl: medialis dorsalis pars paralamellaris; MDmc: medialis dorsalis pars magnocellularis; MDpc: medialis dorsalis pars parvocellularis; PM: lateral premotor cortex; PMv: ventral lateral premotor cortex; PPC: posterior parietal cortex; SC: somatosensory cortex; SMA: supplementary motor area; SNr: substantia nigra pars reticulata; STG: superior temporal gyrus; VAmc: ventralis anterior pars magnocellularis; Vapc: ventralis anterior pars parvocellularis; VLm: ventralis lateralis pars medialis; VLo: ventralis lateralis pars oralis; X: area X of Olszewski.

input is processed via the basal ganglia and the thalamus to finally target only one of the cortical input areas. The assumption of segregated striato-cortical loops has been confirmed in studies using functional resting state connectivity analysis (Di Martino et al., 2008; Postuma & Dagher, 2005) and newer reviews kept the basic framework (Nambu et al., 2005; Obeso, Marin, et al., 2008; Parent & Hazrati, 1995). However, integration and exchange of information between the loops have since been emphasised (Haber, 2003). Moreover, the proposal that thalamo-cortical projections target only one among the input areas has been questioned (Joel & Weiner, 1994). Indeed, it is now acknowledged that information is projected back to all input areas in parallel (Middelton & Strick, 2000; Nambu et al., 2005; see Figure 3B). Therefore, the five loops that Alexander and colleagues proposed can be rather understood as ‘families’ of functionally related parallel loops, although the singular term ‘loop’ will be used throughout this work as done by Alexander et al. (1986) for reasons of simplicity. One of the loops connects the primary motor cortex and premotor areas to the basal ganglia and therefore was termed the ‘motor loop’. As part of this loop, the primary motor cortex, the somatosensory cortex, the SMA and the PM project to the dorsal putamen.

The SMA is situated on the midline cortical surface of Brodmann’s area 6 anterior to the leg representation of the primary motor cortex. In humans the SMA is mainly involved in planning and preparing bimanual movements, internally determined and well-learned movements, complex and sequential movements and the timing of motor initiation (Cunnington et al., 1996). Classically, the SMA was described as one coherent zone on each hemisphere (Penfield & Welch, 1951), but recent approaches show that the SMA can be further differentiated (Tanji, 1994; Zhang, Ide, & Li, 2011). Its caudal part, the somatotopically organised SMA proper, receives input from the putamen and has direct connections to the

primary motor cortex and the spinal cord. The rostral part of the SMA, the pre-SMA, is targeted by projections from the caudate and is densely connected to prefrontal areas. The supplementary eye field is located between the SMA proper and the pre-SMA and is involved in the coordination and preparation of eye movements. Note that the differentiation of these three areas probably rather represents gradual differences in anatomical structure, connectivity and function than discrete subregions (Nachev, Kennard, & Husain, 2008).

The lateral part of Brodmann's area 6, the PM, is involved in matching visual, auditory and somatosensory input with motor programs. It can be subdivided into a dorsal and a ventral part at the level of the superior frontal sulcus (Schubotz, Anwander, Knösche, von Cramon, & Tittgemeyer, 2010; Tomassini et al., 2007). Both areas participate in different fronto-parietal circuits and are proposed to underlie complementing aspects of sensorimotor transformation, i.e., direct sensorimotor processing in the ventral PM and indirect sensorimotor mapping in the dorsal PM (Hoshi & Tanji, 2007).

The different projections of the motor loop partially overlap in the putamen; about one-fourth of striatal neurons receive convergent inputs from the primary motor cortex and the SMA (Nambu, 2008). The cortical inputs are processed in parallel in the basal ganglia and send back to the oral and medial part of the ventral lateral nucleus of the thalamus which projects to the primary motor cortex, the SMA and the PM (Middelton & Strick, 2000). The motor loop is organised in a somatotopic way, i.e. areas of the motor cortex responsible for a specific motor effector are not intermingled with projections of other effectors throughout the loop (Alexander & Crutcher, 1990). The disbalance of activity within the inner basal ganglia pathways of PD patients causes dysfunctions of the cortico-basal ganglia-thalamo-cortical loops including the motor loop. Although the dynamics within the basal ganglia are not fully understood, there are two treatment approaches that effectively ameliorate the patient's motor symptoms by improving the information flow within the motor loop. These approaches will be described in the following, as they give further insight to the pathologic mechanisms involved in PD.

1.2.4 Treatment approaches

The primary aim of PD treatment is to restore normal information processing in the basal ganglia and thus the cortico-basal ganglia-thalamo-cortical loops. Therefore, either dopamine levels are increased by drugs or the untuned neuronal firing within the inner basal ganglia pathways is addressed directly via electric stimulation of specific basal ganglia nuclei, i.e., deep-brain stimulation (DBS) of the STN or GPi.

In 1960, clinical trials revealed an immense impact of levodopa on the motor syndrome of PD and thereby confirmed the disease's relation to dopamine (Hornykiewicz, 2008), as levodopa is a prodrug of dopamine and converted to dopamine in the brain. Levodopa still is the gold standard of antiparkinsonian medication, but a broad spectrum of effective drugs is available nowadays (Calne, 1993). They include direct dopamine agonists like apomorphine or drugs that raise dopamine levels indirectly, for instance by prohibiting dopamine from being metabolised in the synaptic gap. Some medication takes effect via interactions with other neurotransmitter systems. For example, anticholinergic medication can be effective because it restores the shifted balance of acetylcholine and dopamine. Unfortunately, the available drugs help to ameliorate the motor symptoms of PD, but do not hinder the progression of the underlying pathology (Rinne, 1981). For example, the effect of levodopa declines over the years and in the long term induces additional imbalance in the basal ganglia because dopamine levels vary highly in the course of the day during standard therapy (Obeso, Rodríguez-Oroz, et al., 2008). As a consequence, up to 80% of patients develop motor side-effects over five to ten years such as severe "on" vs. "off" treatment fluctuations or involuntary ballistic movements called dyskinesias (Hammond, Bergman, & Brown, 2007). Likewise, dopaminergic medication improves some cognitive disabilities, but has detrimental overdose effects on other aspects of cognition (Cools et al., 2001; Rodriguez-Oroz et al., 2009). Moreover, it increases the risk of dementia (Rinne, 1981).

To circumvent the dopaminergic medication's side-effects, the out-dated surgery method of pallidotomy was re-established in the form of DBS (Benabid, Chabardes, Mitrofanis, & Pollak, 2009). In the 1990s a procedure was developed to safely implant macroelectrodes either to the STN or the GPi of patients to manipulate neuronal firing in the surrounding tissue. Stimulation parameters are set individually, typically to 2.0 to 3.5 Volt impulses at frequencies around 130 Hz with an impulse length of 60 μs, as these settings show the best symptom improvement combined with the least motor side-effects. DBS alters dysfunctional basal ganglia output and thereby decreases dyskinesias and ameliorates tremor, rigidity and bradykinesia. This allows reductions of dopaminergic medication which further diminishes dyskinesia and other drug induced side-effects (Krack et al., 1998) leading to an improvement of the patient's quality of life compared to best medical therapy. Nevertheless, DBS sometimes accelerates cognitive decline (Benabid et al. 2009; Massano & Garrett, 2012; Weaver et al., 2009) and can induce impulsivity (Frank, Samanta, Moustafa, & Sherman, 2007).

The mechanisms by which stimulation improves motor functions are still not fully understood (Boertien et al., 2011). One assumption is that DBS does not normalise basal ganglia

functions, but rather diminishes noisy and disruptive output to cortical areas (Wichmann & DeLong, 2016). However, there is evidence that the connectivity patterns of basal ganglia output structures are normalised under DBS. Confirming the conception of overactive indirect and hyperdirect pathways, DBS of the STN decreases its cortical input and diminishes its connection to the GPe (Marreiros, Cagnan, Moran, Friston, & Brown, 2013). Additionally, connectivity within the direct pathway was found to be strengthened by stimulation of the STN (Kahan et al., 2014). Notably, this normalisation of connectivity is not achieved by a simple increase or decrease in the firing rate of targeted nuclei, but rather mirrors dynamic changes in the temporal patterns of neural activity (Montgomery, 2007; Obeso, Marin, et al., 2008). Without treatment, STN and GPi firing patterns are highly correlated during movements (Brown et al., 2001) and cortical motor areas evolve pathologically synchronised oscillations of 15 to 30 Hz (Esposito et al., 2013) as measured by electroencephalography. This excessive neural coupling is reduced during DBS (Silberstein et al., 2005) as well as under dopaminergic medication (Brown et al., 2001; Esposito et al., 2013; Silberstein et al., 2005). Similarly, subcortical and cortical hypoactivity is alleviated during DBS and under medication corresponding to attenuated inhibitory overactivity in the indirect pathway. The pathological pattern of brain activity within the motor loop and its normalisation via treatment will be explained in detail in the next section.

1.3 Motor loop dysfunction in Parkinson's disease

As described above, the motor loop is constituted by projections from the primary motor cortex, the SMA and the PM to the basal ganglia and back to the cortex via the thalamus. Alexander and colleagues (1986) supposed the motor loop to be responsible for PD motor symptoms which they presumed to be mainly characterised by SMA dysfunction. Since the early 1990s these assumptions were largely substantiated by evolving brain imaging techniques, that is, positron emission tomography (PET) and functional magnet resonance imaging (fMRI) that indicate local brain activity via measurements of regional cerebral blood flow and blood oxygenation levels, respectively (for a description of brain imaging techniques be referred to Orrison, Lewine, Sanders, & Hartshorne, 2017). Adopting the classical approach to PD, the following sections focus on the neural causes of motor symptoms to overview changes of motor loop activity in patients. By doing so, the contributions of the SMA and PM will be differentiated to highlight their functional interplay in PD.

1.3.1 Motor loop activity during movements

The first studies that investigated PD related alterations of brain activity compared patients in later disease stages with healthy control participants while performing self-paced joystick movements (Playford et al., 1992; Rascol et al., 1992; Rascol et al., 1994). Brain activity during these movements was contrasted against brain activity during rest and, as a result, both groups were found to specifically recruit the PM, the parietal cortex, the primary sensorimotor and motor cortex and the cerebellum during the motor task. Healthy participants showed additional activation of the SMA, the putamen, the thalamus, the anterior cingulate cortex and the dorsolateral prefrontal cortex which was lacking in PD patients after withdrawal of their dopaminergic medication. Reduced SMA activity can be understood as a result of overactivity in the indirect pathway of the motor loop that increases cortical inhibition. Indeed, hypoactivity of the SMA was found to be ameliorated after infusion of apomorphine (Jenkins et al., 1992; Rascol et al., 1992) and under regular medication (Rascol et al., 1994) assuring a relation of SMA hypoactivity to disease status and motor impairment. Although sometimes found differently (Cerasa et al., 2006; Nakamura et al., 2001), multitudinous studies confirmed SMA hypoactivity to be prominent in PD patients "off" medication. For example, SMA hypoactivity was found during simple motor tasks (Catalan, Ishii, Honda, Samii, & Hallett, 1999; Haslinger et al., 2001; Jahanshahi et al., 1995; Rascol et al., 1997; Samuel et al., 1997; Wu et al., 2010) even in early disease stages (Buhmann et al., 2003), during walking (Hanakawa, Katsumi, et al., 1999), during motor imagery (Samuel, Ceballos-Baumann, Boecker, & Brooks, 2001; Snjiders et al., 2011), in motor timing tasks (Elsinger et al., 2003; Yu, Sternad, Corcos, & Vaillancourt, 2007) and during performance of more complex motor sequences (Mallol et al., 2007; Sabatini et al., 2000). Furthermore, SMA activity was found to be enhanced by medication (Buhmann et al., 2003; Elsinger et al., 2003) and DBS (Ceballos-Baumann et al., 1999; Grafton et al., 2006; Limousin et al., 1997; Strafella, Dagher, & Sadikot, 2003). Finally, the intimate relation of SMA hypoactivity and motor dysfunction was shown by using high-frequency repetitive transcranial magnetic stimulation of the SMA which reduced the motor impairment of PD patients (Hamada, Ugawa, & Tsuji, 2008). An animal model of PD confirmed decreased glucose metabolism of the SMA to be a characteristic pathological feature of PD as it distinguished monkeys with parkinsonian symptoms from monkeys in a pre-symptomatic phase (Bezard, Crossman, Gross, & Brotchie, 2001). Accordingly, the firing rates of SMA neurons in parkinsonian macaques were found to be severely decreased in a delayed motor task, especially during motor preparation (Escola et al., 2003).

Contrary to reduced SMA functionality, patients "off" medication commonly show more activity than healthy controls in the PM, usually combined with additional involvement of the parietal cortex or the cerebellum (Catalan et al., 1999; Hanakawa, Fukuyama, et al., 1999; Haslinger et al., 2001; Nakamura et al., 2001; Sabatini et al., 2000; Samuel et al., 1997; Wu et al., 2010). Furthermore, PM hyperactivity was accompanied by SMA hypoactivity in most of these studies (Haslinger et al., 2001; Sabatini et al., 2000; Samuel et al., 1997; Wu et al., 2010). For example, Haslinger and co-workers (2001) observed decreased SMA involvement in PD patients compared to healthy controls during self-initiated joystick movements and found concurrent hyperactivity in the primary motor cortex and the PM. Both the SMA hypoactivity and the PM hyperactivity normalised after levodopa intake compared to "off" medication. Similarly, electroencephalography studies showed that the readiness potential reflecting motor preparation is altered in PD patients, i.e., the early component driven by SMA activity was diminished during simple finger movements (Jahanshahi et al., 1995), while a later negative component indicating PM activity was concurrently increased (Dick et al., 1989). The role of PM hyperactivity co-occurring with SMA hypoactivity can be interpreted in the framework of Goldberg (1985) which will be outlined in the following.

1.3.2 Medial versus lateral premotor involvement

Goldberg (1985) proposed that the SMA is more involved in the execution of internally guided movements based on memory, whereas the PM rather adjusts movements to current environmental input. He established this differentiation by assuming that both premotor areas have distinct phylogenetic origins and are thus connected to different subcortical and cortical structures which determine their respective function. It is emphasised that the SMA is tightly linked to medial prefrontal areas and the limbic system and that its primary subcortical input stems from the basal ganglia. Therefore, the SMA is conceptualised to link the motivation to act to the selection and execution of actions based on mnemonic representations of motor programs. On the contrary, adjustments of chosen behaviours to current external contexts are proposed to be controlled by lateral frontal areas including the PM. Accordingly, it is stressed that the PM receives cerebellar input and polymodal sensory information processed in the visual and parietal cortex that allow refinement of movements according to environmental requirements. More recently, Seitz, Stephan and Binkofski (2000) proposed a similar interplay of the PM and SMA.

Single cell recordings in monkeys back this approach, as neurons in the SMA were found to fire preferentially during the performance of a learned motor sequence from memory, whereas those in the PM were more active when a light guided the monkeys' arm movements (Halsband, Matsuzaka und Tanji, 1994; Mushiake, Inase, & Tanji, 1991). As the authors emphasise, this pattern represents a functional preference rather than a strict double-dissociated dichotomy and is only found in sequential, but not single movements. A study by Shima and Tanji (2000) impressively demonstrated how the SMA supervises the correct execution and timing of motor sequences with help of different types of specialised neural populations. For example, one type of neurons was found to fire in advance of a specific sequence to be performed, while some neurons coded transitions between two movement elements.

Many brain imaging studies that investigated internally versus externally driven movements in humans are less instructive of the lateral-mesial interplay, because often single self-initiated movements and single externally triggered movements were compared (Deiber et al., 1991; Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000; Weeks, Honda, Catalan, & Hallett, 2001; Wiese et al., 2004) or well-learned memory guided sequences were defined as externally driven when only their initiation or timing was triggered by a sensory cue (Boecker, Jankowski, Ditter, & Scheef, 2008; Cunnington et al., 2002; Taniwaki et al., 2006). Still, most of these studies confirmed a higher involvement of the SMA in self-initiated conditions (Boecker et al., 2008; Deiber et al., 1991; Jenkins et al., 2000; Taniwaki et al., 2006; Wiese et al., 2004). Studies that successfully compared memory driven sequential movements to externally guided movements largely found clear evidence of a functional bias between SMA and PM (Crosson et al., 2001; Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003; Heuninckx, Wenderoth, & Swinnen, 2010; Larsson, Gulyás, & Roland, 1996; Lu, Arai, Tsai, & Ziemann, 2012; but not all: Elsinger, Harrington, & Rao, 2006).

Accordingly, patients with premotor lesions that include parts of the SMA were confirmed to be most impaired in memory-based bimanual and sequential movements (Dick et al., 1986; Halsband, Ito, Tanji, & Freund, 1993; Lepage et al., 1999). PD patients were found to have difficulties during self-initiated movements due to SMA hypoactivity but had no difficulties during an externally triggered condition (Jahanshahi et al., 1995). These findings are further corroborated by animal lesion studies (Shima & Tanji, 1998; Thaler, Chen, Nixon, Stern, & Passingham, 1995). Macaques were found to perform worse in motor tasks after lesioning their SMA but showed significantly less difficulties when external cues were provided (Thaler et al., 1995). Furthermore, animals with lesions of the PM were less impaired during the self-paced task than their conspecifics with SMA lesions. Another study confirmed the

dissociation of internally and externally guided movements to be an essential part of parkinsonism (Franco & Turner, 2012). After dopamine receptors in the putamen of macaques were artificially blocked, the monkeys' visually guided movements were scarcely affected whereas self-initiated movements often froze up to 25 seconds. Therefore, Goldberg's proposal can be useful to understand the role of PM hyperactivity in PD, described in more detail in the next section.

1.3.3 Lateral hyperactivity as compensatory mechanism

To further clarify the interplay of the PM and the SMA in PD, one may consider an interesting phenomenon sometimes referred to as *paradoxical movement*: PD patients that suffer from freezing of gait, i.e., the feeling of being unwillingly stuck during walking, can walk smoothly when they are provided with external cues such as auditory rhythms or vertical lines on the floor as visual aids (Azulay et al., 1999; Glickstein & Stein, 1991; McIntosh, Brown, Rice, & Thaut, 1997; Rochester et al., 2005; Spaulding et al., 2013). To account for this observation, it was proposed that the basal ganglia's dysfunction in PD can be compensated by the recruitment of alterative motor pathways bypassing deficient basal ganglia input, for example by involving the PM that receives more information about external stimulus properties via parietal and cerebellar regions than the SMA (Berardelli et al., 2001; Glickstein & Stein, 1991; Marsden & Obeso, 1994; see also Figure 3B).

Supporting this proposal, the SMA of PD patients was found to be less connected to the basal ganglia and some prefrontal areas compared to healthy subjects during bimanual movements, whereas the connectivity of the SMA to the PM, the primary motor cortex, the parietal cortex and the cerebellum was increased (Wu et al., 2010). Likewise, a shift of connectivity away from medial prefrontal-SMA processing towards a lateral prefrontal-premotor pathway was observed in PD patients during finger tapping (Rowe, Hughes, Barker, & Owen, 2010). A direct compensative effect of PM involvement was demonstrated in patients that suffer from freezing of gait. The patients showed gait disturbances and decreased SMA activity when they walked on a treadmill (Hanakawa, Katsumi, et al., 1999); however, if the treadmill was equipped with horizontal lines, patients were enabled to walk smoothly and concurrently showed higher PM activity (Hanakawa, Fukuyama, et al., 1999). This hyperactivity was not found after placing unhelpful vertical lines on the treadmill, thus demonstrating the close relation of PM activation to restored performance. Further support stems from a study with carriers of gene mutations that cause inherited PD (Nuenen et al.,

2009). To find preclinical indicators of the disease, carriers of Parkin and PINK1 mutations without motor symptoms were compared to non-carriers. No behavioural differences were found in a finger sequence task, but carriers showed higher activity in SMA and dorsal PM. The authors interpreted this hyperactivity as early compensatory response to yet subclinical dopaminergic depletion, supporting studies which suggest that the PM hyperactivity in PD is of compensatory nature (Hanakawa, Fukuyama, et al., 1999; Haslinger et al., 2001). Consequently, PM hyperactivity probably corresponds to the general observation that PD patients are less impaired if external cues are available, e.g., during finger tapping (Freeman, Cody, & Shady, 1993) and grasping (Majsak, Kaminski, Gentile, & Flanagan, 1998), in reaction time tasks (Michely et al., 2012; Siegert, Harper, Cameron, & Abernethy, 2002) and when performing a sequence of button presses (Georgiou et al., 1994).

Summing up, the motor syndrome of PD is characterised by SMA hypoactivity which is caused by defective processing within the motor loop. Probably, the SMA is prone to deficient basal ganglia outflow because the number of projections from the GPi to the SMA is three to four times higher than the number of cells projecting from the cerebellum to the SMA (Akkal, Dum, & Strick, 2007), whereas the PM and the primary motor cortex receive massive cerebellar input (see Figure 3B). Consistent with Goldberg's (1985) proposal, the patient's motor dysfunctions are more pronounced during memory-dependent, internally guided actions and improve if the environment contains movement relevant cues, presumably because the PM processes information about external stimuli circumventing the basal ganglia. This interaction may also take place during cognitive tasks, as behavioural studies and brain imaging results question a strict distinction of cognitive and motor dysfunction and highlight a possible contribution of the motor loop to early cognitive impairment, as illustrated in the following chapter.

1.4 Motor cognition in Parkinson's disease patients and healthy participants

Alexander and co-workers (1986) stated that their framework of distinct cortico-basal ganglia-thalamo-cortical circuits allows for relating selective deficits in motor or cognitive functions to damage of different portions of the basal ganglia and thus to dysfunctions of different loops. Following this line of reasoning, cognitive dysfunctions were soon attributed to the three prefrontal loops described by Alexander and colleagues, in most cases to the dorsolateral prefrontal loop (Brown & Marsden, 1990; Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Owen et al., 1992; Saint-Cyr, Taylor, & Lang, 1988; Taylor, Saint-Cyr, & Lang, 1990). At first

glance, the idea is appealing that motor and cognitive symptoms can be clearly separated along physiologic lines. However, the validity of this concept is questioned in the following sections and complemented with research linking motor loop activity and cognitive impairment in PD.

1.4.1 Relation of motor and cognitive impairment

Most authors consent that cognitive impairment is associated with hypoactivity of the caudate nucleus and the dorsolateral prefrontal cortex (Brück et al., 2001; Cheesman et al., 2005; Cools, Barker, Sahakian, & Robbins, 2001; Dagher, Owen, Boecker, & Brooks, 1999, 2001; Gawrys et al., 2014; Grahn, Parkinson, & Owen, 2008; Lewis et al., 2003; Nagano-Saito et al., 2014; Owen, 2004; Polito et al., 2012; Rinne et al., 2000; Zgaljardic et al., 2006) or the anterior cingulate loop and the orbitofrontal loop (Polito et al., 2012; Sawamoto et al., 2008; Zgaljardic et al., 2006). Although some of these studies found dysfunctions of the caudate nucleus and the putamen to co-occur and both structures to be related to poorer cognitive performance (Cheesman et al., 2005; Dagher et al., 1999; Gawrys et al., 2014; Nagano-Saito et al., 2014; Rinne et al., 2000), affection of the motor loop was generally considered to add to sensorimotor, but not cognitive dysfunction.

Importantly, cognitive dysfunction is not one-dimensional. Instead, it is highly variable between patients and within one patient in the course of her or his disease (see chapter 1.1.2). To better understand the neural underpinnings of cognitive deficits, it is therefore necessary to take two aspects into consideration: First, different sets of cognitive functions are provided by different neural populations, wherefore performance and brain activity crucially depend on the specific tasks applied. Second, the time course of neural pathologies must be considered, as different cognitive functions are affected to different degrees during disease progression (Dirnberger & Jahanshahi, 2013). These two aspects are exemplified by the observation that some cognitive tasks are improved under dopaminergic medication, while performance in other tasks is not affected or even deteriorated, depending on the disease's progression (Cools et al., 2001; Gotham, Brown, & Marsden, 1988; Kehagia, Barker, & Robbins, 2010). This pattern can largely be explained by the "*overdose hypothesis*" which states that medication restores dopamine depleted pathways, but concurrently interferes with normal processing in unaffected structures (Cools et al., 2001). Dopaminergic deafferentation starts in the posterior putamen and initially progresses to the anterior putamen and further to the dorsal caudate nucleus (Kish, Shannak, & Hornykiewicz, 1988; Rodriguez-Oroz et al., 2009). This means that the motor loop and, to a lesser degree, the dorsolateral prefrontal loop are affected in early disease stages, while

the anterior cingulate loop, the orbitofrontal loop and the mesocortical dopaminergic pathway are still mostly spared. Accordingly, medication of patients in early disease stages has a detrimental effect on feedback-based learning related to functions of preserved prefrontal loops, whereas most early cognitive impairments are normalised under dopaminergic medication in yet untreated patients (Kehagia et al., 2010). The latter observation highlights the possibility that MCI depends on early dopamine deficiency in the putamen.

Accordingly, most studies (but not all, cf. Muslimović et al., 2005; Aarsland et al., 2009; Cooper et al., 1991) that investigated MCI found significant correlations of bradykinesia and other motor symptoms with cognitive decline in early disease stages (Aarsland et al., 2010; Mortimer, Pirozzolo, Hansch, & Webster, 1982; Pfeiffer, Løkkegaard, Zoetmulder, Friberg, & Werdelin, 2014) and in newly diagnosed and yet untreated patients (Domellöf, Elgh, & Forsgren, 2011; Elgh et al., 2009; Foltynie et al., 2004; Poletti et al., 2012; Williams-Grey et al., 2007). For example, two studies noted a negative correlation of bradykinesia scores with set shifting abilities measured in the Wisconsin Card Sorting Test and the Trail Making Test (Domellöf et al. 2011; Poletti et al., 2012). The authors of both studies concluded that bradykinesia and cognitive inflexibility probably result from the same early nigrostriatal deficiency. In line with this assumption, akinetic-rigid compared to tremor-dominant patients are characterised by higher rates of dopaminergic deafferentation in the dorsal putamen (Eggers, Kahraman, Fink, Schmidt & Timmermann, 2011) and have an increased risk of MCI (Alves, Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006; Burn et al., 2006). Complementing this correlational evidence, several results will be described in the next section that point to a direct involvement of the motor loop in MCI.

1.4.2 Motor loop involvement in cognitive impairment

Recent experimental studies show altered activity in the motor loop of PD patients during cognitive tasks. A study identified the neuronal pattern in PD patients associated with reduced performance in several different cognitive tasks including Stroop Tests, the Wisconsin Card Sorting Test, the Trail Making Test and working memory tasks and found decreased activity in the PM and SMA among prefrontal, occipital and parietal regions (Huang et al., 2007). Corroborating a direct relation between motor loop activity and cognitive dysfunctions, patients' performance in the Wisconsin Card Sorting Test and the Trail Making Test was found to depend on their putamen's activity level in a 2-back fMRI paradigm (Gawrys et al., 2014). Furthermore, Nagano-Saito et al. (2014) showed that patients with MCI showed less PM

activity compared to patients without MCI when adjusting to a rule change during the Wisconsin Card Sorting Test. Both studies suggest that the motor loop's dysfunction contributes to set shifting difficulties in PD, which is self-evident when considering a meta-analysis that found the SMA and the putamen to be reliably active during the Wisconsin Card Sorting Test in healthy participants (Buchsbaum, Greer, Chang, & Berman, 2005). The putamen and the PM of healthy participants were also specifically engaged in the reception of negative feedback and the mapping of stimuli to a new rule after negative feedback indicated a change of set (Monchi, Petrides, Petre, Worsley, & Dagher, 2001). This involvement was not confounded with motor execution, as all conditions were contrasted with control trials that required the same movements. Another study with PD patients noted the presynaptic dopamine storage capacity in the left anterior putamen to be correlated to the performance in a verbal working memory task (Cheesman et al., 2005). This task required the patients to internally retain or change the order of a given sequence of four consonants and to compare its structure to a target sequence. These results are particularly interesting, because they suggest that the basal ganglia's contribution to sequence learning and monitoring is not restricted to the motor domain.

Against this background, it is striking that an involvement of premotor areas in cognitive tasks is scarcely discussed in the PD literature. This is probably neglected because, on the one hand, motor loop activation is traditionally considered purely motor, while, on the other hand, most cognitive tasks require some form of response, i.e., overt movement. Therefore, motor loop activity is naturally interpreted as movement artefact in most studies. This attitude against motor components of cognitive tasks can be exemplified by the approach of Muslimović et al. (2005). They acknowledged the close relationship of motor functions and cognition by including 'psychomotor' tasks in their assessment of PD patients. Though, these tasks were excluded because of their motor components in a regression analysis that should indicate measures best suited to differentiate patients with MCI from healthy controls.

To investigate the influence of premotor areas on cognitive functions, tests of sequence processing without confounding motor components should be applied, such as the serial prediction task introduced in the next section.

1.4.3 Cognitive functions of the premotor areas

Unlike commonly used serial reaction time tasks, the serial prediction task (SPT) developed by Schubotz (1999) disentangles motor output and sequence learning. In the SPT, purely sensory

sequences are presented to the participants and behavioural responses are only required to indicate violations of the stimulus order after the sequence is completed. Therefore, motor components do not interfere with sequence learning and monitoring itself. There are various versions of the SPT with stimuli of different modalities (Binder et al., 2014; Bubic, von Cramon, Schubotz, 2009; Philipp, Kalinich, Koch, & Schubotz, 2008; Schubotz, Anwander, Knösche, von Cramon, & Tittgemeyer, 2010; Schubotz, Sakreida, Tittgemeyer, & von Cramon, 2004; Schubotz & von Cramon, 2001a, 2001b, 2002a, 2002b, 2002c, 2004a, 2004b; Schubotz, von Cramon, & Lohmann, 2003; Wolfensteller, Schubotz, & von Cramon, 2004, 2007), but the common principle is to implement and occasionally violate sensory stimulus sequences. The participants are instructed to focus on one property of the stimuli, such as their position, size or timing, and to find deviants within the sequence which is structured in this regard. For example, circles of differing sizes are repeatedly shown in a certain chronological order, e.g., medium, large, small, very small, whereas their screen positions and presentation times may be constant or chosen randomly. Then, in half of the trials the order of two circle sizes is switched during the last sequence presentation, e.g., the medium, small, large, and very small circles are shown in succession. This violation must be indicated by the participants who at the end of each trial decide by button press if there was a switch in the relevant stimulus dimension of the sequence, or not.

This paradigm revealed exciting and previously unacknowledged properties of premotor areas. Most importantly, they were shown to provide a prospective monitoring of serial events independent of motor output (Schubotz, 2007; Schubotz & von Cramon, 2003). This conclusion draws on several pieces of evidence collected in various studies as shortly outlined in the following. Participants engaged the SMA and the PM along with the basal ganglia, the parietal cortex and the occipital cortex, whereas no task specific prefrontal activations were observed (e.g., Schubotz & von Cramon, 2001a, 2002a, 2002b, 2002c; Schubotz, von Cramon, & Lohmann, 2003). Notably, brain activity during the SPT was contrasted with brain activity during control tasks that included serially presented stimuli and behavioural responses but did not require the participants to engage in processing of the serial structure of the stimuli. Furthermore, activity in the SMA and PM was shown to vary with properties of the sequences such as their complexity (Schubotz & von Cramon, 2002a, 2002c) and the stimulus modality (Schubotz & von Cramon, 2002c, Schubotz, von Cramon, & Lohmann, 2003). These results prohibit an interpretation of premotor engagement in terms of a merely supportive function to other frontal areas or as plain motor preparation or reaction to other unspecific general task properties. Further substantiating this conclusion, activity in the parietal-premotor network

even occurred if participants were told to monitor sequential violations although there was no sequential pattern in the stimulus train (Schubotz & von Cramon, 2003). These results indicate that the engagement of the premotor areas depends on the participant's intention to derive sequential information, and thus provides an action independent, cognitive function. Referring to the framework of forward motor control (Desmurget & Grafton, 2000; Wolpert & Flanagan, 2001), it was proposed that this cognitive premotor function should not be characterised as passive sequence monitoring but can be understood as a prediction of upcoming sensory events (Schubotz, 2007; Schubotz & von Cramon, 2003). In short, the premotor cortex is assumed to predict future sensory states based on dynamic environmental and proprioceptive patterns via a transformation of these sensory cues into pragmatic motor features. This transformation happens independent of actual motor execution, but in terms of the motor effectors that either affect the sensory event or normally are affected by the event. For example, a sequence of circles of different sizes would activate the part of the PM that corresponds to picking-up movements of the hand or opening of the mouth.

Relating these findings to cognitive deficits in PD, the question arises if premotor impairment causes serial prediction difficulties. Three previous studies directly tested the impact of motor loop dysfunction on non-motor versions of serial reaction time tasks. A study conducted by Helmuth, Mayr and Daum (2000) showed no impairment of PD patients when they predicted the spatial position of stimuli, but curiously found a deficit of healthy control participants compared to PD patients in spatial learning, preventing a straightforward interpretation of the results. On the contrary, Vakil, Kahan, Huberman and Osimani (2000) found that patients with basal ganglia lesions were impaired in sequential processing compared to a healthy control group. Finally, PD patients were less likely to implicitly learn the serial order of numbered spatial positions in a verbal version of the serial reaction time task (Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998).

Regarding the SPT, a study with stroke patients revealed that the performance of patients with premotor and parietal lesions was impaired, whereas prefrontal patients did not perform differently from healthy control participants (Schubotz et al., 2004). Putting this study together with all the evidence that the cognitive performance of PD patients is influenced by motor loop dysfunction, the following question needs to be asked: Are PD patients impaired in serial prediction, and if so, via which neural mechanisms? This and all related questions that motivated this thesis will be elaborated in the next chapter after a summary of all information given so far.

1.5 Summary, research questions and hypotheses

PD is a complex and multi-faceted neurodegenerative disease that comprises various symptoms including motor and cognitive impairment (Braak et al., 2004; Jankovic, 2008; Rodriguez-Oroz et al., 2009). Its motor and early cognitive symptoms are caused by cell demise in the substantia nigra pars compacta which sends dopaminergic projections to the striatum. The resulting lack of dopamine in the striatum first comprises the posterior putamen and proceeds to the anterior putamen and further to the caudate nucleus during the disease (Kish et al., 1988). The putamen is part of the motor loop that connects the primary motor cortex and the premotor areas to the basal ganglia, whereas the caudate is part of several prefrontal loops (Alexander et al., 1986; Nambu et al., 2005; Middelton & Strick, 2000). In both cases, cortical input enters the striatum to be processed via inner basal ganglia pathways in a way that corresponding neurons in the thalamus can either be inhibited or selectively activated (Marsden & Obeso, 1994; Obeso, Marin, et al., 2008; Redgrave et al., 2010; Wichmann & DeLong, 1996). Decreased dopamine levels cause undifferentiated over-inhibition of thalamic neurons, wherefore noisy or reduced signals re-enter the cortical participators of the loop. Dopamine replacement therapy (Calne, 1993) or DBS (Benabid et al., 2009) can be applied to restore dopamine levels or to directly normalise disrupted information processing in the basal ganglia, respectively.

Motor symptoms, such as increased muscle stiffness and slowness during movement sequences, can be explained by defective processing within the motor loop. The medially located SMA is *hypoactive* in patients during movements (Buhmann et al., 2003; Catalan et al., 1999; Elsinger et al., 2003; Hanakawa, Katsumi, et al., 1999; Haslinger et al., 2001; Mallol et al., 2007; Playford et al., 1992; Rascol et al., 1992; Rascol et al., 1994; Sabatini et al., 2000; Samuel et al., 1997, 2001; Snjiders et al., 2011; Wu et al., 2010; Yu et al., 2007) while the PM is often observed to be *hyperactive* (Catalan et al., 1999; Hanakawa, Fukuyama, et al., 1999; Haslinger et al., 2001; Nakamura et al., 2001; Sabatini et al., 2000; Samuel et al., 1997; Wu et al., 2010). PM hyperactivity was found to play a compensatory role in PD (Hanakawa, Fukuyama, et al., 1999; Haslinger et al., 2001), which probably is grounded in its anatomical connectivity. Both premotor areas are linked to the basal ganglia, but the motor loop's mesial part connecting the SMA and the putamen is more dependent on basal ganglia function then the lateral part that receives more cerebellar input (Akkal, Dum, & Strick, 2007). According to their connections with other brain regions, both premotor areas fulfil different roles in preparing and controlling motor sequences (Debaere et al., 2003; Goldberg, 1985; Halsband et al., 1994; Lu et al., 2012; Mushiake et al., 1991; Seitz et al., 2000). As Goldberg (1985) put it, the SMA is more involved in providing memory-based internal cues to trigger upcoming actions, whereas

the PM rather relates (upcoming) sensory states to motor patterns. This approach explains why PD patients are impaired in implicitly building sequential knowledge (Clark et al. 2014; Siegert et al., 2006) and why they have more difficulties to perform movements that are internally guided than externally triggered (Freeman, et al., 1993; Georgiou et al., 1994; Jahanshahi et al., 1995; Majsak et al., 1998; Michely et al., 2012; Siegert et al., 2002). Interestingly, some evidence indicates that the distinction between internally and externally guided conditions might also apply to cognitive tasks in PD patients (Brown & Marsden, 1988a, 1988b), suggesting a contribution of premotor areas beyond a classical motor-centred perspective.

Indeed, some studies showed that premotor areas contribute to cognitive deficits of PD patients (Cheesman et al., 2005; Gawrys et al., 2014; Huang et al., 2007; Nagano-Saito et al., 2014). For example, cognitive flexibility during set shifting and internal manipulation of short letter sequences were found to partly depend on motor loop activity. However, cognitive impairment is commonly attributed to dysfunctions of prefrontal loops (e.g., Cools et al., 2001; Dagher et al., 1999; Gawrys et al., 2014; Rinne et al., 2000; Taylor et al., 1990) while possible contributions of the more severely affected motor loop are mostly neglected. Closing this gap, the current thesis addresses premotor contributions to cognitive impairments in PD by investigating the neural correlates of a specific cognitive task, the SPT (Schubotz, 1999). Studies using the SPT demonstrated that the premotor areas process sequential information that is necessary to succeed in this task by facilitating the prediction of sensory events independent of motor functions (Schubotz, 2007; Schubotz & von Cramon, 2003).

Therefore, the objective of this work is to investigate possible effects of motor loop dysfunction on cognitive performance of PD patients as measured in the SPT. The three main research questions that evolve from the literature and guided the experimental process are presented in the following sections. Importantly, all questions are addressed in each of the conducted experimental studies, i.e., each study contributes to answering all three questions albeit implementing different methodical approaches. Study 1 (behavioural study) provided initial behavioural results of healthy control participants and patients “on” and “off” dopaminergic treatment in the SPT and SPT+ and cognitive control tasks. These results were complemented with measurements of brain activity in Study 2 (fMRI study) and Study 3 (PET study) that involved patients “on” and “off” medication and “on” and “off” DBS, respectively. Thus, the three studies have slightly different angles, but mainly differ in the methods applied, and therefore complement each other in examining the following questions and corresponding sets of hypotheses.

1.5.1 Question 1: Are Parkinson's disease patients impaired in serial prediction because of motor loop dysfunction?

As the study by Schubotz and colleagues (2004) demonstrated, premotor dysfunction affects serial prediction performance. We wondered if this relation would apply to reduced motor loop functionality in patients suffering from PD, raising two questions: Would serial prediction deficits of PD patients be observed compared to healthy controls? And if so, would the deficits be directly related to motor loop dysfunction? These questions were first addressed in a behavioural study followed by the two brain imaging studies to provide direct evidence of motor loop impairment.

Based on all presented evidence we assumed patients to show performance deficits in the SPT compared to healthy control participants matched regarding age and cognitive status (hypothesis 1.1). The matching procedure was supposed to rule out that performance differences would be driven by other factors than the disease itself. To further ensure a relation of disease status to serial prediction performance, patients "on" compared to "off" dopaminergic medication should perform better concordant with restored motor loop functionality (hypothesis 1.2). Furthermore, we assumed that a direct relation of motor loop status and cognitive impairment would condense in a negative correlation of SPT performance and motor symptom severity (hypothesis 1.3).

In both brain imaging studies, we expected that performance deficits would co-occur with less activity of the SMA and the putamen in patients compared to healthy controls (hypothesis 1.4a) and in untreated compared to treated patients (hypothesis 1.4b). This hypoactivity should be the more pronounced, the higher the patients' severity of motor impairment (hypothesis 1.5). Furthermore, we hypothesised that serial prediction deficits would be caused by an affection of the motor loop independent of prefrontal dysfunction, i.e., we expected to find no concurrent prefrontal hypoactivity (hypothesis 1.6). Finally, to directly relate motor loop dysfunction to cognitive deficits, we assumed to find positive correlations of SPT performance with activity in the SMA (hypothesis 1.7).

Study 3 additionally tested if DBS would have a similar influence on SPT performance and motor loop activity as the regular medical treatment. It was expected that DBS should have a similar effect on SPT performance as medication as both improve motor loop function (hypothesis 1.8). Because magnetic resonance imaging poses a risk on patients with implanted DBS electrodes, this study was carried out as a PET study avoiding potential harm to the patients.

1.5.2 Question 2: Are the deficits more pronounced during internally than during externally guided predictions?

As described in detail in section 1.3, the neural dysfunction in PD is not characterised by a simple hypoactivity of the motor loop. Rather, the motor loop's impairment manifests as a shift in the normal balance between activity in medial and lateral premotor areas indicated by decreased SMA activity co-occurring with heightened PM activity. According to Goldberg (1985), the SMA facilitates memory-based movements, whereas the PM rather aids the adjustment of movements according to the environment. It therefore was investigated whether this interplay of premotor areas could explain some properties of cognitive impairment in PD, i.e., if memory-based processing of serial information would be more impaired in patients than sensory guided processing of serial information.

Schubotz and von Cramon (2004) addressed the functional roles of the SMA and PM by testing a modified version of the SPT that replaced some stimuli with uninformative wildcards within in the presented sequences. This version, termed SPT+, effectively enforced internally driven processing, and hence SMA engagement, in serial prediction in healthy participants. PM and prefrontal areas were also involved in this task version, but prefrontal activity was rather linked to general workload and PM activity showed less correspondence to the SPT+ condition than activity in the SMA.

The SPT+ modification was thus implemented in all three studies to offer a new perspective on cognitive impairment in PD and approach the following question: Is there a common principle of motor function and cognition in Parkinson's disease? If so, PD patients should be more impaired in serial prediction if they are forced to use more internally driven processing which is normally provided by the SMA. Accordingly, we expected a drop of performance in the SPT+ compared to the SPT0 version, both in comparison to healthy controls (hypothesis 2.1a) and after withdrawal of treatment (hypothesis 2.1b). In both cases, poorer performance of patients should be combined with SMA hypoactivity (hypothesis 2.2).

1.5.3 Question 3: Does compensatory hyperactivity of the lateral premotor cortex occur?

As noted by Berardelli and colleagues (2001), the clinical features of PD are the result of a mixture of primary dysfunctional and additional compensatory processes. Because of the evidence of compensatory PM hyperactivity in motor tasks, we were interested in the role of PM activity during serial prediction. Would patients show PM hyperactivity during serial

prediction? And in case we would find this hyperactivity, could it be interpreted as compensatory mechanism, as found in pure motor tasks? It has to be considered that increased cortical activity in PD can either reflect an activation of compensatory cortical circuits or indicate a dysfunction in the filter mechanism of the basal ganglia (Beeler, Petzinger, & Jakowec, 2013). The scaffolding theory (Park & Reuter-Lorenz, 2009) and the concept of cognitive reserve (Barulli & Stern, 2013) interpret neuronal hyperactivity in the context of age-related and pathologic neurobiological changes, respectively. Both theories propose that increased activity in a brain region co-occurring with equal performance compared to a younger or healthy control group indicates a compensatory mechanism. Therefore, the pattern of task performance should be considered when interpreting the results.

Accordingly, the relation of PM activity to the performance of PD patients should be analysed to directly answer the question if PM involvement could be interpreted as compensatory mechanism. If we observed PM hyperactivity in PD patients compared to controls (hypothesis 3.1a) and after withdrawal of medication (hypothesis 3.1b), we expected it to be more pronounced during the SPT+ condition, as in this constellation SMA involvement would be necessary, but impeded in PD patients. If PM activity would be helpful, the level of PM activity should be positively related to the serial prediction performance of the patients. Alternatively, PM hyperactivity could rather indicate the patients' motor loop dysfunction without effectively helping during the tasks resulting in a negative or no correlation of performance and PM activity in PD patients. It was expected that if the performance rates of patients would be preserved despite SMA hypoactivity, PM hyperactivity should indeed be positively related to the patients' performance (hypothesis 3.2).

The studies testing these hypotheses are presented in the following chapter in the order of their implementation and publication.

2 RESEARCH ARTICLES

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Joint principles of motor and cognitive dysfunction in Parkinson's disease

Anna R. Schönberger [a,b,*], Michael T. Barbe [b,c], Klara Hagelweide [d], Anne B. Kühn [a], Gereon R. Fink [b,c], Ricarda I. Schubotz [a,b,d]

[a] Max Planck Institute for Neurological Research, Gleueler Str. 50, D-50931 Cologne, Germany
[b] Department of Neurology, University Hospital Cologne, Kerpener Str. 62, D-50937 Cologne, Germany
[c] Institute of Neuroscience and Medicine (INM3), Cognitive Neuroscience, Research Centre Jülich, Leo-Brandt-Straße, D-52425 Jülich, Germany
[d] Department of Psychology, University of Muenster, Fliednerstr. 21, D-48149 Münster, Germany

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ABSTRACT

Traditionally, the lateral premotor cortex (PM) is assigned a role in stimulus-driven rather than memory-driven motor control, whereas the opposite holds for the mesial premotor cortex (supplementary motor area, SMA). Consistently, patients with Parkinson's Disease (PD), in which a specific functional degradation of the mesial loop (i.e., SMA-Striatum) occurs, show impaired memory-driven but relatively preserved stimulus-driven motor control. However, both parts of the premotor cortex are involved in perceptual prediction tasks as well. Here we tested whether the functional bias described on the motor level (i.e., memory-driven/mesial versus stimulus-driven/lateral) can also be detected in perceptual prediction tasks thereby suggesting that PD patients exhibit the same pattern of impaired memory-driven and preserved stimulus-driven control in the cognitive domain. To this end, we investigated 20 male PD-patients "on" and "off" dopaminergic medication while performing a serial prediction task (SPT). A specific modification was implemented to the classical SPT (SPT0) that caused shifts from stimulus- to memory-based prediction (SPT+). As a result, PD patients showed a significantly impaired performance "off" compared to "on" medication for SPT+, whereas no significant "on"/"off"-effects were found for SPT0. Descriptively, the "off"-performance decreased gradually with increasing demands on memory-based prediction. Furthermore, the severity of motor deficits according to the UPDRS III correlated significantly with impaired performance in SPT0 "on" medication. Importantly, an even stronger dependency was found for UPDRS III and SPT+. These findings point to a role of the SMA-striatal loop in memory-driven serial prediction beyond the motor domain.

1. Introduction

Apart from motor deficits, cognitive impairments have a major influence on the quality of life in Parkinson's disease (PD) (Schrag, Jahanshahi, & Quinn, 2000; Ziemssen & Reichmann, 2007). Characteristic neuropsychological symptoms of PD such as deficits in attention, working-memory, concept formation, planning, and set-shifting are reminiscent of those detected in patients with prefrontal cortex lesions (Brown & Marsden, 1988; Kulisevsky, 2000; Muslimovic, Post, Speelman, & Schmand, 2005; Van Spaendonck, Berger, Horstink, Buytenhuijs, & Cools, 1996) and are therefore often subsumed under the notion of a "dysexecutive syndrome" (Martinez-Horta & Kulisevsky, 2011). In PD, frontal dysfunction is most probably caused by deficient input from the caudate nucleus (Dubois & Pillon, 1997; Saint-Cyr, Taylor, & Lang, 1988; Taylor, Saint-Cyr, & Lang, 1990) which receives no longer sufficient dopamine projections from the degenerating substantia nigra (Alexander, DeLong, & Strick, 1986; Dubois & Pillon, 1997; Taylor, Saint-Cyr, & Lang, 1986). Frontal functions may be further deteriorated due to degeneration of the dopaminergic mesocortical pathway emanating from ventral tegmental area (Javoy-Agid & Agid, 1980). In contrast to the caudate-prefrontal loops, the so-called "motor loop" (Alexander et al., 1986) that connects the putamen to the lateral premotor cortex (PM) and the supplementary motor area (SMA), is hardly ever considered as potential origin of cognitive dysfunction in PD. However, evidence has accumulated that some cognitive functions draw particularly on the premotor loops (Jeannerod, 2001; Schubotz, 2007).

In a review addressing PD-associated cognitive impairment, Brown and Marsden (1990) argued that cognitive impairment in PD is present when patients have to rely on internal strategies, whereas performance is preserved when external cues or guidance

* Corresponding author at: Department of Neurology, University Hospital Cologne, Kerpener Str. 62, D-50937 Cologne, Germany. Tel.: +49 163 6318153.
E-mail address: anna.schoenberger@uk-koeln.de (A.R. Schönberger).

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are provided (e.g., Dubois & Pillon, 1997; Flowers, Pearce, & Pearce, 1984; Flowers & Robertson, 1985). Notably, difficulties in internal guidance and relatively preserved external guidance of behaviour are well-known features of motor control in PD. A striking example of this bias is provided by the phenomenon of "paradoxical kinesis": Patients who suffer from hypokinesia or akinesia are able to improve their gait with help of external cues like rhythmic auditory stimulation (McIntosh, Brown, Rice, & Thaut, 1997) or visual stimuli such as transversely oriented lines on the walking surface (Azulay et al., 1999; Hanakawa, Fukuyama, Katsumi, Honda, & Shibasaki, 1999; Martin, 1967).

It has been suggested that the neurofunctional mechanisms underlying paradoxical kinesis may be related to a functional dichotomy in the (pre)motor loops: Goldberg (1985) proposed that the supplementary motor area (SMA) is associated with internally or memory guided processing, whereas the lateral premotor cortex supports externally or stimulus driven processing. This view is largely (but not always, cf. Cunnington, Windischberger, Deecke, & Moser, 2002; Weeks, Honda, Catalan, & Hallett, 2001) in keeping with imaging studies comparing internally to externally guided movements (Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2003; Heuninckx, Wenderoth, & Swinnen, 2010). In Parkinson's disease, dopamine depletion is worst in the putamen (Brooks et al., 1990), whose main cortical target is the SMA (Alexander et al., 1986). Accordingly, PD patients performing motor tasks show a decreased blood flow in the SMA and putamen compared to age-matched controls (Playford et al., 1992). In contrast, they exhibit an increased blood flow of the lateral premotor cortex during motor tasks (Haslinger et al., 2001; Samuel et al., 1997). Moreover, administration of Levodopa in PD restores SMA-activation at least to a certain amount and decreases lateral hyper-activation (Haslinger et al., 2001). Lateral premotor activity is significantly higher when patients improve their motor abilities by relying on external cues (Hanakawa et al., 1999). Against the background of these observations, it has been suggested that lateral premotor activity may reflect compensatory processes for reduced SMA function in PD (Hanakawa et al., 1999).

We here aimed at investigating whether the known functional dichotomy of the lateral and mesial premotor cortex for motor tasks, i.e., lateral=stimulus–driven, mesial=memory–driven, holds also for tasks drawing on cognitive functions of the motor system. The serial prediction task (SPT) (Schubotz, 1999) has been shown to activate both the lateral premotor cortex and the SMA in the absence of motor demands (Schubotz & von Cramon, 2003). We modified the SPT in order to parametrically increase dependency on sequence memory, and hence internal guidance. Thus our motivation was to test PD patients (1) in a cognitive task that is known to engage the premotor system, which in turn is known to be particularly impaired in PD patients and (2) to vary the degree to which patients can rely on external cues. By this means we tested to what extent PD patients are able to compensate for occasional absence of prediction-triggering and prediction-confirming stimuli. Moreover, in order to uncover the direct role of dopaminergic supply, we examined the modulatory effect of dopaminergic medication on the described task by comparing the patients' performance "on" and "off" medication to that of healthy age, gender and education matched control subjects.

In the SPT, subjects monitor a repetitive stimulus sequence that accords to the structure 1-2-3-1-2-3-1-2-3; subsequently they have to indicate in a forced choice mode whether the sequence's last repetition ended orderly (1-2-3) or not (1-3-2 or 2-1-3). Note that the SPT is a purely cognitive task. In this regard, it clearly differs from otherwise related sequential paradigms such as the serial reaction time task (SRT) (Nissen & Bullemer, 1987). The parametric modification we implemented to the classical SPT (SPT+, hereafter) was a masking of a varying number of stimuli in the sequence (0–4 out of 15) during which subjects are forced to keep track of the correct stimulus order on memory basis.

We hypothesized that, due to a functional degradation of the motor system, (i) PD patients show a deficit in serial prediction when compared to healthy controls, (ii) performance correlates with PD-related motor symptoms (according to UPDRS III), and (iii) dopaminergic medication can restore performance significantly. More importantly, due to the particular detriment in the striatal-SMA-loop in PD, we furthermore expected the impairment of PD patients to be even more prominent when prediction is less regularly informed by external stimuli (i.e., in the SPT+ condition).

2. Methods

2.1. Participants

Twenty male PD patients with a mean age of 57.9 years (range 45–70 years) participated in the study. Patients were acquired from the neurologic outpatient clinic of the University Hospital of Cologne. All patients treated in the outpatient clinic and diagnosed with idiopathic Parkinson's disease according to the UK PD Society Brain Bank Criteria (Hughes, Daniel, Kilford, & Lees, 1992) were asked for participation in our study if they were less than 80 years old. No subject had undergone surgical treatment of the disease and no subject had a history of any other neurological or psychiatric diseases. Sixteen patients belonged to the rigid-akinetic and four to the equivalence type according to Spiegel et al. (2007). Symptoms of seven patients were left-dominant, and symptoms of thirteen patients were right-dominant (with onset of symptoms as criterion). All patients received dopaminergic medication (see Table 2 for levodopa equivalent daily dose [LEDD] according to Tomlinson et al. 2010) and were tested once on their regular medication and once "off" medication. "Off"-state was defined as at least 14 h of withdrawal of dopaminergic medication; long acting dopamine agonists were discontinued up to 36 h and replaced by short acting dopamine agonists until complete cessation 14 h before testing. The severity of clinical symptoms was defined according to Hoehn and Yahr (1967) and the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS III) (Fahn & Elton, 1987). UPDRS III was assessed on video tapes by a movement disorder specialist blinded for state of medication. Mean UPDRS III scores were 17.6 "on" and 26.6 "off" medication. Hoehn and Yahr ratings ranged between I and III under regular medication.

Twenty healthy male participants comparable to the patients regarding age and level of school education served as control subjects. Patients or controls with any evidence of dementia or depression were excluded from the study. All participants scored between 18 and 30 points in the Parkinson Neuropsychometric Dementia Assessment (PANDA; 18–30 points="age adequate cognitive performance") (Kalbe et al., 2008) and lower than 16 points in the Beck depression inventory-II (BDI-II; cut-off for depression: ≥20 points) (Hautzinger, Keller, & Kühner, 2006).

All subjects gave written informed consent prior to participation. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee.

2.2. Stimuli and tasks

In the serial prediction task (SPT) a sequence of fifteen stimuli had to be monitored for any violation (Fig. 1A). Stimuli consisted of twelve concentric circles that differed in size, each composed of an outer circle and a smaller circle placed in

Table 1
Subject demographics and neuropsychological test data.

Characteristic or test	PD patients ($n=20$)	Healthy controls ($n=20$)	p value[a]
Age, y	57.85 ± 1.52	58.10 ± 1.33	.555
Education, y	10.85 ± .48	11.35 ± .43	.212
PANDA	25.65 ± .70	26.70 ± .59	.312
LPS 4	25.53 ± 1.19	25.90 ± .79	1.000
BDI-II	1.70 ± 5.40	4.75 ± 1.05	.570
TAP divided attention "on"	.055 ± .013	.029 ± .010	.085
TAP divided attention "off"	.042 ± .012	.027 ± .007	.418
TAP go/ nogo "on"	.003 ± .003	.000 ± .000	.34
TAP go/ nogo "off"	.003 ± .003	.002 ± .002	1.00

Data are shown as mean ± standard error;
PD: Parkinson's Disease; PANDA: Parkinson Neuropsychometric Dementia Assessment; LPS 4: Leistungsprüfsystem; BDI-II: Beck Depression Inventory-II; TAP: Testbatterie zur Aufmerksamkeitsprüfung.

[a] p value of paired t-tests.

Table 2
Patient's clinical and neuropsychological data "on" and "off" dopaminergic medication.

Characteristic or test	PD patients ($n=20$) "on" medication	PD patients ($n=20$) "off" medication	p value[a]
UPDRS III	17.60 ± 1.97	26.55 ± 2.03	< .001*
levodopa equivalent daily dose	639.5 ± 85.71	–	–
TAP divided attention	.055 ± .013	.042 ± .012	.459
TAP go/ nogo	.003 ± .003	.003 ± .003	1.000

Data are shown as mean ± standard error;
PD: Parkinson's Disease; UPDRS III: Unified Parkinson's Disease Rating Scale; TAP: Testbatterie zur Aufmerksamkeitsprüfung.

[a] p value of paired t-tests;
* $p < 0.05$.

its centre. All stimuli were presented on a white rectangular frame as background figure, so that the impression arose that pictures on playing cards were shown. Occurrence of the twelve different stimuli was counterbalanced across trials. One trial comprised always a sequence of three different stimuli that were shown one after the other (1-2-3). This three-stimuli-sequence was repeated five times. Each stimulus was presented 600 ms with an inter-stimulus-interval of 125 ms. Every trial was preceded by a 1 s fixation cross and followed by a forced-choice-response phase: After presentation of stimuli subjects had a period of 3.5 s to indicate whether the sequence was regular until its end or not. Therefore, two response-buttons were provided: one for answering "YES" (=sequence was correct till its end) and the other for responding "NO" (=sequential switch occurred). In 50% of the trials the sequence was violated. Here, the position of two stimuli within the last repetition was switched: instead of the previously presented sequence 1-2-3 the order 1-3-2 or 2-1-3 was shown. After subject's responses a feedback indicating either the correct or the false response was presented for 1 s. One trial lasted 18.75 s in total. The inter-trial-interval was 4 s.

The parametric modulation that aimed at enhancing internal sequencing comprised so-called "occluders", i.e., non-informative stimuli which replaced one stimulus of the sequence (Fig. 1B). This means that in case of an occluder only the white rectangular frame similar to a blank playing card appeared.

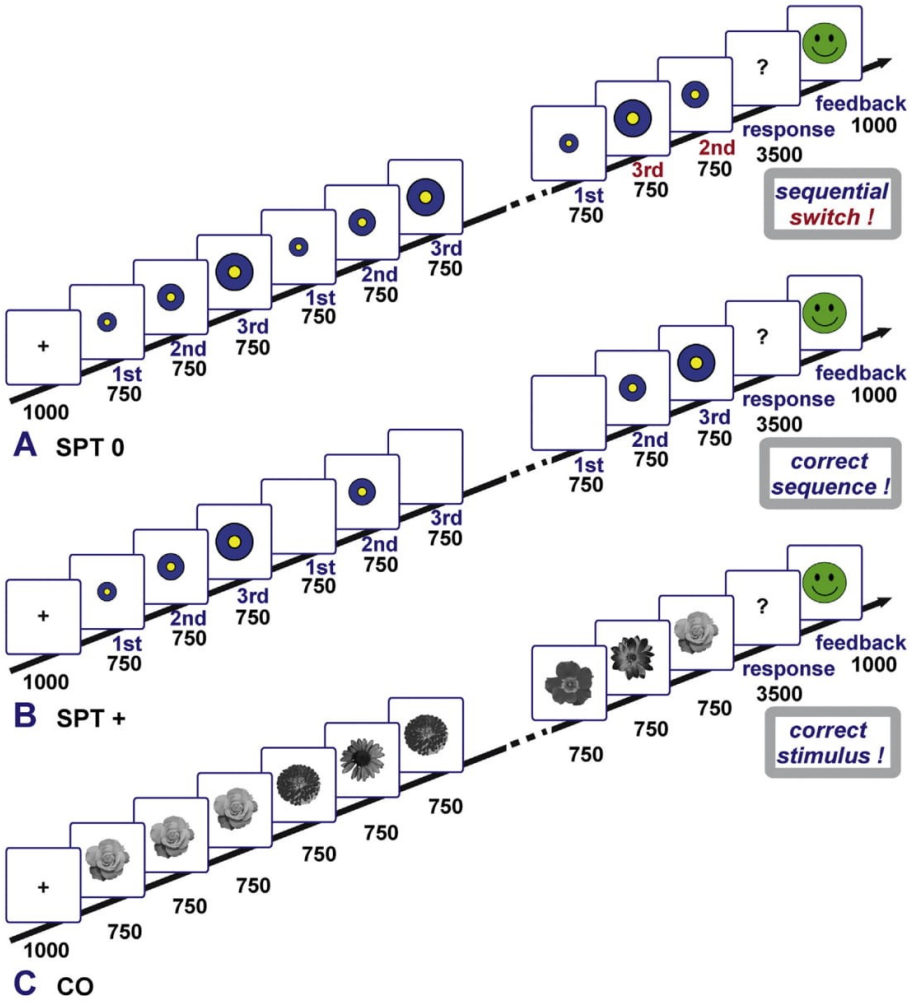

Fig. 1. Stimulus material and trial structure. Every trial was preceded by a fixation cross (1 s). Subsequently, 15 stimuli followed (note that catch trials (20%) consisted only of 12, 9, or 6 stimuli). After a forced-choice-response phase with maximum 3.5 s to deliver a response, a valid symbolic feedback was provided for 1 s. (A) SPT 0 (serial prediction task). Subjects were asked to monitor a sequence of three circles (1-2-3) that differ in size. At the end of each trial, subjects had to indicate whether the sequence ended as predicted or not (i.e., a sequential switch occurred). In 50% of all trials, the order of two of the last three stimuli in a trial was flipped (25%: 1-3-2; 25%: 2-1-3; 50%: 1-2-3). (B) SPT+(serial prediction task with occluders). Subjects had to perform in the same manner as in SPT 0, except that 1-4 stimuli of every trial were replaced by so-called occluders: instead of a circle, a blank card was shown. (C) CO (control task). Here, the first stimulus was presented three times in order to allow proper memorization. Afterwards, a random sequence of similar stimuli was presented. At the end of each trial, subjects had to indicate whether the last stimulus matched exactly the first one. Length of trials varied (15, 12, 9, or 6 stimuli) to ensure a continuous high level of attention.

In order to mark the blank card as a replacement of a standard stimulus and so to enable the subject to keep track of the sequence a flash-light signalling each stimulus (both occluder and standard stimulus) was provided. The first three stimuli were never replaced by an occluder because they were essential to define the sequence for each trial. For the following twelve stimuli 0%, 8.3%, 16.7%, 25% or 33.3% were masked by occluders. Never an occluder followed directly onto another one, and for the last three stimuli maximally one occluder occurred in order to preserve a moderate level of difficulty. Position of occluders was counterbalanced across trials. 40 trials with one to four occluders (10 trials for every occluder-condition) and 24 trials without any occluder were presented.

In addition to the SPT we applied a serial match to sample task to control for effects of no interest such as perception, attention and response (Fig. 1C). Here, also fifteen stimuli were shown consecutively with presentation parameters identical to those of the SPT. Stimuli were selected in a randomized order out of 200 different stimuli. Stimulus material consisted of 50 different monochrome photos of blossoms. Each photo was graphically modified, so that four versions with different grey values were generated, resulting in 200 different stimuli. Stimuli were also shown on the white rectangular background as in the SPT.

In this control task the first stimulus of every trial was presented three times. Subjects were instructed to memorize this stimulus. Subsequently, twelve other randomized stimuli were shown. At the end of the trial participants had to indicate whether the last stimulus was identical to the very first one. Occluders appeared also in that task in order to make the perceptual effects similar to those of the SPT, although occluders did not have any relevance for correctly answering the control task, because the last or first stimulus was never an occluder.

Twelve SPT-trials and four control task-trials that ended unexpectedly after six, nine or 12 stimuli were added in order to ensure a high level of attention. These trials had to be answered like the standard trials. All conditions were presented in a randomized order (mixed trial design). Trials were distributed across three blocks of 10.3 min with two breaks in between where subjects could take a rest for approximately 5 min. In total 99 trials were shown: 76 were SPT-trials and 23 control task trials. In each condition, 50% of the trials had to be answered with "YES" and 50% with "NO".

2.3. Study-design

Every participant attended our study on three consecutive days. The first day, every subject received training on the SPT with and without occluders and on the control task. Furthermore, each subject completed a neuropsychological test-battery including BDI-II (Hautzinger et al., 2006), PANDA (Kalbe et al., 2008) and LPS 4 (subtest 4 of the German intelligence test battery "Leistungsprüfungssystem") (Horn, 1983). BDI-II was used for assessment of depressive symptoms. LPS 4, a tool measuring reasoning, and PANDA, a screening for cognitive impairment in PD, were employed to estimate general cognitive performance. On day 1 all patients were on their regular dopaminergic medication, so that they were able to familiarize with the SPT and the control task "on" medication. The following day, 50% of patients were tested "on" medication and 50% were tested "off" medication. Healthy controls did not receive any medication. Participants first performed the two subtests "divided attention" and "go/no go" for selective attention of the TAP ("Testbatterie zur Aufmerksamkeitsprüfung") (Zimmermann & Fimm, 1992) to assess individual levels of attention that day. Subsequently, the 99 trials of the SPT and the control task were completed and the UPDRS-III was conducted for all patients. The third day was arranged in the same way as day two, except that the other 50% of patients were now tested "off" medication and vice versa.

2.4. Statistical analysis

Statistical analyses were conducted using the statistical software package SPSS (SPSS Statistic 17.0, IBM, Chicago, IL). Behavioural performance was assessed by probability of recognition (P_r=hit rate−false alarm rate) and corresponding bias index (B_r=false alarm rate/ $(1-P_r)$; Snodgrass & Corwin, 1988). The hit rate was defined as the sum of trials that were correctly answered with "YES" relative to the sum of all trials that had to be answered with "YES". The false alarm rate was defined as the sum of trials that were falsely answered with "YES" relative to the sum of trials that had to be answered with "NO". Reaction times were not included in our analysis in order to avoid any motor influence.

Paired t test for comparison of patients and controls were conducted for age, years of school education, PANDA, LPS 4 and BDI-II. Further t tests were calculated to assess differences in "on"- versus "off"-state regarding UPDRS III and performance in TAP.

We conducted an analysis of variance (ANOVA) in order to compare the performance of an increased internal and a comparatively more external sequencing and performance in the control task contrasting patients ("on" and "off" medication) with healthy controls. The analysis involved a $3 \times 2 \times 2$ design with the within-subject factors TASK (control task [CO] vs. SPT without occluders [SPT0] vs. SPT with occluders [SPT+]), GROUP (patients vs. controls) and MEDICATION ("on" vs. "off" dopaminergic medication). Healthy controls did not receive medication, but were also tested in two sessions in order to control for learning effects: session one and two were classified "on" or "off" for control subjects depending on what session was "on" or "off" medication for their matched patient.

To test whether a difference in SPT-performance was accompanied by a specific strategy, e.g., a conservative answering pattern with few positive reactions, a $2 \times 2 \times 2$ analysis of variance with factors TASK (SPT0 vs. SPT+), GROUP (patients vs. controls) and MEDICATION ("on" vs. "off") was conducted with B_r as dependent variable. B_r values greater than 0.5 indicate a liberal response bias, and values less than 0.5 indicate a conservative bias.

To estimate the effect of increasing occluders including every single occluder level we calculated a $5 \times 2 \times 2$ ANOVA with the within-subject factors TASK (SPT with zero vs. one vs. two vs. three vs. four occluders), GROUP (patients vs. controls) and MEDICATION ("on" vs. "off").

An additional analysis was carried out to assess the effect of increasing occluders in "on"- and "off"-state with respect to the individual cognitive abilities of the patients. Although patients were matched with healthy controls regarding age and level of education, this is not a very precise method to control for differences in general cognitive performance. Therefore we conducted a 2×2 ANCOVA for patients only using the extreme occluder values with the within-subject factors TASK (SPT0 vs. SPT with four occluders) and MEDICATION ("on" vs. "off") and included PANDA and LPS 4 as covariates to control for different cognitive abilities.

In all analyses, Greenhouse–Geisser epsilon was used where the assumption of sphericity was violated.

To further investigate the impact of severity of disease, correlation analyses for UPDRS III and performance in SPT0, SPT+, CO, PANDA and LPS 4 were carried out for "on"- and "off"-state, respectively. To examine if akinetic-rigid symptoms are more closely related to performance in SPT than tremor symptoms, UPDRS III-items were split into tremor-items and non-tremor-items according to Spiegel et al. (2007) and separately correlated with performance in SPT0 and SPT+. Note that PD patients belonged to the rigid-akinetic or equivalence type and no group comparison of tremor dominant and rigid-akinetic patients was possible. For tremor-items, the sum of UPDRS items 20 (tremor at rest) and 21 (action or postural tremor of hands) was calculated. For non-tremor-items, the sum of UPDRS items 18 (speech), 19 (facial expression), 22 (rigidity), 27 (arising from chair), 28 (posture), 29 (gait), 30 (postural stability) and 31 (body bradykinesia and hypokinesia) was calculated.

Furthermore, correlations between age and performance in SPT0, SPT+ and CO "on" and "off" medication were calculated. All correlation analyses were computed using standard Pearson's correlation coefficient and significance.

3. Results

3.1. Neuropsychological test performance and demographic data

Neuropsychological and demographic data of both patients and healthy controls are shown in Table 1. Paired t tests comparing patients and their corresponding healthy match exhibited no differences for age, education, BDI-II-scores and performance in PANDA, LPS 4, and both subtests of TAP. Table 2 provides clinical and neuropsychological data of patients "on" and "off" dopaminergic medication. Paired t tests revealed a significant difference between UPDRS III "on" medication and UPDRS III "off" medication ($p < .001$). No "on"/"off"-differences were observed for performance in both subtests of TAP (divided attention and go/nogo).

3.2. Performance and response bias in CO, SPT0 and SPT+ of patients "on" and "off" medication compared to healthy controls

The $3 \times 2 \times 2$ ANOVA examining the performance in CO, SPT0 and SPT+ for patients "on" and "off" medication and healthy controls yielded a main effect of GROUP ($F(1,19)=8.57$, $p = .009$). Healthy controls ($.74 \pm .03$; mean ± standard error) exhibited a better performance than patients ($.57 \pm .05$) independently of TASK and MEDICATION. There was also a significant main effect for TASK ($F(2,38)=49.01$, $p < .001$). Post hoc test with Bonferroni adjusted α-level indicated that performance in CO ($.84 \pm .02$) was significantly increased compared to performance in SPT0 ($.65 \pm .04$) ($p < .001$) and SPT+ ($.46 \pm .043$) ($p < .001$) and performance in SPT0 was significantly increased compared to SPT+ ($p < .001$). Furthermore, the interaction GROUP × MEDICATION × TASK was significant ($F(2,38)=3.28$, $p=.048$) (Fig. 2). Post hoc tests with Bonferroni adjusted α-level addressing the effect of medication

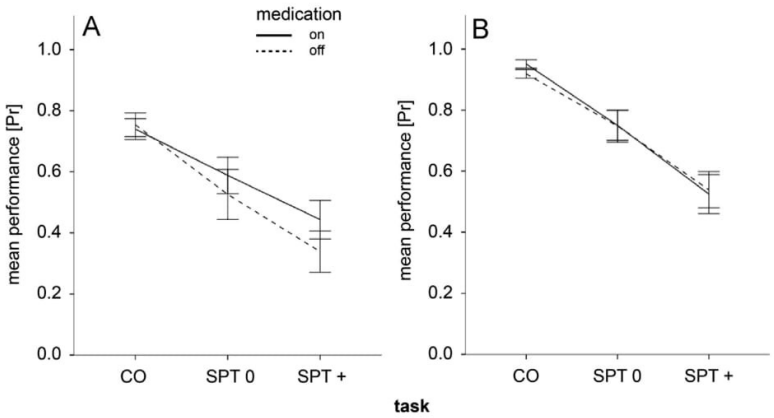

Fig. 2. Performance of patients "on" and "off" dopaminergic medication and healthy controls in the SPT with and without occluders and in the control task: ANOVA with the within-subject factors: TASK (CO vs. SPT 0 vs. SPT +) × GROUP (patients vs. healthy controls) × MEDICATION (on vs. off). Healthy controls did not receive any medication, but were classified "on" or "off" according to their matched patient. Performance was assessed by P_r (probability of recognition). CO = control task; SPT 0 = serial prediction task without occluders; SPT+ = serial prediction task with occluders. Data are shown as mean ± standard error.

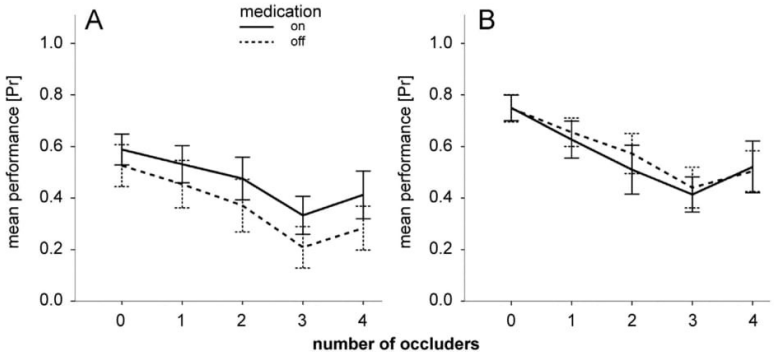

Fig. 3. Performance of patients "on" and "off" dopaminergic medication and of healthy controls for increasing levels of occluders in SPT. Note that healthy controls did not receive medication, but were classified "on" or "off" according to their matched patient. Performance was assessed by P_r (probability of recognition). Data are shown as mean ± standard error.

in patients corroborate our hypothesis: in the patient-group there was a significant decrease in performance "off" compared to "on" medication only for SPT+ ($p = .041$), whereas no significant "on"/"off"-differences for SPT0 and CO were found. Healthy controls did not exhibit a significantly different "on"/"off"-performance in any task. Note that controls did not receive any medication, but their performance on day 1 and day 2 was classified as "on" or "off" depending on whether their matched patient was "on" or "off" dopaminergic medication that day.

Because the performance of controls did not differ "on" and "off", their mean performance in SPT was calculated for comparison with patients' performance in SPT. Patients "on" medication ($.47 \pm .06$) show a trend towards poorer performance in serial prediction compared to healthy controls ($.64 \pm .05$) ($p = .054$) and patients "off" medication ($.43 \pm .07$) performed significantly worse than controls ($p = .032$). Examining both SPT-variants separately, patients "on" medication exhibited significantly poorer performance than controls in SPT0 ($p = .05$), but not in SPT+ ($p = .315$).

Regarding differences in performance in SPT+ and SPT0, *t* tests showed that patients "on" medication ($p = .012$), patients "off" medication ($p = .006$) and healthy controls ($p < .001$) showed better performance in SPT0 than in SPT+.

The $2 \times 2 \times 2$ ANOVA examining differences in response bias in SPT yielded no significant effects, i.e., healthy controls and patients did not show different response biases, "on" as well as "off" medication, both in SPT0 and in SPT+. Mean response bias was $.5 \pm .02$, indicating a neutral response pattern in SPT.

3.3. Performance "on" and "off" medication in SPT with increasing number of occluders

The $5 \times 2 \times 2$ ANOVA including all occluder levels and comparing performance "on" and "off" for patients and control subjects yielded a significant main effect for TASK ($F(4,76) = 17.97$, $p < .001$). Post hoc tests with Bonferroni adjusted α-level exhibited that performance in SPT0 differed significantly from performance in SPT with one occluder ($p = .041$), two occluders ($p = .015$), three occluders ($p < .001$) and four occluders ($p = .001$). Furthermore, performance in SPT with one occluder differed significantly from performance in SPT with three occluders ($p < .001$) and four occluders ($p = .030$). Controls ($.57 \pm .06$) performed better than patients ($.42 \pm .06$), though this trend was not significant ($F(1,19) = 3.57$, $p = .074$). In addition, a significant interaction GROUP × MEDICATION ($F(1,19) = 6.13$, $p = .023$) was observed. Post hoc tests revealed that performance in both groups differed significantly "off" medication ($p = .029$), but not "on" medication ($p = .248$) (Fig. 3).

The 2×2 ANCOVA comparing extreme occluder values (zero vs. four occluders) for patients "on" and "off" medication exhibited a

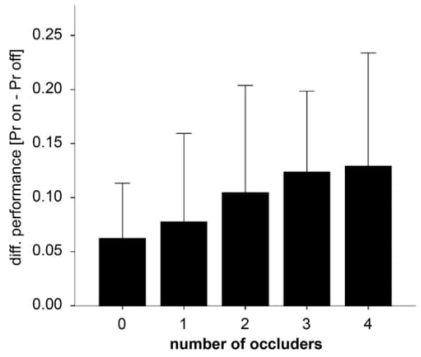

Fig. 4. Difference scores for patients' performance "on" and "off" dopaminergic medication (P_r "on"–P_r "off"). Performance was assessed by P_r (probability of recognition). SPT 0 up to SPT 4 refers to serial prediction task with 0–4 occluders. Data are shown as mean ± standard error.

main effect for TASK ($F(1,14)=5.59$, $p=.033$): Patients performed better in SPT0 ($.63 \pm .07$) than in SPT with four occluders ($.37 \pm .07$). The interaction MEDICATION × TASK shows a trend towards significance ($F(1,14)=4.16$, $p=.061$).

Descriptive patient data in Fig. 4 show the mean "on"/"off"-difference (P_r "on" medication−P_r "off" medication) of performance for all SPT trials with zero to four occluders.

3.4. Correlations of cognitive performance with UPDRS III and age

The correlation between UPDRS III "on" medication and performance in SPT0 "on" medication was significant ($r=-.514$, $p=.02$) for patients, but did not reach significance "off" medication. Also performance in SPT+ "on" correlated significantly with UPDRS III "on" ($r=-.628$, $p=.003$), while performance in SPT+ "off" and UPDRS III "off" did not correlate. There were neither correlations "on" nor "off" for UPDRS III and patients' performance in the control task, PANDA or LPS 4.

Separating UPDRS III into tremor-items and non-tremor-items the non-tremor-items "on" medication correlated significantly with performance in SPT0 ($r=-.466$, $p=.038$) and SPT+ ($r=-.601$, $p=.005$) "on" medication. In "off"-state no correlations for performance in SPT0 or SPT+ and non-tremor-items were found. The tremor-items did not correlate with performance in SPT0 or SPT+ neither "on" nor "off" medication.

Investigating the influence of age on performance in CO, SPT0 and SPT+ in patients "on" and "off" medication only a correlation of age and performance in SPT0 "off"-state was found ($r=-.487$, $p=.03$). There were also no correlations for age and performance in all tasks for healthy controls.

4. Discussion

This study was conducted to determine whether principles underlying motor dysfunction in Parkinson's disease (PD) extend to the cognitive domain. Conceptually, we focused on the phenomenon of paradoxical kinesis: Here, PD patients can improve their motor abilities with the help of external cues. This improvement is associated with the increased activation of the lateral premotor cortex, presumably reflecting a compensation of SMA-hypoactivation.

PD patients "on" and "off" medication and healthy controls were tested in a serial prediction task that does not entail motor demands and that activates both the medial and lateral premotor cortex (Schubotz & von Cramon, 2003). A parametric modulation (SPT+) that increases the memory-based load by the use of stimulus occluders was implemented to the classic SPT (SPT0). In SPT+, several stimuli of the sequence were masked by an occluder and hence had to be recalled internally to decide if the sequence was orderly repetitive or contained a sequential deviant.

We expected patients to be impaired in both SPT-variants. This hypothesis was only partly corroborated. Patients "off" medication were found to be significantly impaired in serial prediction (including all levels of occluders) compared to controls, whereas patients "on" medication performed worse than controls only in SPT0.

We further expected the impairment in SPT+ to be particularly prominent "off" dopaminergic medication. Actually the significant interaction GROUP × MEDICATION × TASK and subsequent post hoc tests revealed a significant impairment in SPT+ for patients "off"-state compared to "on"-state but no significant "on"/"off"- differences in patients' performance for SPT0 or the control task. Even though, there was a descriptive but statistically insignificant trend for "off"-patients to be also impaired in SPT0 compared to "on"-patients (see Figs. 2–4). The impairment in "off"-performance, however, descriptively enlarged when memory-based processing became more relevant with increasing number of occluders (Figs. 2–4).

Our data indicate that PD patients' cognitive deficits due to less dopaminergic supply in putamen-SMA-loop parallel their motor deficits: Impairment increases when both rely on internally initiated processing. Though patients "on" medication were not generally impaired in SPT compared to healthy subjects, but only in SPT0, our expectations were further corroborated when we compared task performance with the motor score of the UPDRS (UPDRS III). Note that UPDRS III refers to a set of motor tasks that are internally, not externally driven. Here, a significant correlation between UPDRS III and SPT0 performance was found in "on"-state, and an even stronger correlation between UPDRS III and SPT+. These results indicate that the impairment in serial prediction, particularly in internally guided serial prediction, depends upon the individual severity of PD, even though patients "on" medication did not show general deficits in SPT+ compared to controls. On the basis of an informal post-experimental survey, we suggest that patients "on" medication did not perform worse than controls in SPT+ because patients were exceptionally motivated, possibly to be able to match with healthy participants, particularly with increasing task difficulty. We therefore consider the observed medication effect within the patient group to be more meaningful and reliable than the absence of expected impairment of patients "on" medication compared to healthy controls in SPT+.

Importantly, performance in other cognitive tasks such as the control task, PANDA or LPS 4 did not correlate with the UPDRS III "on" or "off" medication, showing that our findings are not due to a general correlation of motor and cognitive abilities in our cohort of patients. Rather, our results point to a specific impairment of the premotor system (due to loss of striatal input) that affects both cognition and motor performance in a characteristic manner. This finding corroborates the assumption that the premotor system sub-serves the prediction of both re-afferent as well as afferent states (Schubotz, 2007).

When the UPDRS III was further split into tremor- and non-tremor-items, only the non-tremor-items or akinetic-rigid items correlated significantly with SPT performance. Tremor-dominant PD patients without other Parkinsonian symptoms such as balance- or gait-disturbances exhibit cognitive decline to a much lesser extent (Alves, Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006; Burn et al., 2006). This suggests that tremor and cognitive impairment in PD result from different pathomechanisms. Consistent with this assumption, tremor-dominant patients show dopaminergic depletion predominantly in the lateral putamen

and the caudate nucleus, whereas in akinetic-rigid PD patients the dorsal putamen is predominantly affected (Eggers, Kahraman, Fink, Schmidt, & Timmermann, 2011). Since the dorsal putamen projects to the SMA, whereas the lateral putamen predominantly connects to the primary motor areas (Leh, Ptito, Chakravarty, & Strafella, 2007), it makes sense that akinetic-rigid symptoms correlate with performance in SPT, i.e., a task that is known to activate the SMA but not primary motor areas. Still the interpretation of correlations of tremor- and non-tremor-items with performance has to remain tentative, as no tremor-dominant PD-patients were included in the sample.

When we consider the fact that PD patients' "off"-performance was more impaired, if occluders were present in a trial, we should discuss the exact effect of these occluders in a sequence and how we believe them to increase task load. SPT in its classical version has both an internal (memory-based) and an external (stimulus-based) component: The sequence which is specified at the beginning of a trial has to be maintained in memory and participants have to match this memorized sequence to externally presented stimuli to detect possible mismatches (i.e., externally and internally guided processing takes place concurrently). Note that not three discrete stimuli have to be encoded, but only the relative changes (here: circle diameter increments or decrements) from one stimulus to the other. When occluders mask a regular stimulus in SPT+, the external validation of the current internal model is withdrawn. Participants have to fill in mentally the missing item by reference to the previous and the subsequent stimulus. In that case PD patients "off" compared to "on" medication revealed remarkable problems. For them the strategy to rely on an internally represented sequence was no longer successful.

Deficits in internal processing in contrast to the preserved performance when external guidance was provided were also detected in previous studies examining cognitive deficits in PD. As mentioned above, Brown and Marsden (1990) found that PD patients did not exhibit a general impairment in various cognitive tasks, but were only impaired when internal control was required, e. g., in spontaneous generation of task-specific planning. In contrast, their performance did not differ from controls when external guidance was present such as choosing the correct results from a number of alternatives provided.

Impairment in internal control is especially present when PD patients have to initiate a new action step or mental operation. On the motor level, PD patients with freezing of gait exhibit deficits when they have to initiate a movement by showing an inability to step or extremely short steps (Nutt et al., 2011). Also on the cognitive level patients have difficulties when they need to apply a newly generated strategy to solve a problem: PD patients were able to solve a tower of London task (Shallice, 1982) with the same number of moves as their healthy controls, but exhibited significantly longer deliberation before making the initial move (even after controlling for putatively confounding influences of motor initiation and executive times) (Morris et al., 1988).

For related reasons, PD patients are impaired in task-switching-paradigms where it is necessary to switch between two competing internal strategies and to apply one of them; this impairment is abolished when external cues indicate which strategy has to be chosen (Brown & Marsden, 1988). PD patients were not impaired in understanding the different strategies, e.g., answering an odd-man-out task, but exhibited deficits in alternating between the two competing rules on successive trials (Flowers & Robertson, 1985). In line with these findings, Werheid, Koch, Reichert, and Brass (2007) reported that PD patients in contrast to healthy controls relied to a significantly greater extent on external cues than on a learned task-sequence (schematic sequence: AAB-BAABB), even when the utility of the visual cue was low due to a short pre-cueing interval (100 ms).

When thinking about external and internal processing, we must not forget that switching from internal to external guidance is a behaviour that we all apply in everyday life in various situations: One example for a highly automatic or internally guided behaviour is driving a car. Especially when doing it in a familiar environment, we are able to focus our attention on something else like a conversation. But when we drive in a foreign city, we have to focus our attention on the foreign environment. Transferring this example to the behaviour of PD patients, we can say that they are generally more dependent on input from the external world. So patients would always drive as if in an unfamiliar environment and it would be very difficult for them to do something else simultaneously. Several studies investigating freezing of gait (FOG) point in this direction: Gait in PD is certainly one of the best-investigated internally controlled behaviours and FOG is a disturbance of this behaviour. Many patients with FOG have to "stop walking while talking" (SWWT) (Giladi & Hausdorff, 2006; Lundin-Olsson, Nyberg, & Gustafson, 1997). There is also broad evidence that gait is impaired when PD patients have to perform another motor task simultaneously (dual-tasking) or in cognitively challenging situations (Bond & Morris, 2000; Giladi & Hausdorff, 2006; Knobl, Kielstra, & Almeida, 2012; Rochester et al., 2005). Spildooren et al. (2010) reported that patients with FOG exhibited an impairment of gait parameters when performing a cognitive task while walking and made concurrently more errors in that cognitive task than healthy controls. Interestingly, the use of external cues or attentional strategies (e.g., a request to focus on big steps) reduces the interference effect of a dual task (Baker, Rochester, & Nieuwboer, 2007; Rochester et al., 2005). Rochester et al. (2005) suggested that this interference effect in PD patients is due to an increased competition for attention because of the inability to use automatic movement control. Cues which help initiating movements as well as maintaining initiation may potentially free up attentional resources. In other words, PD patients exhibit problems in performing two tasks simultaneously because neither of them can be performed completely, automatically or internally guided. When, however, control for one of the tasks is supported by an external source, the patients can focus their attention on the other task and both tasks can be performed adequately.

Taken together, our study revealed that a cognitive paradigm which is proven to activate the premotor system (Schubotz & von Cramon, 2004) shows a dependency on dopaminergic medication in PD patients and that task performance correlates with motor function. This stands in stark contrast to the classical view that only the non-motor loops of the five basal ganglia-thalamocortical circuits proposed by Alexander et al. (1986) contribute to cognition. Especially the role of the dorsolateral prefrontal loop (including dorsolateral prefrontal cortex and dorsolateral caudate) and that of the orbitofrontal or ventral prefrontal loop (including lateral orbitofrontal cortex and ventromedial caudate) were previously highlighted in cognitive or more precisely executive dysfunction in PD (Cools, Barker, Sahakian, & Robbins, 2001; Owen, 2004). Dopaminergic denervation of the caudate nucleus, which is involved in both loops, was proven to correlate with the degree of dementia (Rinne et al., 2000) and with cognitive decline in PD, e.g., executive dysfunction and impaired sequence learning (Bruck et al.,2001; Carbon et al., 2004; Marie et al., 1999). Additionally, cortical components of both loops, the dorsolateral and ventrolateral prefrontal cortex, were shown to serve executive functions (Owen, Evans, & Petrides, 1996). Due to the degenerative pattern of the caudate nucleus in PD, the dorsolateral prefrontal loop is affected primarily in progression of the disease (Yeterian & Pandya, 1991), and so are higher level executive functions (Owen et al., 1992). Therefore, a contribution of these two loops to cognitive dysfunction in PD seems very likely.

Our findings, however, indicate that also the so-called "motor loop" of the basal ganglia-thalamo-cortical circuits, including SMA and putamen, contributes to certain cognitive impairments in PD. Further support for this view comes from a study that found dopamine transporter (DAT) density not only of the caudate but also of the putamen to correlate significantly with performance in a prefrontal test-battery in PD patients (Muller, Wachter, Barthel, Reuter, & von Cramon, 2000). Decline in patients' "off"-performance in the present study may correspond to the SMA-hypoactivation described for motor tasks in PD patients "off" dopaminergic medication (Haslinger et al., 2001). In SPT0, the relatively preserved "off"-performance might be attributed to the continuous stimulus-based guidance, analogous to a continuous pacing signal in motor tasks. Our assumption that internal guidance is based on SMA/putamen (and external guidance on the lateral premotor loop), however, has yet to be proved in further studies including neuroimaging, because our study was not made to test a functional-neuroanatomical hypothesis. Moreover, apart from positive evidence for a functional-neuroanatomical dichotomy between the mesial and the lateral motor loop (Debaere et al., 2003; Heuninckx et al., 2010), there are also mixed findings (Ballanger et al., 2006; Cunnington et al., 2002; Weeks et al., 2001), suggesting that the neuroanatomical basis of internally and externally guided control may reflect a certain trend rather than a strict regional dichotomy (Schubotz, 2004, p. 52f; see also Jahanshahi et al., 1995).

Note that beyond dopamine denervation of the striatum, other pathologies in the brain affected by Parkinson's disease are discussed to contribute to impaired cognition in PD. Thus, the impact of disturbances of other neurotransmitter-systems (i.e., the noradrenergic, serotonergic, and cholinergic system), the direct cortical involvement as evidenced by the presence of Lewy bodies, and the degeneration of the mesocortical dopaminergic system also have to be considered (Dubois & Pillon, 1997; Kulisevsky, 2000). Future studies have to address the relevance of these different factors including the role and interaction of different basal ganglia-thalamocortical circuits influencing behaviour in both motor and cognitive function.

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Motor loop dysfunction causes impaired cognitive sequencing in patients suffering from Parkinson's disease

Anna R. Schönberger [a,b], Klara Hagelweide [a,d], Esther A. Pelzer [a,b], Gereon R. Fink [a,c], Ricarda I. Schubotz [a,d,*]

[a] Department of Neurology, University Hospital Cologne, Kerpener Str. 62 D-50937 Cologne, Germany
[b] Max Planck Institute for Neurological Research, Gleueler Str. 50 D-50931 Cologne, Germany
[c] Institute of Neuroscience and Medicine (INM3), Cognitive Neuroscience, Research Centre Jülich, Leo-Brandt-Straße D-52425 Jülich, Germany
[d] Department of Psychology, University of Muenster, Fliednerstr. 21 D-48149 Münster, Germany

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ABSTRACT

Cognitive impairment in Parkinson's disease (PD) is often attributed to dopamine deficiency in the prefrontal-basal ganglia–thalamo-cortical loops. Although recent studies point to a close interplay between motor and cognitive abilities in PD, the so-called "motor loop" connecting supplementary motor area (SMA) and putamen has been considered solely with regard to the patients' motor impairment. Our study challenges this view by testing patients with the serial prediction task (SPT), a cognitive task that requires participants to predict stimulus sequences and particularly engages premotor sites of the motor loop. We hypothesised that affection of the motor loop causes impaired SPT performance, especially when the internal sequence representation is challenged by suspension of external stimuli. As shown for motor tasks, we further expected this impairment to be compensated by hyperactivity of the lateral premotor cortex (PM).

We tested 16 male PD patients ON and OFF dopaminergic medication and 16 male age-matched healthy controls in an functional Magnetic Resonance Imaging study. All subjects performed two versions of the SPT: one with on-going sequences (SPT0), and one with sequences containing non-informative wildcards (SPT+) increasing the demands on mnemonic sequence representation. Patients ON (compared to controls) revealed an impaired performance coming along with hypoactivity of SMA and putamen. Patients OFF compared to ON medication, while showing poorer performance, exhibited a significantly increased PM activity for SPT+ vs. SPT0. Furthermore, patients' performance positively covaried with PM activity, corroborating a compensatory account. Our data reveal a contribution of the motor loop to cognitive impairment in PD, and suggest a close interplay of SMA and PM beyond motor control.

1. Introduction

Parkinson's disease (PD) results from the degeneration of dopaminergic neurons in the substantia nigra. While motor symptoms are very prominent (Rodriguez-Oroz et al., 2009), patients also suffer from cognitive deficits even at very early stages of the disease (Muslimović et al., 2005). These cognitive impairments are commonly assumed to result from frontal lobe dysfunction consecutive to dopamine depletion (Saint-Cyr et al., 1988; Taylor et al., 1990; Dubois and Pillon, 1997) of cortico-basal ganglia–thalamo-cortical circuits (Alexander et al., 1986; Sawamoto et al., 2008). In particular, circuits connecting the caudate nucleus and the prefrontal lobe are supposed to contribute to cognitive deficits (Rinne et al., 2000; Brück et al., 2001; Cools et al., 2001; Owen, 2004; Zgaljardic et al., 2006; Grahn et al., 2008; Polito et al., 2012).

In contrast to the caudate–prefrontal loops, the "motor loop" (Alexander et al., 1986) that connects the putamen to the lateral premotor cortex (PM) and the supplementary motor area (SMA) is scarcely considered to underlie cognitive dysfunction in PD. However, evidence has accumulated that some cognitive functions draw specifically on premotor loops: For example, imagining, planning or observation of actions have been shown to activate the same motor network as used when performing an action (Decety et al., 1994; Stephan et al., 1995; Jeannerod, 2001). Moreover, the premotor system contributes to predictions of upcoming events even if they are not related to actions which we are able to perform ourselves. Therefore, the premotor system contributes to

* Corresponding author at: Department of Psychology, University of Münster, Fliednerstr. 21, 48149 Münster, Germany.
E-mail address: rschubotz@uni-muenster.de (R.I. Schubotz).

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processes beyond classical motor functions (Schubotz, 2007).

A motor–cognitive relation has also been established in PD, as recent studies report an intra-individual correlation between severity of freezing of gait and lower scores of frontal tests (Amboni et al., 2008; Vandenbossche et al., 2011; Vercruysse et al., 2012). Furthermore, we found the severity of motor impairment to significantly correlate with patients' deficits in the serial prediction task (SPT), a cognitive sequencing task (Schönberger et al., 2013). The SPT requires subjects to monitor a structured stimulus sequence for structure-violating items in a non-speeded response regime (Schubotz, 1999). It reliably engages PM and SMA in healthy participants (Schubotz and Von Cramon, 2003; Schubotz, 2007), although it does not imply any motor abilities. Hence, the question arises whether the observed deficits of patients suffering from PD when performing the SPT result from premotor or prefrontal dysfunction.

In PD, the most significant premotor dysfunction is a SMA hypoactivity when patients perform motor tasks (Playford et al., 1992; Haslinger et al., 2001). SMA hypoactivity is often accompanied by PM hyperactivity (Samuel et al., 1997; Haslinger et al., 2001) which implies a compensatory mechanism (Haslinger et al., 2001). Moreover, external cues such as auditory rhythms may be used to ameliorate motor impairment (Martin, 1967; McIntosh et al., 1997; Azulay et al., 1999). Hanakawa et al. (1999) showed that improved motor function under external guidance co-occurs with increased PM activity compared to conditions where external help is lacking. These findings can be explained in terms of a functional dichotomy within the premotor cortex as proposed by Goldberg (1985): According to his review, the SMA accounts for internal motor control rather than for an external or stimulus-driven one, whereas the opposite holds for the PM. This assumption was largely (but not always, cf. Weeks et al., 2001; Cunnington et al., 2002) confirmed by imaging studies comparing externally versus internally guided movements (Debaere et al., 2003; Heuninckx et al., 2010), although these may constitute a relative functional bias rather than a strict double-dissociated functional dichotomy (Jahanshahi et al., 1995). Taken together, findings suggest that patients' difficulties in internally initiating movements reflect the hypoactive SMA, whereas the hyperactive PM ameliorates this deficit by exploiting external cues.

Using functional Magnetic Resonance Imaging (fMRI) we investigated whether this interplay of impairment in internal motor control and compensatory external control extends to cognitive functions supported by the premotor network and thus adds to cognitive impairment in PD. To this end, patients suffering from PD were tested ON and OFF dopaminergic medication in the SPT. Two versions of the SPT were implemented which differed by their demand on keeping an internal representation of a stimulus sequence: In "SPT0", sequences of stimuli were continuing while in "SPT+" parts of the sequence were replaced by void stimuli, thereby increasing the demand for keeping track of the sequence based on an internal sequence representation (Schönberger et al., 2013). Previously, we found patients suffering from Parkinson's disease to be particularly impaired in SPT+ after withdrawal of their medication (Schönberger et al., 2013) suggesting a relation of internal sequence representation to SMA and striatal hypoactivity. Using fMRI allows to extend these results and to examine if compensational brain hyperactivity of the PM is found where no behavioural deficit is yet evolving. Note that PM hyperactivity during SMA hypoactivity can only be interpreted as effective functional compensation as long as there are no behavioural differences between PD and healthy controls (Samuel et al., 1997; Sabatini et al., 2000; Haslinger et al., 2001; Mallol et al., 2007).

Drawing on our previous findings we expected patients' performance to be impaired when compared to healthy controls. Furthermore, we expected the patients' performance to be worse during OFF medication compared to ON medication, most notably in SPT+ where internal sequence representation is necessary. We assumed this impairment to be accompanied by SMA and putamen hypoactivity. This pathological activity pattern should be more pronounced for SPT+ than for SPT0, and should be attenuated ON as compared to OFF medication. Moreover, in case that patients' performance is preserved, we expected SMA hypoactivity to be accompanied by PM hyperactivity. In case we should observe preserved SMA activity as well as compensating PM activity, they should be related to better performance. Finally, we expected the degree of hypoactivity of SMA and putamen to depend on the severity of motor impairment.

2. Materials and methods

2.1. Participants

Sixteen male patients suffering from PD and sixteen healthy male controls participated in the study. Patients had a mean age of 60.1 years (range: 44–72 years; see Table 1 for further demographical, clinical and neuropsychological data). Diagnosis of idiopathic PD was made according to the UK Parkinson's disease Society Brain Bank Criteria (Hughes et al., 1992). No subject had undergone a surgical treatment for the disease or had a history of any psychiatric or any other neurological disease. The severity of clinical symptoms defined according to Hoehn and Yahr (1967) ranged between I and III under regular medication. The motor score of the UPDRS (unified Parkinson's disease rating scale; Fahn and Elton, 1987) was assessed in each of the two experimental sessions independently by two movement disorder specialists blinded to the state of medication.

All patients received dopaminergic medication. Patients were tested once ON their regular medication and once OFF medication. OFF-state was defined as at least 14 h of withdrawal of dopaminergic medication; long-acting dopamine agonists were discontinued up to 36 h. Four additional patients were excluded from the analysis: One due to a depression score above the cut-off-value in the Beck depression inventory-II (BDI-II; cut-off for depression: $\geq$20 points; Hautzinger et al., 2006) and the other three due to behavioural performance at chance level for SPT0 and SPT+ both ON and OFF.

Sixteen healthy male participants comparable to the patients regarding age and level of school education served as control subjects. All 32 analysed participants scored between 18 and 30 points in the Parkinson neuropsychometric dementia assessment (PANDA; Kalbe et al., 2008), i.e., showed an age-adequate cognitive performance, and scored below the cut-off for depression (see above).

All participants gave their written informed consent prior to participation. The study was performed according to the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty, University of Cologne, Germany.

PANDA=Parkinson neuropsychometric dementia assessment; BDI-II=Beck depression inventory-II; LEDD=Levodopa-equivalent daily dose calculated according to Tomlinson et al. (2010); UPDRS ON=UPDRS III scores ON dopaminergic medication; UPDRS OFF-=UPDRS III scores OFF dopaminergic medication.

2.2. Stimuli and tasks

We employed three tasks: The serial prediction task in two versions (SPT0 and SPT+) and a serial match-to-sample task (SMTS) which served as a control task (Fig. 1). The SMTS requires holding a particular target stimulus in working memory while watching a series of non-target stimuli. It does not enable a

Table 1
Subject demographics and neuropsychological test data.

Characteristic	Mean ± standard error		p^a
	Patients ($n=16$)	Controls ($n=16$)	
Age, years	60.13 ± 2.12	59.56 ± 1.42	0.567
Education, years	11.12 ± 2.06	11.81 ± 1.90	0.385
PANDA	25.81 ± 0.98	26.25 ± .75	0.595
BDI-II	6.69 ± 1.46	3.94 ± 1.04	0.109
Time since diagnosis, years	5.81 ± 3.52	–	–
LEDD	600.91 ± 125.57	–	–
UPDRS ON	15.3 ± 1.48	–	–
UPDRS OFF	23.6 ± 2.69	–	–

[a] Significance of differences between groups, computed with paired *t*-tests.

prediction of the order of stimuli as in the serial prediction task and thus controls for working memory processes apart from serial prediction.

In both versions of the serial prediction task, participants had to decide whether a sequence of 15 stimuli ended orderly or with a sequential violation. Stimuli consisted of concentric circles that differed in size (12 sizes, diameters ranging from 0.5° to 3.5° of visual angle). Three different consecutively presented stimuli formed a triplet (1-2-3) which was shown five times per trial. In 50% of the trials, the position of two stimuli in the last triplet was switched: instead of the original triplet (1-2-3) a new triplet (1-3-2 or 2-1-3) was presented. The first four presentations always showed the original triplet to allow learning of the sequence. Only the last triplet could be switched. In a forced-choice-response phase of 3.5 s participants had to indicate whether the sequence contained a switch or not. Overall, one trial lasted 18.75 s including response and feedback. The inter-trial-interval varied from 4.0 to 5.5 s depending on jitter times (0, 500, 1000, or 1500 ms).

The SPT+ condition was identical to SPT0 except for a parametric modulation of the necessity of internal sequential recall: In SPT+ trials one, two, three or four stimuli were replaced by so-called "occluders", i.e., non-informative stimuli that replaced standard circle-stimuli of the sequence. Similar to SPT0 a switch could only appear in the last triplet which the participants had to indicate in the response phase.

To ensure an overall high level of attention, catch trials were presented in all tasks: 12 SPT-trials and four SMTS-trials were added that ended after six, nine or twelve stimuli. These trials were answered like standard trials but did not enter either the fMRI or the behavioural analysis. For further details regarding the paradigms, see our previous behavioural study (Schönberger et al., 2013).

Further, 11 empty trials (null-events) were implemented. Each of them lasted 18.75 s like standard trials. All conditions (i.e., SMTS, SPT0, SPT+, and null-events) were presented in a randomized order (mixed trial design). Between trials there were no cues to signalise which trial started next. The experiment lasted in total 34.8 min with a total of 99 trials (19 SMTS trials, 24 SPT0 trials, 40 SPT+ trials, 10 for each number of occluders per trial, and 16 catch trials) and 11 null-events.

SPT0 (serial prediction task): Subjects were asked to monitor a sequence of three circles (1st-2nd-3 rd). In this example the order of circle-sizes is ascending, but it could as well be descending or intermingled. Each trial was preceded by a fixation cross (1 s). Every stimulus was presented for 600 ms with an inter stimulus interval of 125 ms. Subjects had to indicate whether the sequence ended as predicted (50%: 1st–2nd–3rd) or not (25%: 1st–3rd–2nd; 25%: 2nd–1st–3rd) in a forced-choice-response phase with maximum 3.5 s to deliver a response. Two response buttons were provided: one for answering "correct sequence" and one for responding "a sequential switch occurred". Answers were delivered with the right index and middle fingers, with finger response association balanced across subjects. A valid feedback indicated a correct, false or missing answer.

SPT+ (serial prediction task with occluders): Subjects had to perform in the same manner as in SPT0, except that 1-4 stimuli of every trial were replaced by so-called occluders: instead of a circle a blank card was shown. The first three stimuli of a trial were never replaced by an occluder, and never two consecutive stimuli

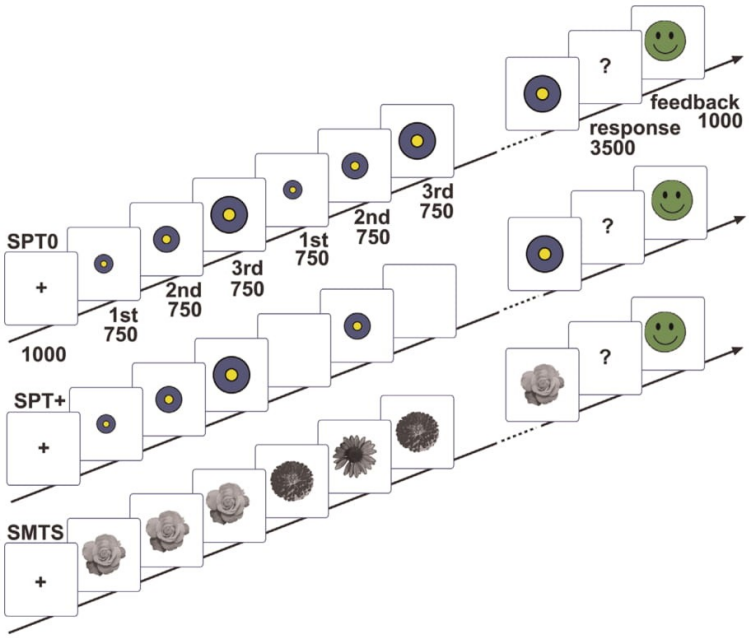

Fig. 1. Stimulus material and trial structure.

were replaced. The last triplet contained maximal one occluder.

SMTS (serial match-to-sample task as control task): Subjects were instructed to memorise the first stimulus, one out of 50 monochrome blossoms, which was presented three times. Subsequently, twelve (or less in case of a catch trial) other randomized blossoms, sometimes replaced by an occluder, were shown with presentation parameters identical to those of the SPT. Subjects had to indicate whether the last blossom was identical to the very first one. Occluders were used to make the perceptual effects similar to those of the SPT, but did not have any relevance for correctly answering the task as the last blossom never was an occluder.

2.3. Procedure

Every patient attended the study on three consecutive days and each control subject on two consecutive days. On the first day, every subject received training on SPT0, SPT+ and SMTS outside the scanner and all patients were on their regular dopaminergic medication. On the second day, 50% of patients were tested ON and 50% OFF. Healthy controls did not receive any medication. The third day was arranged in the same way as day two, except that patients who had been tested ON the day before were now tested OFF and vice versa. Patients were randomly assigned to measuring ON or OFF first.

2.4. Functional MRI data acquisition

In the fMRI sessions, participants lay on the scanner bed in a supine position with their right index and middle fingers placed on two different buttons of a response box. The visual stimuli were presented on a 30-inch MRI display (OptoStim, medres GmbH, Cologne, Germany). Imaging was performed at a 3T scanner (Siemens TRIO, Erlangen, Germany) equipped with a standard birdcage head coil. Thirty axial slices (210 mm field of view, 64×64 pixel matrix, 3 mm thickness; 1 mm spacing) positioned parallel to the bicomissural plane (AC-PC) were acquired using a single-shot gradient echo-planar imaging (EPI) sequence (TE 30 ms, flip angle 90°, TR 2000 ms; serial recording) sensitive to blood oxygenation level dependent (BOLD) contrast. Prior to functional imaging, 29 anatomical T1-weighted modified driven equilibrium Fourier transform (MDEFT) images (Uğurbil et al., 1993; Norris, 2000) were acquired.

In a separate session prior to the fMRI sessions, high-resolution whole-brain images were recorded for every participant using a T1-weighted 3D-segmented MDEFT sequence (128 slices, field of view 256 mm, 256×256 pixel matrix, thickness 1 mm, spacing 0.25 mm).

2.5. Behavioural analysis

The statistical software package SPSS (SPSS Statistic 20.0, IBM, Chicago, IL) was used for statistical analyses. Behavioural performance was assessed by probability of recognition (P_R, Snodgrass and Corwin, 1988) defined as the difference of hit rate and false alarm rate (cf. Schönberger et al., 2013). Chance performance level relates to 0.25 in SPT0 (24 trials) and 0.225 in SPT+ (40 trials). All participants included in the statistical analysis performed above these chance levels in at least one SPT version. As patients and controls were matched for their gender, age and level of education all comparisons between these groups were carried out as paired *t*-tests or repeated measures ANOVA.

Paired *t*-tests were conducted comparing age, years of school education, PANDA and BDI-II of patients and controls. Further, a paired *t*-test was calculated for UPDRS III scores ON and OFF to ensure a significant effect of medication.

Performance in SMTS was compared between groups (patients ON vs. controls) and within patients (OFF vs. ON) in two paired-t-tests to control for differences in working memory capacity. Differences in SPT performance were calculated in two 2×2 ANOVAs, first between patients ON and controls [within-subject factors TASK (SPT0 vs. SPT+) and GROUP (patients ON vs. controls)] and second between performance of patients ON and OFF [within-subject factors TASK (SPT0 vs. SPT+) and MEDICATION (ON vs. OFF)]. Note that response times are not of interest as all participants were instructed to give correct, but non-speeded responses. Nevertheless, to rule out the possibility of a speed-accuracy trade off, we also conducted these two 2×2 ANOVAs with response time as the dependent variable. Furthermore, the number of missing responses was used as dependent variable in the two 2×2 ANOVAs to suspend that group differences in brain activity were caused by differences in the number of motor responses. Finally, all comparisons with the factor MEDICATION were also conducted with a covariate which coded if a patient was ON or OFF medication on the first day of testing. By this means possible practice effects that could mask differences between ON and OFF state were controlled. An interaction between medication, task and testing day could not be directly tested since the testing days' influence is not independent of medication state since patients were either ON or OFF medication on their first day of testing.

Additionally, correlation analyses for UPDRS III, age, and PANDA with performance in SPT0, SPT+, and SMTS were carried out for ON- and OFF-state, respectively. Controls' age and PANDA-scores were correlated with performance in SPT0, SPT+ and SMTS. All correlation analyses were computed using standard Pearson's correlation coefficient, with p-Values < 0.05 regarded as significant.

2.6. fMRI data processing

Motion correction of the functional data was performed with the Siemens motion correction protocol (Siemens, Erlangen, Germany). All further analyses were conducted with the software package LIPSIA (Lohmann et al., 2001). A high-pass filter with a cut-off frequency of 1/120 Hz was applied and spatial smoothing was performed with a Gaussian filter of 5.65 mm FWHM (full width half maximum). Functional data sets were aligned with a three-dimensional (3D) stereotactic coordinate reference system by co-registration of the low-resolution MDEFT datasets onto the individual high-resolution 3D MDEFT reference set. Due to technical problems some of the low-resolution anatomical datasets were not recorded properly; in these cases functional data were aligned with the individual 3D MDEFT reference sets by taking the 20th time-step of each fMRI time course. The resulting parameters formed a transformation matrix with three rotational and three translational degrees of freedom. This matrix was normalised to a standardized Talairach brain size (Tailarach and Tournoux, 1988) and applied to the functional slices using trilinear interpolation. The generated output had a spatial resolution of $3 \times 3 \times 3$ mm^3.

Statistical evaluation was based on a least-squares estimation using GLM (general linear model) for serially auto-correlated observations (Worsley and Friston, 1995). The design matrices were generated with a delta function, convolved with the hemodynamic response function (gamma function).

In the first analysis, brain activations were analysed time-locked to onset of the trials, and the analysed epoch comprised the duration of a complete fifteen-stimuli-sequence without the response and feedback time window, i.e. 11.25 s. In the employed GLM, the conditions SMTS, SPT0, SPT+, and null-events were modelled. Null-events were also modelled with a length of 11.25 s. Six contrast images were generated for each participant (SMTS > resting, SPT0 > resting, SPT+ > resting, SPT0 > SMTS, SPT+ > SMTS, SPT+ > SPT0). These contrast images entered

paired-*t*-tests for analyses of group differences (patients ON vs. controls) and medication effects (patients ON vs. OFF). Furthermore, the contrasts SPT0 > SMTS and SPT+ > SMTS were used in one-sample-*t*-tests to verify the expected premotor involvement in serial prediction beyond working memory processes in all participants.

To strengthen the ability to detect differences in sequential processing in SPT0 and SPT+ a second, event-related analysis was carried out. Instead of the whole epoch of SPT+ and SPT0 trials only one event per trial was modelled where the processing in both tasks should be maximally different. In every SPT+ trial one stimulus was selected which was presented directly after an occluder. At this time point the processing in SPT+ is diverging from the processing in SPT0 while the stimuli themselves are identical. In case of more than one occluder within a SPT+ trial it was randomly determined which stimulus after an occluder was chosen; occluders at the end of a trial were not considered. Likewise, one stimulus out of every SPT0 trial was selected which matched the position of a selected SPT+ stimulus. The resulting SPT+and SPT0 events were modelled with the duration of 1 s. Because the remaining stimuli in both SPT tasks were presented too densely to enter them in the GLM, SPT trials were additionally modelled as epochs of 11.25 s. SMTS trials and null events were also modelled as epochs of 11.25 s. Complementing the contrast of SPT+ > SPT0 in the first analysis, the contrast of SPT+ events > SPT0 events was computed for each participant and compared in controls vs. patients ON medication and patients ON vs. OFF medication.

The comparison of controls with patients ON medication demanded consideration of the day of data acquisition: Half of the patients were measured ON medication on their second day and the other half on their third day of participation, while the matched controls' data were all collected on the second day. Differences between controls and patients ON medication resulting from more frequent execution of SPT, in the case of patients who were ON medication on the third day, should not be considered as reliable group difference. Therefore the effect of the day of data acquisition was calculated in patients (second vs. third day) to be controlled in the comparison of controls and patients ON medication: activations less pronounced on the third day than on the second day of patients' participation should not be interpreted in favour of our hypothesis of hypoactivation in comparison to controls, and activations more pronounced on the third day than on the second day could not support our hypothesis of hyperactivation.

Finally, *t*-values were transformed into *z*-scores. To correct for false positive results data were whole-brain corrected at $p < 0.05$ by setting an initial voxelwise *z*- threshold to $z = 2.33$ ($p \leq 0.01$, uncorrected) and correcting for multiple comparisons using cluster-size and cluster-value thresholds obtained by Monte Carlo simulations at a significance level of $p = 0.05$ (Lohmann et al., 2008).

2.7. Region of interest analysis: correlation between BOLD, performance and UPDRS III

Beta-values of four regions of interest (ROI), left and right SMA and left and right PM, were calculated to assess the hypothesised relationships between severity of disease as well as SPT performance level with hypoactivity of SMA and compensating PM hyperactivity. ROI were derived from a previous fMRI study that tested young healthy participants performing SPT0 and SPT+ (Schubotz and von Cramon, 2004). Execution of both SPT versions compared to a control task was found to significantly increase activity in left SMA (Talairach coordinates of peak voxel: $x = -5$, $y = -1$, $z = 52$), right SMA ($x = 1$, $y = 5$, $z = 52$), left PM ($x = -56$, $y = 7$, $z = 23$) and right PM ($x = 52$, $y = 4$, $z = 34$). Based on these coordinates a ROI was defined as the peak voxel and its six adjacent voxels (inferior, superior, left, right, anterior and posterior to the peak voxel). The four resulting ROI were used to extract beta-values of activation during execution of SMTS (compared to resting), SPT0 (compared to resting), SPT+ (compared to resting), and during SPT+ compared to SPT0 (SPT+ > SPT0). Note that this procedure avoids double dipping as the ROI were derived from an independent data set (Kriegeskorte et al., 2009).

To analyse the relationship of SMA and PM activity with performance, beta-values of each ROI were correlated with performance (P_r) as follows. For patients ON, patients OFF and controls performance in SPT0 was correlated with beta-values of the contrast SPT0 > resting. Likewise, performance in SPT+ was correlated with beta-values of the contrast SPT+ > resting and SPT+ > SPT0. To test if the activity of SMA and PM exclusively predict SPT performance and not working memory capacity, correlations of SMTS performance with beta-values of the contrasts SMTS > resting, SPT0 > resting, SPT+ > resting and SPT0 > SPT+ were also calculated.

Finally, for each ROI UPDRS III scores ON were correlated with beta-values of patients ON and UPDRS III scores OFF with beta-values OFF (SPT0 > resting, SPT+ > resting, SPT+ > SPT0 and SMTS > resting).

In order to control for the number of comparisons, *p*-Values were multiplied with the number of ROI, i.e. 4, and considered significant when $p < 0.05$.

3. Results

3.1. Behavioural results

No significant differences were found between patients and healthy controls with regard to age, level of school education, BDI-II or PANDA scores (Table 1). The comparison of the UPDRS III motor-scores ON and OFF showed a highly significant difference ($t = -4.74$, $p < 0.001$).

Performance in SMTS did not differ significantly between ON and OFF ($t = 1.01$, $p = 0.33$) or between patients ON and controls ($t = 1.53$, $p = 0.146$; see Fig. 2). There also was no influence of medication when controlling in which state the patient was first [$F(1,15) < 1$]. The repeated-measures ANOVA with the two 2-level factors GROUP (patients ON, controls) and TASK (SPT0, SPT+) yielded a main effect for TASK [$F(1,15) = 12.66$, $p = 0.003$] as well as an almost significant main effect for GROUP [$F(1,15) = 4.49$, $p = 0.051$], but no interaction [$F(1,15) < 1$]. The repeated-measures ANOVA with the two 2-level factors MEDICATION (ON vs. OFF) and TASK (SPT0 vs. SPT+) exhibited a main effect of TASK [$F(1,15) = 13.45$, $p = 0.002$], but no main effect for MEDICATION [$F(1,15) < 1$] and no interaction [$F(1,15) < 1$]. Taking into account if patients were in ON or OFF

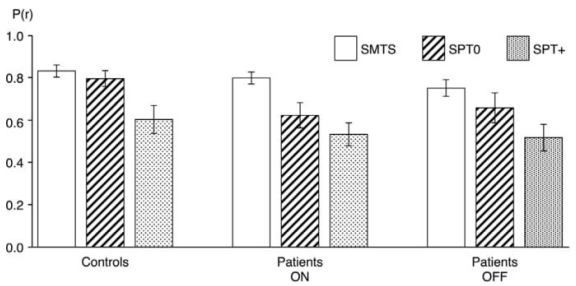

Fig. 2. Behavioural performance in all tasks. Bars show mean performance (± standard error) calculated as probability of recognition (Snodgrass and Corwin, 1988).

state on the first day of testing, there was a significant effect of MEDICATION [F(1,15)=6.45, p=0.024], but no effect of TASK [F (1,15)<1] and no interaction [F(1,15)=1.91, p=0.188]. These results *mostly* met our expectations, as patients tended to perform worse than controls and showed poorer performance in SPT+ than SPT0. In contrast, the controls' advance in performance was not more pronounced in SPT+ (Fig. 2). Furthermore, patients showed the expected difference in performance OFF compared to ON when controlling for practice effects.

Regarding response times the analysis showed that patients ON (mean=956 ms, standard deviation=235 ms) responded significantly slower than controls [mean=796 ms, standard deviation=211 ms;$F(1,15)=8.823$, $p=0.01$]. There was no significant effect of TASK [$F(1,15)<1$] and no interaction of GROUP and TASK [$F(1,15)=1.12$, $p=0.307$]. The ANOVA with the two 2-level factors MEDICATION (ON vs. OFF) and TASK (SPT0 vs. SPT+) exhibited no significant effects [all *F*-values (1,15)<1]. When controlling for practice effects, the tendency of SPT+ patients to respond faster when OFF (mean=937 ms, standard deviation=300 ms) than ON [mean=965 ms, standard deviation=235 ms) did not reach significance [F(1,15)=4.05, p=0.064]. Neither were the factor TASK [F (1,15)<1] or the interaction [F(1,15)=1.39,p=0.257] significant.

There was no effect of GROUP [$F(1,15)=1.667$, $p=.216$] or TASK [$F(1,15)<1$] and no interaction [$F(1,15)<1$] on the number of missing responses when comparing controls and patients ON. Further, there was no main effect of MEDICATION and TASK or interaction of both factors when comparing patients ON with patients OFF and when controlling for possible practice effects [all *F*-values (1,15)<1]. This means that controls and patients regardless of medication state exhibited the same number of responses.

Correlations between age and performance revealed a trend for patients to be more impaired with increasing age both in SPT+ ($r=-0.473$; $p=0.065$) and in SPT0 ($r=-0.475$; $p=0.063$) in OFF- but not ON-state. Correlations of patients' BDI, PANDA, and UPDRS III with their performance were not significant. Like patients OFF, controls performed worse in SPT0 with increasing age ($r=-0.53$; $p=0.035$), while good performance in SPT+ was related to higher PANDA scores ($r=0.586$; $p=0.017$).

SMTS=serial match-to-sample task; SPT0=serial prediction task; SPT+=serial prediction task with occluders.

3.2. fMRI results

3.2.1. BOLD during serial prediction in all participants

To ensure that the premotor network's activity in the SPT generally exceeded activation during the SMTS we calculated one-sample-*t*-tests of the contrasts SPT0 > SMTS and SPT+ > SMTS in all groups and conjoined them [patients ON (SPT0>SMTS) ∩ patients ON (SPT+>SMTS) ∩ controls (SPT0>SMTS) ∩ controls (SPT+>SMTS) ∩ patients OFF (SPT0>SMTS) ∩ patients OFF (SPT+>SMTS)]. Indeed, this analysis revealed the expected higher activation in SMA, PM and inferior parietal lobule and additionally in the superior temporal gyrus during the SPT than the SMTS (Table 2).

3.2.2. BOLD differences of patients and healthy controls

We expected that patients ON, when engaged in the SPT, would show a hypoactivity of SMA and putamen when compared to healthy controls. This hypothesis was tested by calculating differences between patients ON and controls during the SPT vs. SMTS and during the SPT vs. resting: First, patients ON and controls were compared in SPT0 > SMTS and in SPT+ > SMTS separately and the results were conjoined in a second step [patients ON (SPT0 > SMTS) vs. controls (SPT0>SMTS) ∩ patients ON (SPT+ > SMTS) vs. controls (SPT+ > SMTS)]. This analysis did not reveal any significant differences.

Table 2
Areas more activated during the SPT than SMTS in all groups [patients ON (SPT0>SMTS) ∩ patients ON (SPT+>SMTS) ∩ controls (SPT0>SMTS) ∩ controls (SPT+>SMTS) ∩ patients OFF (SPT0>SMTS) ∩ patients OFF (SPT+>SMTS)].

Localisation	BA	Size	Coordinates			Z
			x	y	z	
SMA (L)	6	1701	−8	3	54	3.04
Lateral premotor cortex (L)	6	2052	−50	−3	42	3.53
Precentral gyrus/lateral premotor cortex (R)	6 / 44	5400	49	6	15	3.35
Inferior parietal lobule (R)	40	4752	46	−36	45	3.26
Superior temporal gyrus (L)	42 / 13	3429	−50	−39	15	3.71
Superior temporal gyrus (R)	42	1566	55	−33	12	3.45

Talairach coordinates of cluster peak voxel ($p<0.05$, whole-brain corrected for multiple comparisons). BA=Brodmann Area; *L*=left hemisphere; *R*=right hemisphere; Size=cluster in mm^3; *Z*=maximal *Z*-scores.

Comparing SPT vs. resting [patients ON (SPT0 > resting) vs. controls (SPT0>resting) ∩ patients ON (SPT+ > resting) vs. controls (SPT+ > resting)] we found bilateral hypoactivity for patients ON as compared to controls in SMA and in right striatum; further hypoactivity was recorded in left primary motor cortex, left primary somatosensory cortex, bilateral inferior temporal gyrus, inferior occipital gyrus, precuneus and cuneus (Table 3 and Fig. 3). Against our expectation we did not observe a concurrent hyperactivity in PM. No area revealed a significantly higher BOLD response in patients ON than controls.

To support our hypothesis, the observed hypoactivations in patients must not have been caused by practice effects accompanying the day of patients' data acquisition. To suspend this possibility, second vs. third day's BOLD response of patients were compared for the contrast SPT0 > resting and SPT+ > resting in two paired-*t*-tests. The conjunction of both *t*-tests [second day (SPT0 > resting) vs. third day (SPT0>resting) ∩ second day (SPT+>resting) vs. third day (SPT+>resting)] showed no differences in activation between the second and third day of patients' participation while performing the SPT.

To examine if the hypoactivity in putamen and SMA was specific for the engagement in the SPT, we conducted a paired *t*-test of the contrast SMTS > resting in patients ON vs. controls and conjoined it with the conjunction of SPT0 > resting and SPT+ > resting. The same pattern of hypoactivity in right putamen, SMA, left and right primary somatosensory and motor cortex, left middle temporal gyrus, inferior occipital gyrus and cuneus in patients ON compared to controls was observed (Table 4 and Fig. 3). Therefore, the hypoactivity of putamen and SMA emerged when the patients were engaged in either the SPT or the SMTS.

To test for a pronounced hypoactivity of SMA in patients performing SPT+, the contrast SPT+ > SPT0 was compared between

Table 3
Areas more activated in controls than in patients ON medication during performance of SPT compared to resting [controls (SPT0>resting) vs. patients ON (SPT0>resting) ∩ controls (SPT+>resting) vs. patients ON (SPT+>resting)].

Localisation	BA	Size	Coordinates			Z
			x	y	z	
SMA (L+R)/primary motor cortex (L)/ primary somatosensory cortex (L)	6/4/3	4401	−5	−12	54	3.46
Putamen (R)		3564	22	9	−6	3.77
Precuneus (L)	7/19	2403	−20	−78	30	3.30
Cuneus (L)	18	8775	−14	−84	21	4.21
Middle temporal gyrus (L)	21	1863	−50	−15	−3	3.60
Inferior temporal gyrus (R)	19/37	2187	43	−60	−9	3.26
Inferior temporal gyrus (L)	19	2187	−56	−66	0	3.30

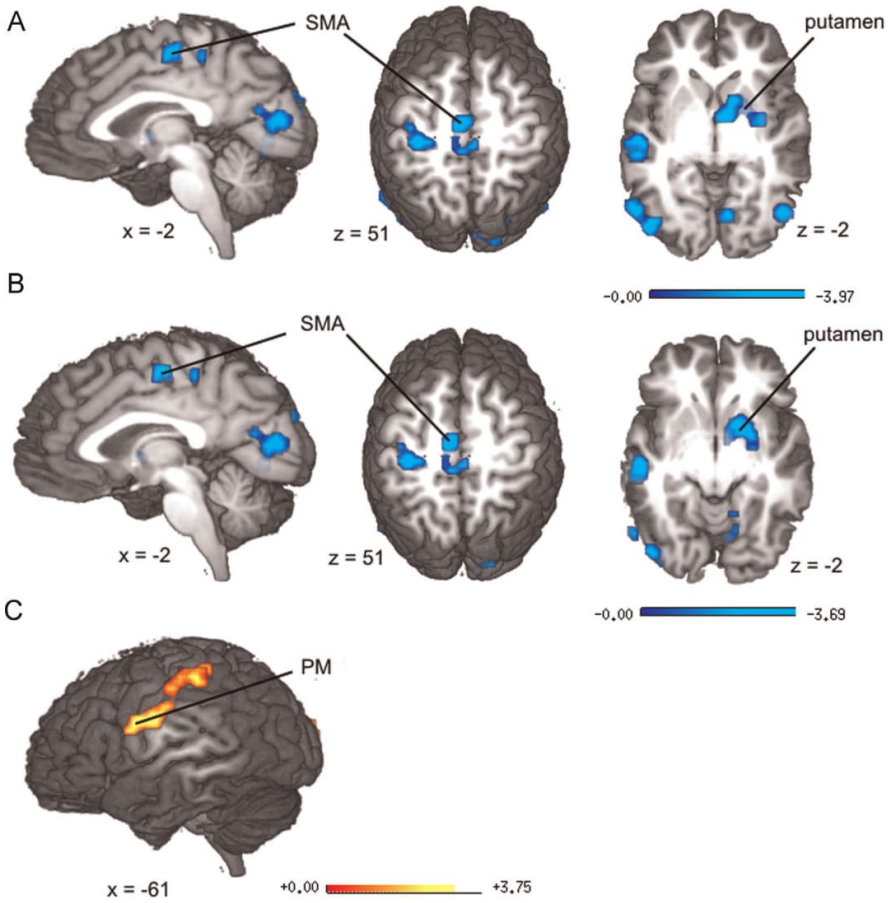

Fig. 3. Significant activation differences in serial prediction tasks. (A) Hypoactivity of patients ON compared to controls during the SPT [(controls (SPT0 > resting) vs. patients ON (SPT0 > resting)) ∩ controls (SPT+ > resting) vs. patients ON (SPT+ > resting)]. (B) Hypoactivity of patients ON compared to controls during the SMTS [(controls (SMTS > resting) vs. patients ON (SMTS > resting)) ∩ controls (SMTS > resting) vs. patients ON (SMTS > resting)]. (C) Hyperactivity in patients OFF compared to ON medication [patients OFF (SPT+ > SPT0) vs. patients ON (SPT+ > SPT0)]. Paired *t*-tests ($p < 0.05$) whole-brain corrected for multiple comparisons. Significant areas of hypoactivity (in blue) and hyperactivity (in red) are superimposed on 3D brain rendering.

Table 4
Areas more activated in controls than in patients ON medication during performance of SMTS and SPT compared to resting [controls (SMTS>resting) vs. patients ON (SMTS>resting) ∩ controls (SPT0>resting) vs. patients ON (SPT0>resting) ∩ controls (SPT+>resting) vs. patients ON (SPT+>resting)].

Localisation	BA	Size	Coordinates			Z
			x	y	z	
SMA (bilateral)	6	1566	−8	−18	60	3.37
Primary motor cortex (L)/primary somatosensory cortex (L)	4 / 3	1566	−29	−21	48	3.23
Putamen (R)		2214	31	−3	6	2.88
Cuneus (L)	18	6966	−14	−84	18	3.88
Middle temporal gyrus (L)	21	1296	−50	−18	−3	3.50

patients ON and controls in a paired-*t*-test [patients ON (SPT+ > SPT0) vs. controls (SPT+ > SPT0)]. No significant differences were found here. There also were no significant differences in the contrast SPT+ events > SPT0 events in the event-related analysis.

3.2.3. BOLD differences in patients ON and OFF

Regarding the comparison of patients ON vs. OFF, we expected that hypoactivity in SMA and putamen would be attenuated by medication. The conjunction of two paired-t-tests comparing the effect of medication in SPT0 > SMTS and SPT+ > SMTS yielded no significant activations [patients ON (SPT0 > SMTS) vs. OFF (SPT0 > SMTS)∩patients ON (SPT+ > SMTS) vs. OFF (SPT+ > SMTS)]. Further, there was no medication effect during the SPT compared to resting [patients ON (SPT0 > resting) vs. OFF (SPT0>resting) ∩ patients ON (SPT+ > resting) vs. OFF (SPT+ > resting)]. However, a paired-t-test calculating differences between patients ON and OFF in SPT+ compared to SPT0 [patients ON (SPT+ > SPT0) vs. OFF (SPT+ > SPT0)] revealed a significantly enhanced BOLD effect OFF in the left ventral PM, extending into the parietal lobe via primary motor and somatosensory areas (Table 5 and Fig. 3). Parietal areas are usually co-activated with the premotor system during serial prediction (Schubotz, 2007), reflecting premotor-parietal loops (Rizzolatti and Luppino, 2001).

Furthermore, the event-related analysis also showed more activity in the left ventral PM of patients OFF than ON when comparing SPT+ with SPT0 [patients ON (SPT+ events > SPT0 events) vs. OFF (SPT+ events > SPT0 events)]. The dorsolateral prefrontal cortex and anterior cingulate cortex were also significantly higher activated (Table 5).

Table 5
Areas significantly more activated in patients OFF than patients ON medication during performance of SPT+ compared to SPT0 (A) in the epoch based analysis [patients ON (SPT+ > SPT0) vs. patients OFF (SPT+ > SPT0)] and (B) the event-related analysis [patients ON (SPT+ event > SPT0 events) vs. patients OFF (SPT+ events > SPT0 events)].

Localisation	BA	*k*	Coordinates			*Z*
			x	*y*	*z*	
(A) Epoch based analysis						
Lateral premotor cortex extending into primary motor and somatosensory areas	6/4/2/3/40	1809	−62	−8	27	4.05
Lateral occipital gyrus (R)	18/19	2376	34	−92	9	3.64
(B) Event-related analysis						
Lateral premotor cortex extending into primary motor cortex	6/4	1755	−62	−8	27	4.17
Dorsolateral prefrontal cortex extending into anterior cingulate cortex	8/9/32	3078	25	10	33	3.93

These analyses implicate that medication did not attenuate hypoactivity in SMA and putamen; instead PM was more active OFF than ON medication, as expected, but only when load on the SMA-putamen loop was increased. Our assumption that this PM hyperactivity represents a compensational mechanism is tested in the following section by relating it to the patients' performance.

3.3. Regions of interest analysis

We expected the patients' SMA activity to be positively correlated with performance, especially in SPT+. Furthermore, activity of PM should be related to preserved performance provided that SMA is hypoactive and compensation via PM is effective.

Considering results in SPT0 first, neither controls nor patients ON showed a significant relation between ROI beta-values (SPT0 > resting) and performance (Table 6). In contrast, patients OFF exhibited a significant positive correlation of performance with beta-values in left PM ($r=0.593$, $p=0.03$). Conducting analyses for SPT+, patients OFF exposed a similar positive correlation of performance with beta-values (SPT+ > resting) in left PM ($r=0.591$, $p=0.032$). This relation also applied to patients ON, whose performance in SPT+ was positively correlated with activity in left PM ($r=0.558$, $p=0.05$), and additionally with activity in left SMA ($r=0.557$, $p=0.05$). Beta-values of controls showed no significant correlation with performance in SPT+ (Table 6). Patients' OFF-performance depended on SMA activity in a specific way: The analysis of beta-values derived from the contrast SPT+ > SPT0 revealed significant positive correlations of left SMA activity ($r=0.676$, $p=0.008$) and right SMA activity ($r=0.607$, $p=0.026$) with performance in SPT+. This relation of better performance to increased activity in SPT+ than SPT0 was not found in patients ON and controls, and did not apply to left or right PM in any of the groups (Table 6).

There were no significant correlations of either SMA or PM activity with performance in the SMTS in any group (Table 7).

Finally, we expected that SMA hypoactivity varies as a function of individual motor impairment according to UPDRS III. Indeed, UPDRS III scores in ON-state were negatively correlated with beta-values (SPT+ > SPT0) in left SMA ($r=-0.584$, $P=0.034$) and right SMA ($r=-0.689$, $P=0.006$). Unexpectedly, this relation was also found in left PM ($r=-0.572$, $P=0.042$). Correlations of UPDRS III with beta-values derived from the other contrasts (SPT0 > resting, SPT+ > resting, SMTS > resting) did not gain significance in medicated patients, pointing to a specific negative relation between severity of PD symptoms and the ability to intensify activity in SMA and left PM during SPT+. No correlations between beta-values OFF and UPDRS III scores OFF were found. All significant correlations of performance and UPDRS III scores with beta-values are diagrammed in Fig. 4.

4. Discussion

In the present study, we investigated how the so-called "motor loop" connecting SMA and striatum (Alexander et al., 1986) contributes to cognitive dysfunction in Parkinson's disease (PD). Drawing on a compensational mechanism implemented by PM, which is known to accompany pathological hypoactivity of SMA and striatum in motor tasks (Samuel et al., 1997; Haslinger et al., 2001; Mallol et al., 2007), we tested whether in a cognitive task PD patients' SMA hypoactivity could also be compensated by PM hyperactivity. We tested 16 male patients suffering from PD ON and OFF dopaminergic medication and 16 male healthy controls in the serial prediction task (SPT), which engages both PM and SMA in healthy subjects (Schubotz and Von Cramon, 2003; Schubotz, 2007). We applied two versions of the SPT, one with on-going sequences of stimuli (SPT0), and one with sequences containing non-informative stimuli, so-called "occluders", increasing the demand to build an internal representation of the sequence (SPT+).

Indeed, the pattern of our behavioural and functional findings show the interplay of SMA hypoactivity disrupting serial prediction performance and point to PM hyperactivity restoring performance: On the one hand, we found less activity in SMA and putamen during SPT and a serial match-to-sample task (SMTS) combined with poor SPT performance when patients were compared to controls. On the other hand, PM was hyperactive after withdrawal of medication in SPT+ while patients OFF showed poorer performance relative to ON medication. Importantly, SMA as well as PM activity positively correlated with the patients' performance.

Considering the group comparison first, patients exhibited poorer SPT performance than controls while the patients'

Table 6
ROI analysis: Correlation (* when significant at $p<0.05$, corrected for multiple comparisons) of beta-values and performance (P_R=probability of recognition) in SPT.

		P_R(SPT0)		P_R(SPT+)			
Group	ROI	with beta-values (SPT0 > Resting)		with beta-values (SPT+ > Resting)		with beta-values (SPT+ > SPT0)	
Hemisphere		*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
Controls	SMA	0.283	0.163	0.396	−0.162	−0.263	−0.306
	PM	0.177	0.278	0.018	0.017	0.109	0.155
Patients ON	SMA	0.440	0.092	0.558*	0.389	0.347	0.065
	PM	0.489	0.396	0.557*	0.498	0.136	0.159
Patients OFF	SMA	0.384	0.305	0.502	0.331	0.676*	0.607*
	PM	0.593*	0.234	0.591*	0.210	0.477	0.311

Table 7
ROI analysis: Correlation (* when significant at $p < 0.05$, corrected for multiple comparisons) of beta-values and performance (P_R = probability of recognition) in SMTS.

Group	ROI	SMTS > Resting		SPT0 > Rest		SPT+ > Rest		SPT+ > SPT0	
		Left	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
Controls	SMA	0.273	0.343	0.344	0.439	0.348	0.431	0.134	0.219
	PM	−0.164	−0.001	0.042	−0.054	0.030	−0.013	−0.028	0.147
Patients ON	SMA	0.064	0.004	0.052	0.115	0.027	0.204	−0.081	0.286
	PM	0.245	0.004	0.058	0.012	0.114	0.169	0.309	0.369
Patients OFF	SMA	0.201	0.023	0.144	−0.281	0.247	−0.203	0.416	0.163
	PM	0.213	0.069	0.229	0.146	0.295	0.256	0.372	0.346

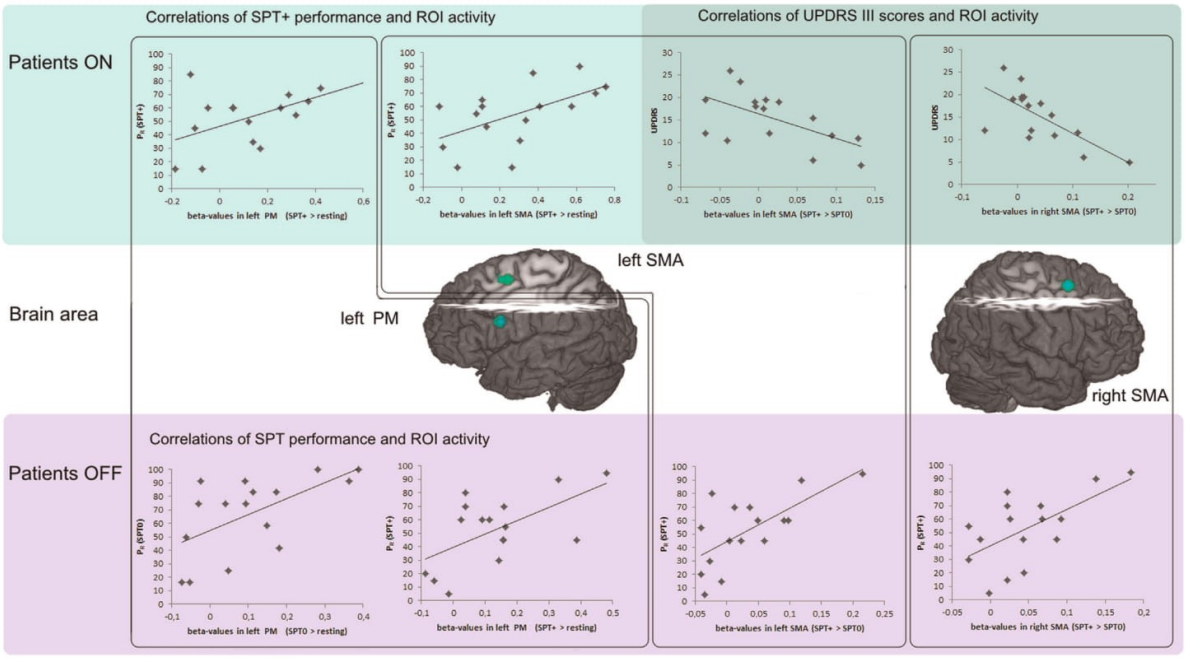

Fig. 4. Scatter plots of significant correlations between SPT performance and beta-values and UPDRS III scores and beta-values. Abbreviations: UPDRS = UPDRS III scores ON dopaminergic medication; P_R = probability of recognition.

performance in SMTS as well as in PANDA was not significantly worse than performance of controls. This suspends the possibility that patients' deficits in SPT resulted from global cognitive dysfunction or working memory deficits. Even more important, the SPT does not rely on prefrontal functions, but recruits primarily the premotor network (Schubotz and Von Cramon, 2003), and we did not observe differential prefrontal activations in controls and patients ON medication. There was only one contrast showing enhanced activity in dorsolateral prefrontal cortex and anterior cingulate cortex in concert with PM when we conducted the event-related analysis.

Relative to healthy controls, PD patients showed a decreased activity in SMA and striatum during both the SPT and the SMTS. We suppose that this hypoactivity emerged in both tasks as they recruited both of these areas due to their serial composition. Note that activation differences in motor areas between groups were not due to differences in the motor responses of controls and patients as there were no differences in the number of responses given by either group. Moreover, it can also be ruled out that activation differences in SMA were due to abnormal resting state activity in PD patients. Skidmore et al. (2013) found that PD patients show a hypoactive SMA during resting conditions and no abnormal pattern in the striatum. This means that we rather underestimated SMA hypoactivation in PD patients, relative to healthy controls, when contrasting SPT and SMTS with resting state.

In contrast to the SMTS, the SPT additionally recruited SMA, PM and parietal projection areas as shown in previous studies (e.g., Schubotz and von Cramon, 2004; Schubotz, 2007). This confirms that all participants showed a specific premotor involvement in serial prediction beyond working memory engagement. Most importantly, the hypoactivity of SMA and putamen affected performance in the SPT whereas patients showed an equal performance to healthy controls in the serial match-to-sample task. These results indicate that accomplishing the serial match-to-sample task draws on other, presumably also prefrontal areas, while successful serial prediction particularly relies on SMA and striatum. We therefore assume that the motor loop's affection caused the observed deficits in serial prediction. This is additionally corroborated with the finding that correlations between BOLD response, UPDRS III scores and task performance showed no significant relation of SMA and PM activity to the serial match-to-sample task,

but significant and specific relations with serial prediction (see Fig. 4): Correlations of UPDRS III scores and SMA activity revealed a close relationship of bilateral SMA activity during the SPT with the individual degree of the motor loop's affection. The more patients suffered from motor impairment, the less their SMA activity increased during SPT+ compared to SPT0. Thus, patients with severe motor symptoms were unable to intensify SMA activity during engagement in SPT+, the task that was significantly more difficult than SPT0 for all participants.

Interestingly, higher motor impairment also came along with reduced enhancement of left PM activity in SPT+ compared to SPT0. Possibly, medicated patients whose SMA was working to capacity in SPT0, so to say, made use of left PM as compensational mechanism, leading to the situation that SMA as well as PM activity could not be further intensified in SPT+. If this interpretation holds true, PM activity should serve as compensational mechanism already in SPT0 in those PD patients whose SMA function via the motor loop is severely impaired. Indeed, this pattern was reflected in the correlations between BOLD response and SPT performance: Controls and medicated patients did not exhibit a significant relation between activity in SMA or PM and performance in SPT0, whereas patients OFF with higher left PM activity showed increased performance in SPT0 as well as SPT+. However, since we found patients to produce more errors OFF than ON medication, it seems that compensatory mechanisms could not fully restore performance. Moreover, performance ON correlated with left PM activity only in SPT+, probably because SMA activity in most patients under medication was still sufficient to perform well in SPT0. The importance of SMA activity for successful engagement in SPT+, especially without medication, was demonstrated by its particular correlation with performance in SPT+: patients OFF performed the better the more they were able to recruit left and right SMA in SPT+ compared to SPT0. Concurrently, intermission of medication caused hyperactivity in left PM during execution of SPT+ that probably compensated the inability to further increase SMA activity despite heightened demand on internal sequence representation. Notably, patients' performance dropped OFF medication in SPT0 as well as SPT+ when controlling for practice effects, whereas in our previous behavioural study (Schonberger et al., 2013) withdrawal of medication led to particularly impaired performance *only* in the SPT+. Possibly, the observed hyperactivity in left PM during SPT+ prevented the patients in the present study from even poorer performance in this more difficult task.

Taken together, medicated patients showed a deficit in serial prediction when compared to controls accompanied by the expected hypoactivity in SMA and striatum which appeared during the serial prediction and the serial match-to-sample task. Further, patients revealed an impaired serial prediction performance after withdrawal of medication together with PM hyperactivity when the necessity to build an internal presentation of the sequence was heightened in SPT+. We assume that PM hyperactivity was compensatory and prevented the patients without medication from an even stronger drop in performance, as correlations between performance and brain activity indicate: Patients' performance in SPT+ depended on the level of left PM and SMA activity and, without medication, on the bilateral increase of SMA activity compared to SPT0 while performance. In contrast, the performance in the serial match-to sample task did not correlate with PM or SMA activity. These results demonstrate for the first time a significant correlation of compensatory PM activity with performance and confirm the assumption of a close interplay between SMA hypoactivity and PM hyperactivity.

By which mechanisms does the interplay of SMA and PM support performance in internal sequence representation in the SPT? SMA has been shown to conduct memory-guided sequential movements in monkeys (Mushiake et al., 1990; Halsband et al., 1994) by activity of specified types of neurons which Shima and Tanji (2000) found in SMA and pre-SMA. One type of these neurons revealed preparatory activity before performing a specific order of movements which can be interpreted as retrieval of the particular sequence. A second type was activated during intervals between movements, thus providing a link to the next movement, and a third type was selective for the rank order (1st, 2nd or 3rd element of the sequence). There was no preparatory and interval-selective neuronal activity under visual guidance, but it developed gradually with trial repetition and sequence learning. In this manner SMA is capable of generating internal sequence representations and controlling a sequence's progress in time. Importantly, many SMA neurons are multimodal (Ikeda et al., 1999) pointing to the possibility that SMA not only codes motor sequences, but also sequences of perceptual events. Therefore, we assume SMA to monitor the sequences of stimuli presented in the SPT and to be crucial for detection of violations of their serial order.

How can we think of PM to support cognitive sequencing when SMA function is deficient? Comparisons between BOLD activation induced by the SPT and, for instance, serial-to-match or serial detection tasks, have shown that PM is more sensitive to the sequential order of stimuli then to the mere occurrence of the stimuli themselves (Schubotz and Von Cramon, 2003). Thus in the current study, PM may promote deficient SMA sequence representation by providing a bias to an expected transition of two stimuli. When presented with a void stimulus, direct cortical input from PM to SMA may even help bridging two missing transitions, though not in the same stable manner warranted by operating striatal loops. The striatal loops' contribution to cognitive sequencing can be understood in the framework put forward by Graybiel (1998), according to which the striatum chunks motor performance in order to allow implicit learning of sequences. This chunking is thought of as an evidence-based probabilistic weighting of the transition between consecutive cortical activation patterns. Importantly, this striatal learning mechanism depends on dopaminergic projections from substantia nigra and should be particularly impaired in patients without medication which we observed to exhibit PM hyperactivity. Since SMA and PM maintain direct reciprocal connections, PM may help generating an internal sequence representation in SMA by providing stimulus information not pre-processed by striatum. Concurrently, input of PM to striatum may be strengthened and result in enhanced input to SMA via the motor loop despite dopaminergic depletion.

As an alternative explanation for our findings, one could assume PM activity to contribute to performance in SPT independent of SMA function. In this case, PM may have improved performance by providing information for other cortical areas, e.g., prefrontal regions which store and update stimulus information in working memory. This interpretation is in line with finding PM and the dorsolateral prefrontal cortex co-activated in the event-related analysis. Maybe, the prefrontal activations represent a working a memory process helping to maintain the internal sequence representation in PM (Curtis and D'Esposi, 2003). However, even in this scenario, the SMA's importance for sequence processing is corroborated, as the possibly stabilising prefrontal function is found to be increased OFF medication when the motor loop's function is impaired.

Our results do not support the common view that cognitive dysfunction in non-demented PD patients, often subsumed under the notion of "executive dysfunction", can be utterly attributed to dopamine deficiency in basal ganglia–prefrontal circuits (Kudlicka et al., 2011; Ray and Strafella, 2012; Dirnberger and Jahanshahi, 2013; Kehagia et al., 2012). The contribution of an impaired dorsolateral circuit to cognitive deficits in PD is well described (Brück

et al., 2001; Cools et al., 2001; Polito et al., 2012), but the role of the motor circuit was neglected so far even though recent studies suggest a close interplay of motor and cognitive decline in PD (Amboni et al., 2008; Vercruysse et al., 2012). Furthermore, akinetic-rigid compared to tremor-dominant patients reveal a higher risk of cognitive decline (Alves et al., 2006; Burn et al., 2006) accompanied by a greater dopamine loss in putamen, i.e., the striatal component of the "motor loop" (Eggers et al., 2011). Thus, associating cognitive dysfunction in PD with executive dysfunction may be an oversimplification.

Rather, our current findings point to a contribution of SMA hypoactivity to deficits in cognitive sequencing. Patients are known to reveal deficits in sequence learning (Jackson et al., 1995; Doyon et al., 1997; Shin and Ivry, 2003; Siegert et al., 2006), but most of the studies investigating sequencing in PD employ motor learning, e.g., the serial reaction time task (Nissen and Bullemer, 1987). However, it is possible to disentangle cognitive sequencing abilities from motor sequence learning by presenting sequences of perceptual stimuli independent of motor responses (Hoffmann and Koch, 1997). The SPT applied in the current study refines this principle and merely draws on perceptual sequencing, thus showing that patients suffering from PD are impaired in a purely cognitive task due to affection of the motor loop. This dovetails with the recruitment of SMA and PM in healthy individuals performing the SPT (Schubotz and von Cramon, 2004; Schubotz, 2007). Further findings point to the fact that impaired cognitive abilities are responsible for reduced performance in the serial reaction time task, since it correlates with scales for outcomes in PD cognition (SCOPA-COG), an assessment tool for cognitive deficits in PD (Vandenbossche et al., 2009). Interestingly, the SCOPA-COG (Marinus et al., 2003) contains four out of ten items that require sequencing (repeating a digit span backwards, pointing to cubes in a given sequential order, naming the months backwards, performing a given sequence of hand movements) and another three items at least partly depend on sequencing abilities (i.e., verbal recall of a sequence of 10 words, counting backwards, delayed recall of the 10 words). As our results suggest, performance in SCOPA-COG is related to motor impairment: patients suffering from freezing of gait compared to those without freezing of gait were found to be significantly impaired in SCOPA-COG (Vercruysse et al., 2012). Another tool often used to assess cognitive abilities in PD is the Trial-Making Test (TMT; Bowie and Harvey, 2006). It also involves cognitive sequencing since it requires switching between two sequences (1-A-2-B-3-C…), and was proven to activate the premotor system (Moll et al., 2003), thus supporting the notion of the motor loops' contribution to cognitive sequencing.

5. Conclusions

Cognitive impairment in Parkinson's disease cannot be explained by a single mechanism. Considering that the basal ganglia are at the core of functional decline, it is plausible to expect that difficulties arise from dysfunction in more than one cortico-striatal–thalamo-cortical loop. Since Alexander and colleagues used the label "motor loop" in their seminal 1986 paper to address the circuit connecting SMA to the putamen, researchers have been prone to interpret motor loop dysfunction, by definition, as solely affecting motor functions. Current findings, together with fMRI studies in healthy subjects, reveal that the PD-associated decline of serial prediction results from motor loop rather than prefrontal loop dysfunction.

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Motor cognition in patients treated with subthalamic nucleus deep brain stimulation: Limits of compensatory overactivity in Parkinson's disease

Klara Hagelweide[a,b,*], Anna R. Schönberger[a], Lutz W. Kracht[c], Theo O.J. Gründler[d,e], Gereon R. Fink[a,f], Ricarda I. Schubotz[a,b]

[a] Department of Neurology, University Hospital Cologne, Kerpener Str. 62, D-50937 Cologne, Germany
[b] Department of Psychology, University of Muenster, Fliednerstr. 21, D-48149 Münster, Germany
[c] Max Planck Institute for Metabolism Research, Gleueler Str. 50, D-50931 Cologne, Germany
[d] Center for Behavioral Brain Sciences, Otto-von-Guericke-University Magdeburg, Universitaetsplatz 2, 39106 Magdeburg, Germany
[e] Faculty of Economics and Management, Otto-von-Guericke-University Magdeburg, Universitaetsplatz 2, 39106 Magdeburg, Germany
[f] Institute of Neuroscience and Medicine (INM3), Cognitive Neuroscience, Research Centre Jülich, Leo-Brandt-Straße, D-52425 Jülich, Germany

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ABSTRACT

Recent fMRI findings revealed that impairment in a serial prediction task in patients suffering from Parkinson's disease (PD) results from hypoactivity of the SMA. Furthermore, hyperactivity of the lateral premotor cortex sustained performance after withdrawal of medication. To further explore these findings, we here examined the impact of deep brain stimulation of the subthalamic nucleus on the activity of the putamen and premotor areas while performing the serial prediction task. To this end, we measured eight male PD patients ON and OFF deep brain stimulation and eight healthy age-matched male controls using [^{15}O] water positron emission tomography to measure regional cerebral blood flow. As expected, PD patients showed poorer performance than healthy controls while performance did not differ between OFF and ON stimulation. Hypoactivity of the putamen and hyperactivity of the left lateral premotor cortex was found in patients compared to controls. Lateral premotor hyperactivity further increased OFF compared to ON stimulation and was positively related to task performance. These results confirm that the motor loop's dysfunction has impact on cognitive processes (here: prediction of serial stimuli) in PD. Extending prior data regarding the role of the lateral premotor cortex in cognitive compensation, our results indicate that lateral premotor cortex hyperactivity, while beneficial in moderate levels of impairment, might fail to preserve performance in more severe stages of the motor loop's degeneration.

1. Introduction

The hallmark of Parkinson's disease (PD) is the loss of dopaminergic neurons projecting from substantia nigra pars compacta to the striatum. The resulting dopamine deficiency in the basal ganglia causes bradykinesia, resting tremor, muscle rigidity, and posture and gait problems, but also depression and cognitive decline (Rodriguez-Oroz et al., 2009) via depletion of different cortico-basal ganglia-thalamo-cortical loops (Alexander et al., 1986; Sawamoto et al., 2008).

When cognitive deficits in PD are investigated, the focus is often put on impairments in executive functions, i.e., set shifting, planning, conflict resolution, response inhibition, and working memory (Dirnberger and Jahanshahi, 2013). Shortcomings in these domains, subsumed under the notion of a dysexecutive syndrome, are ascribed to a dysfunction of the dorsolateral prefrontal loop (e.g., Brück et al., 2001; Gawrys et al., 2014; Owen, 2004; Rinne et al., 2000; Saint-Cyr et al., 1988), the anterior cingulate and the orbitofrontal loop (Polito et al., 2012; Zgaljardic et al., 2006).

On the contrary, the motor loop, which bundles input from the supplementary motor area (SMA), lateral premotor cortex (PM), and primary motor and sensory cortices to the putamen and projects back to the SMA via the internal globus pallidus and thalamus, is often neglected in relation to cognitive deficits. While some studies suggest the dysexecutive syndrome to be distinct of motor impairment (Cooper et al., 1991; Lewis et al., 2003; Muslimović et al., 2005), others considered them to be interdependent (Elgh et al., 2009; Mortimer et al., 1982; Poletti et al., 2012; Williams et al., 2007). For instance, Nagano-Saito et al. (2014) found that patients with mild cognitive impairment showed premotor hypoactivity during the execution of set-shifting in a computer version of the Wisconsin Card Sorting Test, suggesting that

* Correspondence to: Department of Psychology, University of Münster, Fliednerstr. 21, 48149 Münster, Germany.
E-mail address: klara.hagelweide@wwu.de (K. Hagelweide).

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the motor loop may contribute to cognitive processes involved in executive functions.

We examined the motor loop's contribution to cognitive processes in two previous studies by testing PD patients 'on' and 'off' dopaminergic medication in the serial prediction task (Schönberger et al., 2013, 2015). This task requires participants to monitor stimulus sequences and indicate violations of the sequences' structure. Patients showed poor task performance related to motor impairment (Schönberger et al., 2013), particularly in a modified task version (SPT+) which heightened the need for internal sequence representation as supported by the SMA (Goldberg, 1985). In both studies medication mitigated performance deficits which were associated with hypoactivity of the SMA and putamen while successful performance was related to higher SMA activity. After withdrawal of medication, PM hyperactivity emerged, supposedly reflecting a compensatory mechanism as suggested by a positive correlation with serial prediction (Schönberger et al., 2015). Importantly, these results are reminiscent of a pattern also observed in motor tasks, namely SMA hypoactivity in PD patients co-occurring with PM hyperactivity (Haslinger et al., 2001; Mallol et al., 2007; Sabatini et al., 2000; Samuel et al., 1997) when performance is preserved under external guidance (Hanakawa et al., 1999; Michely et al., 2015).

To confirm and extend these findings, the influence of subthalamic nucleus (STN) deep brain stimulation (DBS) on serial prediction performance and its neural underpinnings was examined in the current study. Similar to dopaminergic medication, DBS significantly improves patients' motor symptoms and quality of life (Perestelo-Pérez et al., 2014), but the exact mechanism of DBS to date remains elusive (Alhourani et al., 2015; Chiken and Nambu, 2016; Udupa and Chen, 2015). A plausible hypothesis is that stimulation of STN disrupts the pathological synchronization in the beta frequency band (Silberstein et al., 2005). In particular, DBS may normalize the exaggerated phase amplitude coupling between the beta rhythm in STN and gamma activity in primary motor cortex (De Hemptinne et al., 2013; Oswal et al., 2013) by reducing the pathological beta rhythms' coherence between STN and SMA (Oswal et al., 2016). Studies examining DBS influences on brain activity show that DBS at rest increases activity in the STN region, thalamus, posterior cerebellum, and precuneus while metabolism is reduced in a network including the PM, SMA, dorsolateral prefrontal cortex, and anterior cingulate cortex (Alhourani et al., 2015; Boertien et al., 2011). On the contrary, DBS during tone-paced joystick movements is associated with increased cerebral blood flow in thalamus and putamen (Thobois et al., 2002), PM (Ceballos-Baumann et al., 1999; Grafton et al., 2006), rostral SMA (Ceballos-Baumann et al., 1999; Grafton et al., 2006; Limousin et al., 1997; Strafella et al., 2003), dorsolateral prefrontal cortex (Ceballos-Baumann et al., 1999; Limousin et al., 1997; Strafella et al., 2003; Thobois et al., 2002) and anterior cingulate cortex (Ceballos-Baumann et al., 1999; Strafella et al., 2003). These activity changes are related to stable (Limousin et al., 1997) or reduced movement latencies under stimulation (Ceballos-Baumann et al., 1999; Strafella et al., 2003; Thobois et al., 2002) and are interpreted as normalization of pathological activity (Grafton et al., 2006).

Taken together, prior studies support the idea that DBS restores the normal function of the motor loop and improves sensory processing, while DBS effects on cognition are still debated (Boertien et al., 2011). Experiments testing for changes in cognitive functions with onset of stimulation found some tasks to be improved and some to be impaired during DBS (Boertien et al., 2011; Jahanshahi et al., 2000; Heo et al., 2008). A study which examined the effects of DBS on motor and cognitive symptoms in comparison to medical therapy in a large sample of patients found minor cognitive decrements in the patients receiving DBS compared to levodopa, while motor symptoms were clearly improved with DBS (Weaver et al., 2009). Furthermore, Carbon et al. (2003) investigated effects of internal pallidal DBS on a sequence motor learning task and found a significant enhancement in the underlying neural network resulting in better task performance, while a decrease in network activity and no behavioural changes were observed after levodopa infusion. These findings point to the idea that DBS may have a stronger positive effect on motor symptoms, while levodopa rather improves cognitive measures.

Against this background, we investigated whether performance in serial prediction is heightened during DBS. Similar to other cognitive tasks, serial prediction might not be significantly improved by DBS. But as serial prediction relies predominantly on the functionality of the motor network (Schubotz, 2007), while many other cognitive tasks rather depend on the prefrontal loops, we expected DBS to have positive effects on serial prediction performance. Drawing on our previous findings we hypothesized patients to show impaired serial prediction compared to healthy controls, especially i) with deactivated DBS, and ii) when the need for SMA engagement is heightened (SPT+; hypothesis 1). The performance deficit was expected to be positively correlated with patient's individual motor impairment and to co-occur with hypoactivity of SMA and putamen (hypothesis 2). In addition to the motor loop's dysfunction, we expected patients to show PM hyperactivity, in particular without DBS and in SPT+, providing a compensatory mechanism which therefore should be related to better performance (hypothesis 3).

2. Material and methods

2.1. Participants

Eight male patients suffering from Parkinson's disease according to the UK Parkinson's disease Society Brain Bank Criteria (Hughes et al., 1992) were included in the study. Patients had a mean age of 61.5 years (range: 54–69 years; for further demographical and clinical data see Table 1). In all patients quadripolar electrodes had been implanted bilaterally into the STN (for stimulation parameters see Table 1). The severity of symptoms measured according to Hoehn and Yahr (1967) ranged between II and III under regular medication. The motor score of the UPDRS (Fahn and Elton, 1987) was assessed by a movement disorder specialist once ON DBS and once OFF DBS. All patients received dopaminergic medication regularly which was discontinued at least fourteen hours before testing while withdrawal of long-acting dopamine agonists lasted up to thirty-six hours.

Eight healthy male participants comparable to the patients regarding age were measured as control subjects. No participant had a history of any psychiatric or other neurological disease or suffered from dementia as tested by the Parkinson neuropsychometric dementia assessment (PANDA; Kalbe et al., 2008). Two additional patients were excluded from the analysis due to behavioural performance at chance level for both SPT0 and SPT+.

All participants gave their written informed consent prior to participation. The study was performed according to the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty, University of Cologne, Germany (study number: 09–139). Permission to administer radioactive substances was obtained from the regulatory authorities (Bundesamt für Strahlenschutz).

2.2. Stimuli and tasks

We applied the serial prediction task in two versions (SPT0 and SPT+) in which participants had to indicate whether a sequence of 15 stimuli ended regularly or with a switch in the sequence's order (Fig. 1). Stimuli consisted of concentric circles with twelve differing sizes. To allow learning of the sequence, a triplet of three consecutively presented circles (1-2-3) was repeated five times per trial. In half of the trials a novel triplet with switched positions of two circles (1-3-2 or 2-1-3) was presented during the fifth repetition. Then participants had to decide whether the sequence contained a switch or not in a forced-choice-response phase of 3.5 s. Overall, one trial lasted 18.75 s including response and feedback. After feedback a fixation cross was presented for 2 s before the next trial started.

Table 1
Patient characteristics.

Pat	Age (years)	Disease duration (years)	Medication (mg/day)	LED (mg)	Hoehn & Yahr		UPDRS III		Resting tremor		DBS parameters	
					DBS ON	DBS OFF	DBS ON	DBS OFF	DBS ON (left/right)	DBS OFF (left/right)	Left electrode	Right electrode
1	66	15	8 mg ropinirole	160	2	2	17	32	1/0	1/0	4.3 mA, 60 µs, 174 Hz	4.3 mA, 60 µs, 130 Hz
2	62	4	1 rasagiline, 50 piribedil	150	2	2	13	22	0/0	2/0	1: 3.5 V, 90 µs, 130 Hz; 2: 3.5 V, 90 µs, 130 Hz	4.0 V, 60 µs, 130 Hz
3	59	7	1 rasagiline, 10 rotigotine	400	2	2	9	18	0/0	0/0	1: 2.5 V, 60 µs, 130 Hz; 2: 2.5 V 60 µs, 130 Hz	2.1 V, 60 µs, 130 Hz
4	69	11	500 L-Dopa, 50 carbidopa, 200 piribedil, 75 benserazide	700	2	3	29	50	0/0	2/2	1: 2.7 V, 60 µs, 125 Hz; 2: 1,0 V, 60 µs, 125 Hz	2.3 V, 60 µs, 125 Hz
5	54	20	400 L-Dopa, 100 carbidopa, 1.4 pramipexol, 400 amantadine, 800 entacapone	672	2	3	24	46	2/0	4/2	3.0 V, 60 µs, 130 Hz	2.4 V, 60 µs, 130 Hz
6	54	9	10 ropinirole, 1 rasagiline	300	2	3	13	27	0/1	0/3	1: 3.7 V, 90 µs, 150 Hz 2: 3.7 V, 90 µs, 150 Hz	1.5 V, 60 µs, 150 Hz
7	65	18	150 L-Dopa, 8 rotigotine, 75 benserazide	390	3	4	27	54	0/0	2/2	1.5 mA, 60 µs, 130 Hz	2.8 mA, 60 µs, 130 Hz
8	59	24	450 L-Dopa, 125 carbidopa, 800 entacapone, 25 benserazide, 150 amantadine	598,5	2	3	29	51	0/0	1/1	3.0 V, 60 µs, 130 Hz	2.7 V, 60 µs, 130 Hz

Pat. = Patient number; resting tremor = ratings of item 20 of UPDRS III. LED = Levodopa equivalent dose calculated according to Tomlinson et al. (2010).

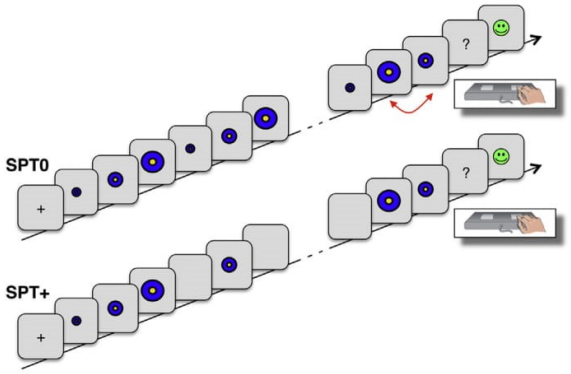

Fig. 1. Set-up of the serial prediction task. SPT0: Participants were instructed to watch a triplet of circles (1st-2nd–3rd), which was repeated five times per trial to allow learning of the sequence. After presentation of a fixation cross (1 s) at the beginning of a trial every circle was presented for 600 ms with an inter stimulus interval of 125 ms. At the end of a trial participants had to respond in a forced-choice-response phase within maximum 3.5 s whether the sequence ended as predicted (50%: 1st–2nd-3rd) or not (25%: 1st–3rd-2nd; 25%: 2nd-1st-3rd). One response button was provided for answering "correct sequence" and one for responding "a sequential switch occurred". Answers were delivered with the right index and middle fingers. A valid feedback indicated a correct, false, or missing answer. SPT+: In modification of SPT0, 1–4 stimuli of every trial were replaced by wildcards: instead of a circle a blank card was shown. The first three stimuli of a trial were not replaced, and never two consecutive stimuli were replaced by wildcards. The last triplet contained maximal one wildcard.

The SPT+ condition was identical to SPT0 except for a parametric modulation of the necessity for internal sequential representations: In SPT+ trials two, three, or four stimuli were replaced by wildcards, i.e., non-informative stimuli that replaced standard circle-stimuli of the sequence.

The SPT+ and SPT0 conditions were presented in blocks of 10 trials each lasting 3.4 min. The experiment contained 12 blocks, always alternating between a SPT0 and SPT+ block. It was inter-individually balanced if the scanning session was started with an SPT+ or SPT0 block.

2.3. Procedure

Participants were measured with positron emission tomography (PET) because of safety concerns regarding functional magnetic resonance tomography in patients with DBS (Finelli et al., 2002; Georgi, Stippich, Tronnier, and Heiland, 2004; Shrivastava et al., 2012).

Every participant attended our study on two consecutive days. On the first day, every subject received training on SPT0 and SPT+ outside the scanner. Furthermore, subjects were asked to complete the PANDA, the Beck depression inventory-II, and the Barratt Impulsiveness Scale Version 11. On the second day the participants attended the experimental PET session. Patients' dopaminergic medication was discontinued at least fourteen hours before testing while withdrawal of long-acting dopamine agonists lasted up to thirty-six hours. The order of DBS ON and DBS OFF measurements was counterbalanced across patients to avoid confounds of the DBS effect with possible training or repetition effects on serial prediction performance. Therefore, the following procedure was applied: In four patients, DBS was switched OFF at least 30 min before the first PET scan and DBS OFF state UPDRS III scores were assessed. Then the patients received six PET scans while performing one task block per scan. The six scans took about 60 min including breaks to allow the radiation to decay between scans. DBS was switched ON again directly after the sixth PET scan. Before starting the seventh scan (after at least 30 min) the patients' UPDRS III scores

were assessed once again to document motor improvement ON DBS. In these patients, DBS stayed ON during the subsequent six PET scans that again lasted about 60 min. In the other four patients, UPDRS III scores were assessed ON DBS and the first six PET scans were performed. Right after the sixth scan, DBS was switched OFF. After at least 30 min, the decay of the stimulation effect was measured with UPDRS III, and the seventh scan was started. DBS remained OFF in these patients until the end of the twelfth PET scan and was switched ON right after the PET scanning. Healthy subjects also performed twelve blocks but were only exposed to six PET scans for reasons of radiation reduction. Because waiting times matching the patients' schedule were applied to the healthy controls, the PET session lasted 150–180 min in total in all participants.

2.4. PET scanning

Regional cerebral blood flow (rCBF) was measured by recording the regional distribution of cerebral radioactivity after the intravenous injection of [^{15}O] water. The PET measurements were carried out using an ECAT EXACT HRRT dedicated brain scanner (CTI Siemens, Knoxville, TN, USA) with a total axial field of view of 252 mm covering the whole brain (Wienhard et al., 2002). Data were acquired in three-dimensional mode. For each measurement of rCBF, 550 MBq of [^{15}O] water were given intravenously as a bolus injection. Each PET scan was started after the participants had performed two trials to make sure that they were involved in the serial prediction task. Emission data were thereafter collected over 45 s. This process was repeated for each emission scan, with 8 min between scans to allow for an adequate decay of radioactivity. All emission scan data were corrected for scattered events and for radiation attenuation by means of a transmission scan taken prior to the first emission measurement. The corrected data were reconstructed using OSEM3D into 207 transaxial images of 256 × 256 pixels (1.218750 mm isotropic voxels). The reconstructed PET images had a resolution of 2.2 mm in the center and 2.5 mm at 10 cm of axis and were regarded to represent rCBF qualitatively.

2.5. Analysis of PET scans

Image processing and statistical analysis of PET scans was conducted using MATLAB version 8.0 (The Mathworks Inc., Natick, MA) and statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK). All PET scans were realigned to the first scan of each session to correct for movements between scans. This resulted in 2 × 6 aligned images for each patient and 6 aligned images for each control plus a mean relative rCBF image compiled for each participant. This mean image was normalized to the standard SPM8 template in MNI space using linear as well as non-linear transformations (Friston et al., 1995) in order to apply this set of normalization parameters to the other scans. The spatially normalized PET images were smoothed using a low-pass Gaussian filter of 12 mm. The resulting voxel size in stereotactic space was 2 × 2 × 2 mm^3.

Finally, analyses of variance (ANOVA) were performed to compare rCBF of patients and healthy controls. Condition related differences in global CBF were removed by treating global activity as a covariate (Friston et al., 1990). Only activations that exceeded a statistical threshold of $p < .05$ (whole brain corrected for multiple comparisons) with a cluster size of at least five voxels were considered significant. In addition, six regions, i.e., left and right SMA, left and right PM and left and right putamen, were selected for region-of-interest (ROI) analyses. Identical to the approach in Schönberger et al. (2015), SMA and PM regions were based on coordinates of maximum activity during performance of SPT0 and SPT+ compared to a control task in young healthy participants (Schubotz and von Cramon, 2004). These peak voxel coordinates were converted from Talairach to MNI space and the resulting coordinates (left SMA: x = − 5, y = − 4, z = 56; right SMA: x = 1, y = 3, z = 53; left PM: x = − 53, y = 2, z = 37; right PM: x = 56, y = 6, z = 25) were used as the centres of spherical volumes of interest with 6 mm radius each. The ROI analysis of putamen activity was based on anatomic masks of the left and right putamen provided by the anatomical atlas (Tzourio-Mazoyer et al., 2002) implemented in the WFU pick-atlas toolbox (Maldjian et al., 2003). The statistical threshold was set to $p < .05$ (small-volume correction) and an extend threshold of at least five voxels was applied.

2.6. Behavioural analysis

The software package SPSS (SPSS Statistic 22.0, IBM, Chicago, IL) was used for statistical analyses. Behavioural performance was assessed by probability of recognition (Pr; Snodgrass and Corwin, 1988) defined as the difference of hit rate and false alarm rate (cf. Schönberger et al., 2013). All participants included in the statistical analysis performed above chance levels (0.22 in SPT0 and SPT+) in at least one version of the task. Note that faster responses do not reflect better performance as participants were instructed to give correct and non-speeded responses. Nevertheless, response times of correct answers were included in the analysis to suspend the possibility of a speed-accuracy trade off. Because of the small sample size, non-parametric tests were conducted. As patients and controls were matched for gender and age, all comparisons between groups were carried out using Wilcoxon tests, i.e., a non-parametric substitute for paired *t*-tests. Correlational analyses were conducted using Spearman's Rho, a rank-based non-parametric measure. Results with p-values < .05 were considered significant.

3. Results

3.1. Behavioural results of the PET study

Wilcoxon tests were conducted comparing age, PANDA, scores in Beck depression inventory-II and scores in the Barratt Impulsiveness Scale Version 11 of patients and controls. No significant differences were found (see Table 2). UPDRS III scores ON DBS (20.13 ± 8.1; mean ± standard deviation) and OFF DBS (37.5 ± 14.4) showed a significant effect of stimulation within the patient group ($Z = 2.53$; $p = .012$).

Performance of all participants was measured in two sessions. Group comparisons were conducted with the controls' data averaged over both sessions as neither performance in SPT0 ($Z = -0.255$, $p = .799$) and SPT+ ($Z = -0.73$, $p = .465$) nor reaction times in SPT0 ($Z = -0.28$, $p = .779$) and SPT+ ($Z = -0.14$, $p = .889$) differed between their two sessions. Average performance rates of controls and patients ON DBS and OFF DBS are depicted in Fig. 2.

While all eight patients performed sufficiently well in SPT0, the individual performance of four patients was below the chance level of

Table 2
Subject demographics and neuropsychological test data.

Characteristic	Mean ± standard deviation		p[a]
	Patients (n = 8)	Controls (n = 8)	
Age, years	61.5 ± 5.1	61.5 ± 6.7	.833
PANDA	27.8 ± 1.8	27.9 ± 1.8	.914
BDI-II	4.3 ± 5.8[b]	5.8 ± 6.6	.686
BIS-11	52.6 ± 7.7[c]	57.9 ± 11.8	.345

PANDA = Parkinson neuropsychometric dementia assessment (dementia cut-off < = 24; max. value = 30); BDI-II = Beck depression inventory-II (depression cut-off > = 19; max. value = 63); BIS-11 = Barratt Impulsiveness Scale Version 11 (scores > = 72 correspond to highly impulsive individuals; max. value = 120).

[a] Significance of differences between groups, computed with non-parametric Wilcoxon tests.

[b] n = 7.

[c] n = 6.

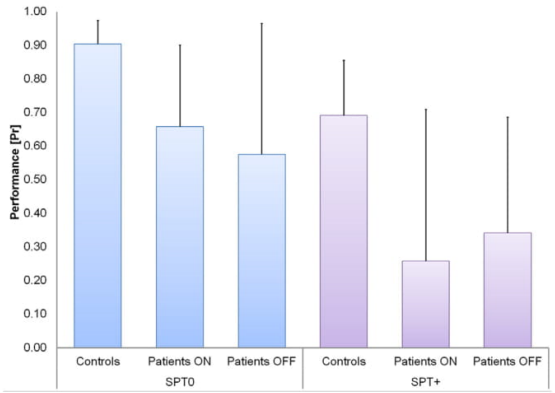

Fig. 2. Average performance in the two applied versions of the serial prediction task (SPT0 = serial prediction task with ongoing stimuli; SPT+ = serial prediction task with wildcard stimuli). Performance is measured as probability of recognition (Pr; Snodgrass and Corwin, 1988); Pr is calculated as the difference of hit rate and false alarm rate. Resulting values represent the ability to correctly differentiate deviant and non-deviant sequences. Values greater than 0.22 indicate performance above chance level. Whiskers depict the standard deviation.

Table 3
Individual performance during SPT0 and SPT+ calculated as probability of recognition.

	Patient		Control	
Number	SPT0	SPT+	SPT0	SPT+
1	0.47	**0.03**	0.97	0.93
2	0.40	**0.04**	0.87	0.50
3	0.97	0.73	0.94	0.87
4	0.27	**0.04**	0.90	0.67
5	0.90	0.64	0.77	0.54
6	0.97	0.80	1.00	0.80
7	0.63	0.30	0.90	0.53
8	0.34	**− 0.17**	0.90	0.70

SPT0 = serial prediction task with ongoing stimuli; SPT+ = serial prediction task with wildcard stimuli; Bold numbers mark performance rates below chance level (< 0.22).

0.22 in SPT+ (Table 3). Because of the poor performance of patients in the SPT+ version, all following analyses that include the patient group are restricted to results of the SPT0 task.

As hypothesized, controls performed significantly better than patients ON DBS in SPT0 ($Z = -2.10$, $p = .035$). Patients' performance OFF DBS showed a trend for deficits in SPT0 ($Z = -1.86$, $p = .063$). In congruence with our previous findings, controls showed higher performance rates in SPT0 than in SPT+ (controls: $Z = -2.53$, $p = .012$). Regarding the effect of DBS, no significant difference between ON and OFF state was found for SPT0 ($Z = -0.63$, $p = .528$).

To estimate the influence of patients' characteristics on their performance, non-parametric correlations were calculated. Age, PANDA scores, UPDRS III scores ON DBS, the years since the diagnosis of Parkinson's disease, and the effectiveness of DBS in ameliorating motor symptoms was correlated with performance in SPT0 in ON and OFF state. The DBS effectiveness was calculated as UPDRS III score OFF minus ON DBS divided by the score OFF DBS (cf. Evans et al., 2006; Weinberger et al., 2006). When testing for intercorrelations of the patients' characteristics, only the duration of Parkinson's disease and the UPDRS III scores ON DBS were found to be correlated ($\rho = .747$, $p = .033$). Results show a significant negative relation of the patients' age and their performance in SPT0 in OFF state, while there was no

Table 4
Correlations of participants' characteristics with performance calculated as Pr (probability of recognition).

Characteristic	Patients		Controls	
	Pr SPT0		Pr SPT0	Pr SPT+
	ON DBS	OFF DBS		
Age	− 0.51	− 0.83*	0.12	0.02
PANDA scores	0.15	0.68	− 0.15	− 0.49
UPDRS III scores ON	− 0.55	− 0.57	–	–
Years since diagnosis	− 0.07	− 0.11	–	–
DBS effectiveness	0.86*	0.74*	–	–

Correlation coefficients computed as Spearman's Rho; *p < .05. SPT0 = serial prediction task with ongoing stimuli; SPT+ = serial prediction task with wildcard stimuli; PANDA = Parkinson neuropsychometric dementia assessment.

significant influence of age in controls (see Table 4). The effectiveness of DBS was positively correlated with SPT0 performance ON and OFF DBS.

No significant differences in response times were found, neither between controls and patients ON DBS in SPT0 (controls: 828 ms ± 181 ms; patients ON: 994 ms ± 609 ms; $Z = -0.14$, $p = .889$), nor between controls and patients OFF DBS in SPT0 (patients OFF: 981 ms ± 626 ms; $Z = 0$, $p = 1$). Furthermore, patients in ON vs. OFF state did not differ in response times in SPT0 ($Z = -0.42$, $p = .671$).

3.2. PET imaging results

Notably, only four patients performed above chance level in SPT+. A statistical analysis based on these four data sets was discarded due to its low statistical power caused by too few independent measurements. Therefore, all eight data sets were used, but restricted to scans during SPT0 performance to ascertain that results reflect brain activity related to successful task performance. Consequently, all reported imaging results and their correlations with performance correspond to the successfully executed SPT0 task. Scans recorded during SPT0 were entered into a general linear model (GLM) comprising patients ON DBS, patients OFF DBS, and controls. Contrasts were calculated comparing controls vs. patients ON DBS, controls vs. patients OFF DBS, and patients ON vs. patients OFF DBS. As there was no baseline measurement included in the experimental protocol, these contrasts contain the pure network effect of stimulation and effects of the evolving resting tremor which was documented in three patients ON DBS and seven patients OFF DBS (see tremor scores in Table 1). Consequently, the stimulation effect is not distinguishable from task activations. To differentiate between patients' and controls' general differences and influences of the stimulation, conjunctions of the comparisons of controls with both patients ON DBS and patients OFF DBS were calculated [(controls vs. patients ON DBS) ∩ (controls vs. patients OFF DBS)]. This conjunction reveals group differences independent of confounding stimulation effects. The influence of DBS is directly tested by comparing patients ON DBS and patients OFF DBS. Resting tremor was previously found to activate a network of cerebellum, primary sensory and motor cortex, cingulate cortex and putamen (Mure et al., 2011) including SMA (Davis et al., 1997; Fukuda et al., 2004). To minimize activations due to resting tremor in all comparisons, the UPDRS III scores of item 20 coding for resting tremor were used as covariates in the following way: the sum of left hand and left foot scores were combined to a left side resting tremor score, and the sum of right hand and right foot were summed to a right side resting tremor score (see Table 1; no patient showed resting tremor of the head). These two measures were included in the GLM as covariates to parcel out the effect of resting tremor on the data. Finally, to test for significant relations between performance and rCBF, the probability of recognition corresponding to each scan was added as

Table 5
Results of the whole brain analysis.

Brain area	BA	H	Peak voxels' MNI coordinates			Peak *t*-value	k
			x	y	z		
(A) Areas hypoactive in patients [(controls > patients ON) ∩ (controls > patients OFF)]							
Thalamus		L	− 20	− 20	2	5.71	21
Medial temporal gyrus	37	L	− 48	− 56	2	5.91	13
Medial temporal gyrus	37/39	R	56	− 64	16	6.91	264
Temporal lobe	37	R	36	− 30	2	5.89	18
		L	− 42	− 30	4	5.47	5
Lingual gyrus/calcarinus/precuneus	18/30	L/R	5	− 56	10	7.33	305
Lingual gyrus	19	L	− 18	− 54	2	5.94	25
Cuneus	18/19	R	2	− 86	16	5.74	160
		L	− 22	− 88	20	6.62	121
		L	− 12	− 84	32	5.27	19
(B) Areas hyperactive in patients [(patients ON > controls) ∩ (patients OFF > controls)]							
Medial frontal gyrus	46/9	L	− 38	46	16	8.866	449
	46 /10	R	38	38	26	6.6375	257
Paracentral lobule	4	R	4	− 30	80	5.8361	79
(C) Areas with increased activity in patients ON (patients ON > patients OFF)							
Thalamus		R	8	− 18	14	5.5247	8
Medial orbital frontal cortex	11	R	20	32	− 20	5.7912	20
(D) Areas with increasing activity in relation to resting tremor (covariate left resting tremor)							
Supplementary motor area	6	L	− 2	0	68	5.5942	15
Inferior frontal gyrus	45	R	50	30	2	5.2773	7
Medial temporal gyrus	39	R	56	− 66	16	5.8124	65
	39	R	42	− 58	22	5.4806	8
(E) Area with increasing activity in relation to performance							
Medial temporal gyrus	39	R	62	− 48	10	5.2127	5

Significant activations at $p < .05$ after FWE correction for multiple comparisons. BA = Brodmann area; H = hemisphere; k = number of significant voxels.

covariate. Whole brain results of all contrasts and covariates are listed in Table 5.

The ROI analysis testing for increased activity in controls compared to patients confirmed the hypothesized hypoactivity in patients' left putamen (peak *T*-value = 4.81; cluster size k = 5), but not in SMA, and no difference of PM activity. Thus, a partial hypoactivity of the motor circuit was found to accompany the patients' deficits in task performance. When testing for increased activity in patients compared to controls, results matched the hypothesized pattern of hyperactivity in the left PM (T = 3.7; k = 41) with no differences of activity in SMA or putamen.

Regarding the stimulation effect, the expected hyperactivity of left PM when OFF compared to ON DBS (T = 4.16; k = 30) was confirmed, while SMA and putamen activity did not change. Patients ON DBS did not show higher activity than OFF DBS in any ROI.

When examining the relation of SPT0 performance and ROI activity, higher probability of recognition was related to increased activity in left PM (T = 3.83; k = 26). This result shows SPT0 blocks with better performance to be related to higher PM activity within each participant, i.e. in both patients and controls. The performance level was not associated with activity in SMA or putamen. No negative correlation of SPT0 performance and activity was found in any ROI. To test if left PM hyperactivity in patients was related to better performance, an additional analysis was conducted. A conjunction of the performance parameter and hyperactivity of patients vs. controls [performance ∩ (patients ON DBS > controls) ∩ (patients OFF DBS > controls)] revealed a significant activation in left PM (T = 3.39; k = 4). On the contrary, a conjunction of the performance parameter and hypoactivity of patients [performance ∩ (controls > patients ON DBS) ∩ (controls > patients OFF DBS)] revealed no significant activity in left PM.

To explore the relation of mean left PM activity to individual performance, which was found to be positive in patients of the fMRI study (Schönberger et al., 2015), the first eigenvariate of this ROI was extracted in SPM (Friston et al., 2006) to correlate the estimated mean rCBF with the individual probability of recognition of each participant (see Fig. 3). The resulting correlations demonstrate in which way the participants' mean activity in PM was related to their overall performance. While the controls' SPT0 performance showed descriptively a positive relationship with left PM activity ($\rho = .561$, $p = .148$), the opposite was found in patients ON DBS ($\rho = -.683$, $p = .062$). The correlation was not significant in patients OFF DBS ($\rho = -.361$, $p = .379$).

3.3. Comparison of the PET sample's disease severity with previous samples

It is noteworthy that only half of the patients performed above chance in the SPT+ task, as the previous studies found 27 of 36 PD patients to pass the SPT+ (Schönberger et al., 2013, 2015). To investigate reasons for the patients' poor SPT+ performance, characteristics of the current study's participants (labelled PET sample in the following) were compared to the previous samples' data (see Table 6). Mann-Whitney *U* tests showed the UPDRS III scores OFF DBS in the PET sample to be higher than the scores of patients OFF dopaminergic medication in the fMRI study (Schönberger et al., 2015) and, by trend, in the behavioural study (Schönberger et al., 2013). Therefore, the data suggest that the PET sample's more severe motor impairment might explain the striking deficits in task performance.

4. Discussion

To examine the effect of DBS on performance in a cognitive task we measured patients suffering from PD and matched healthy controls with PET while subjects performed a serial prediction task. Notably, the serial prediction task is a purely cognitive task, as participants do not give speeded responses, but evaluate the serial structure of visual events. This perceptual sequence processing recruits the SMA and PM in healthy individuals (Schubotz and von Cramon, 2003; Schubotz, 2007) and in PD patients (Schönberger et al., 2015). We hypothesized that performance would be impaired in patients (hypothesis 1) in concurrence with hypoactivity of the mesial motor loop, i.e., SMA and

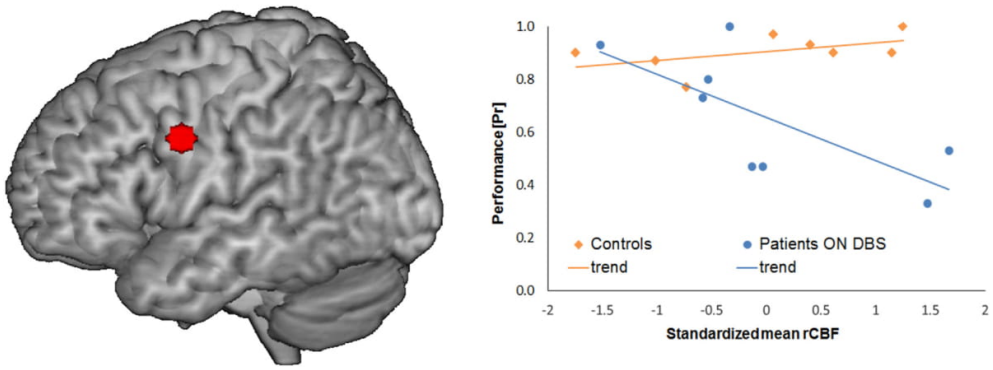

Fig. 3. Scatter plots show the relation of performance in serial prediction (SPT0) and mean regional cerebral blood flow (rCBF) in the left PM ROI in healthy controls and patients ON DBS. Spearman's Rho, a rank-based non-parametric measure, shows a significant correlation of performance and rCBF in patients ON DBS.

Table 6
Comparison of patients' characteristics of the current and previous samples.

Characteristic	Mean ± standard error of the mean			p[a]	
	PET sample (n = 8)	fMRI sample (n = 16)	Behav. sample (n = 20)	PET vs. fMRI	PET vs. Behav.
Age, years	61.5 ± 1.8	60.1 ± 2.1	57.9 ± 1.5	.759	.169
PANDA	27.8 ± 0.6	25.8 ± 0.9	25.7 ± 0.7	.370	.089
UPDRS III ON	20.1 ± 2.9	15.3 ± 1.5	17.6 ± 1.9	.159	.373
UPDRS III OFF	37.5 ± 5.1	23.6 ± 2.7	26.6 ± 2.0	.038	.059

PET sample = patients of the current study; fMRI sample = patients of the study described in Schönberger et al. (2015); behav. sample = patients of the study described in Schönberger et al. (2013); PANDA = Parkinson neuropsychometric dementia assessment. In the behavioural and the fMRI sample UPDRS III ON refers to motor scores under normal medication and UPDRS III OFF to motor scores after withdrawal of medication. In the PET sample, UPDRS III ON refers to motor scores ON DBS after withdrawal of medication, and UPDRS III OFF refers to motor scores after withdrawal of medication and OFF DBS.

[a] Significance of differences between groups, computed with Mann-Whitney *U* tests.

putamen (hypothesis 2). Additionally, we expected to find PM hyperactivity in patients, especially without deep brain stimulation (hypothesis 3). We concentrated on a ROI analysis of SMA, putamen, and PM driven by these hypotheses.

Supporting previous results (Schönberger et al., 2013, 2015), PD patients showed the hypothesized impaired serial prediction performance when compared to healthy controls (hypothesis 1). These deficits were unexpectedly large, as only half of the patients performed above chance level in the task version with increased load on the mesial motor loop (i.e., SPT+). Therefore, the results were limited to the (easier) task version (i.e., SPT0) with continuous stimuli that all participants performed successfully. The deficit in this task was accompanied by hypoactivity of putamen in patients compared to healthy controls, consistent with the expected dysfunction of the motor loop (hypothesis 2). As tremor scores were related to heightened activity of SMA located right dorsal to the area used in the ROI analysis (Table 5), the patients' resting tremor possibly interacted with sequence related processing, preventing to find hypoactivity of SMA as well. Importantly, we rather underestimated the patients' hypoactivity found in putamen because resting tremor activates the dorsal putamen (Mure et al., 2011). Finally, we found more activity in left PM in patients compared to controls and in patients OFF compared to ON stimulation, thereby supporting hypothesis 3.

Unexpectedly, there was no significant improvement of serial prediction performance ON compared to OFF DBS. This may be due to low statistical power because of the small sample size or other limiting factors such as the variability in individual medication and levodopa equivalent dose (see Table 1). However, DBS significantly reduced motor impairment, and therefore possibly was not as effective in restoring serial prediction performance as medication in our previous studies. Notably, DBS effectiveness in ameliorating motor symptoms was positively correlated to task performance in all conditions. Patients who show a good levodopa response and few non-responsive motor symptoms benefit more from DBS (Bronstein et al., 2011), suggesting that patients with a general loss of sensitivity to treatment performed poorly in serial prediction. We therefore argue that the cognitive performance level is attributable to patients' disease progression which causes deficient sequence processing normally provided by the SMA. Consistently, the current sample was more affected OFF DBS than the patients OFF medication in our previous studies.

Although there was no apparent effect of DBS on performance, DBS influenced activity in the motor loop, as patients ON DBS showed less activity of the left PM than patients OFF DBS. Therefore, the lack of performance differences OFF vs. ON DBS may also be related to the involvement of compensatory resources provided by PM hyperactivity when OFF DBS. Notably, PM activity showed specific correlations with serial prediction performance, thus rebutting the possibility that PM hyperactivity was caused by resting tremor: blocks with better performance were correlated to higher levels of PM activity in all participants. In contrast, the general level of PM activity showed a group specific pattern. While well performing controls tended to show more left PM engagement, patients performed the worse the higher levels of left PM activity they exhibited under stimulation (see Fig. 3). This pattern may clarify why half of the patients failed to perform the more difficult task version that challenges the mesial motor loop: The most parsimonious explanation is that DBS could not amplify the patients' severely affected motor loop activity to the required performance level, wherefore PM hyperactivity under these more challenging task conditions could not restore performance. In line with this interpretation, the extent of PM engagement differs from the previous fMRI study which found hyperactivity only when both the load on the mesial motor loop was increased and patients' dopaminergic medication was discontinued (Schönberger et al., 2015). In the current sample, PM hyperactivity was observed in the easier task version (i.e., SPT0) and in patients compared to controls independent of stimulation. This suggests that patients engaged in PM activation earlier, most likely because of advanced dysfunction of the motor loop. Notably, we previously found that the ability to increase SMA activity was related to good performance when internal sequence representation was challenged (Schönberger et al., 2015). This suggests that PM hyperactivity may preserve performance only for moderate PD stages with sufficient SMA engagement, while

compensation via PM involvement is no longer possible in more severe stages, also reflecting that compensatory mechanisms are limited.

Restrictions of compensation via increased activation have been described for the aging brain (Park and Reuter-Lorenz, 2009; Reuter-Lorenz, 2002; Steffener et al., 2009) and have also been observed in PD patients in a motor sequence learning task with different levels of task difficulty depending on sequence length (Mentis et al., 2003a, 2003b). In the latter study PD patients who showed task performance equal to controls exhibited an intensified activation of the same network including premotor and other frontal areas. Particularly, the left hemisphere was additionally activated compared to controls so that the patients showed almost normal performance when task difficulty was moderate. However, PD patients failed to learn long sequences that required bilateral activation in healthy participants. A further study implementing the same task suggested that the ability to compensate through elevated task-specific activation diminished with disease progression (Carbon et al., 2010), resulting in decremented task performance over time. These findings may parallel the limits of compensation via PM hyperactivity that were evident during serial prediction.

Regarding the influence of DBS on serial prediction, the question arises if DBS would have significantly improved performance in a less severely affected sample. It is plausible that DBS is less effective than medication in modulating task performance independent of the disease's progress, as shown in other cognitive tasks (Carbon et al., 2003). To answer this question, further research is needed, ideally comprising a group of DBS patients and non-DBS patients with similar disease status or comparing the effect of both therapies on serial prediction performance in one sample of DBS patients. Nevertheless, we replicated our previous results in the current sample of DBS patients, as we found the expected co-occurrence of hypoactivity in the putamen and cognitive impairments of PD patients. Furthermore, a compensatory involvement of the lateral premotor cortex was shown. We take the results to support our assumption that PD patients' deficits in the prediction of serial stimuli are due to motor loop dysfunction and that PM hyperactivity provides a compensational mechanism that is limited by disease progression.

To conclude, our results point to a contribution of premotor functions to some cognitive abilities of PD patients. Thus, cognitive deficits in PD are not exclusively caused by affected prefrontal loops but can be more appropriately explained by the interplay of multiple mechanisms including motor loop dysfunction. An impairment in perceptual sequence processing, as measured in the serial prediction task, may produce deficits in various cognitive tasks that require the processing of serial information and the prediction of future events. Therefore, it is worth considering to which degree premotor engagement can be advantageous in other cognitive tasks not only as a motor component, but as an interface with other frontal areas.

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3 DISCUSSION

Challenging the common presumption that alterations in motor loop functionality only affect motor behaviour, we expected PD patients to suffer from cognitive impairment because of premotor dysfunction. Furthermore, the possibility of lateral premotor compensation of mesial motor loop dysfunction in a cognitive task was examined in this work. For this purpose, PD patients and healthy control participants were tested in the SPT which requires to monitor a sequence of sensory stimuli in order to detect violations of the sequence's serial structure. The degree to which the participants had to rely on an internal presentation of the sequence was manipulated by introducing two versions of the SPT, i.e., the SPT0, and the SPT+ which demands higher involvement of the SMA.

The two tasks were implemented in three studies: Study 1 examined behavioural deficits of the patients and was complemented by Study 2, an fMRI study, and Study 3, a PET study, to identify underlying brain activity. Across studies, a total of 44 PD patients of akinetic-rigid or mixed subtype was included and compared to the same number of healthy control participants. The influence of motor loop status was investigated by comparing patients under normal treatment and after withdrawal of treatment, i.e., "on" versus "off" medication in the behavioural and the fMRI study and "on" versus "off" DBS in the PET study. Healthy controls were compared to patients under treatment to look at the general influence of the disease on performance and brain activity.

The implications of the studies will be discussed in the following in four main sections. First, the results will be summarised and interpreted in relation to this work's research questions. To evaluate the results, limitations and ideas for future studies that might answer remaining questions are embedded in this section. Second, the main findings will be related to recent research and condensed into conclusions about the contribution of the basal ganglia and the premotor cortex to cognition in PD. In this context, it will be discussed which impairments might be related to motor loop dysfunction beyond serial prediction and how the PM and prefrontal areas may interact in cognitive tasks in PD. Third, the clinical relevance of the results and directions for future research will be outlined. Final conclusions regarding the significance of the results are drawn in the last section.

3.1 Evaluation of findings

In general, most results correspond to the expected differences between groups and SPT conditions and support our assumption that the degree of premotor involvement determines the patients' performance in the SPT. The paradigm was successfully implemented and elicited the expected brain activity comparable to former studies using the SPT (e.g., Schubotz and von Cramon, 2001a, 2002a, 2002b, 2002c). That is, all groups of participants in the fMRI study showed higher activity in the SMA and PM, the inferior parietal lobule and the superior temporal gyrus during the SPT compared to the cognitive control task. Furthermore, the peak of PM hyperactivity in the fMRI study was found in the superior ventral PM that was previously shown to be most active during serial prediction of visual sequences (Schubotz & von Cramon, 2002c).

Nevertheless, some limitations must be considered. In the PET study half of the patients failed in the SPT+ so that the analysis had to be restricted to the SPT0. Therefore, not all hypotheses could be tested in this study which furthermore only included a small number of participants. Generally, the sample sizes are rather small, so that only medium to large effects could be detected. Additionally, the repeated measures design using matched controls for within-group comparisons increases the power of statistic comparisons but concurrently limits the generalisability of results. However, the results of all studies complement each other and thus reduce the probability of incidental findings. Despite a few inconsistencies between the studies and some unexpected additional findings, the main results of the behavioural study were replicated in both ensuing studies and the PET study's results resemble the main fMRI results. Therefore, the studies' findings are not listed in succession but are allocated corresponding to this thesis's research questions, i.e., each of the following three sections is organised as an comprehensive answer to one of the questions.

3.1.1 Patients are impaired in serial prediction because of premotor dysfunction

The first aim of this work was to examine whether PD patients show serial prediction deficits and to test if observed deficits are directly related to motor loop dysfunction. Based on the literature presented in the introduction we assumed patients to show performance deficits in the SPT compared to healthy control participants matched regarding age and cognitive abilities (hypothesis 1.1).

Indeed, patients performed significantly worse than controls or showed a trend towards deficits in all three studies. Corroborating that these deficits depend on motor loop dysfunction, we found a significant influence of antiparkinsonian treatment on serial prediction performance in the behavioural and the fMRI study (hypothesis 1.2). In contrast, DBS showed no significant influence on SPT0 performance in the PET study (hypothesis 1.8). Probably, there was no detectable influence of DBS on serial prediction because of the small remaining sample size and the resulting power issues. Furthermore, the effect of practice possibly interfering with the DBS effect could not be controlled in this study because of the restriction to non-parametric tests. Therefore, it cannot be decided whether DBS benefits SPT performance based on the measured data. Nevertheless, the Study 1 and 2 demonstrate that serial prediction performance is directly influenced by the degree of motor loop functionality.

Furthermore, we assumed that a direct relation of motor loop status and cognitive impairment should result in a negative correlation of SPT performance and motor symptom severity (hypothesis 1.3). As expected, a negative correlation of motor impairment “on” medication with SPT performance was found in the behavioural study. Notably, there was no correlation of motor symptom severity with performance in the cognitive control task and no relation of cognitive ability and SPT performance. These results corroborate our assumption that motor loop dysfunction is the mutual cause of serial prediction deficits and motor impairment. However, the correlation of performance with motor impairment was descriptively negative, but not significant in both brain imaging studies. Instead, in all studies the age of patients had a significant influence on their SPT performance, especially after withdrawal of treatment. On the one hand, age might be indicative of disease specific factors, like early disease onset or treatment duration influencing the motor loop’s degree of deterioration. On the other hand, it might indicate the influence of unspecific factors of the aging process as healthy participants in the fMRI study also performed the worse, the older they were. Future studies could therefore examine the relations of relevant clinical features more carefully. Especially motor impairment, the age at disease onset, disease duration, the significance of dopamine replacement therapy as opposed to other drugs, the efficiency of treatment and some specific cognitive functions like set shifting could be included in future analyses to better understand their effects on serial prediction deficits. In the current studies these aspects were substantially correlated and could not be parcelled out, but a large sample including a broad variety of patients could clarify the contribution of each factor.

Despite the remaining uncertainty about the interplay and effect of different disease characteristics, we gained direct evidence of motor loop dysfunction in both brain imaging

studies. We expected that performance deficits would co-occur with hypoactivity of the SMA and the putamen in patients compared to healthy controls (hypothesis 1.4a) and in untreated compared to treated patients (hypothesis 1.4.b). Supporting the first part of this hypothesis, we found hypoactivity of the SMA and the putamen in patients compared to controls in the fMRI study. This hypoactivity also occurred during the cognitive control task, which presented task irrelevant serial information. Importantly, patients showed no behavioural deficits compared to controls in this task. Therefore, motor loop hypoactivity was not specific to serial prediction but still affected only serial prediction performance, whereas the control task's performance most certainly depended on other brain areas. Accordingly, significant positive correlations of the level of SMA activity and the patients' serial prediction performance, but not their control task performance, were found (hypothesis 1.7). Furthermore, no prefrontal hypoactivity was observed in the fMRI and PET study (hypothesis 1.6), overall confirming that the serial prediction deficits were caused by an affection of the motor loop independent of prefrontal dysfunction.

However, these results must be put into perspective, as unexpectedly no effect of medication or DBS status on motor loop activity could be observed (hypothesis 1.4b). Furthermore, in the PET study, the putamen but not the SMA of patients was hypoactive compared to controls. In the case of the latter study, the small dataset and restricted analyses may be responsible for the null findings. Further studies with a bigger sample could include DBS patients and medicated patients to observe differential influences of treatments on serial prediction. These results would add to our understanding of the mechanism of action of DBS and its effect on premotor activity. If no DBS effect would be observed despite an effect of medication, this could underline the notion of Wichmann and DeLong (2016) that DBS does not directly facilitate proper information processing, but rather blocks the influence of noisy and disruptive input from the basal ganglia to downstream cortical and subcortical areas.

In the fMRI study, the relation of SMA hypoactivity with disease severity was in line with our expectations: SMA hypoactivity in patients was the more pronounced during serial prediction, the higher a patient's motor impairment was despite medication (hypothesis 1.5). This result shows that the level of SMA activity depended on the individual degree of motor loop affection, and therefore probably was disease related. Nevertheless, it remains puzzling that the significant influence of medication on performance was not reflected in activity changes within the mesial motor loop. Possibly, including the effect of practice as a confounding factor in the fMRI analysis might have revealed a significant treatment effect. Instead, to avoid overfitting of the general linear model, only a distinct analysis was conducted that made sure

that practice effects did not accidentally produce the observed differences in brain activity. To circumvent these problems, further studies should apply a different training scheme that prevents the seemingly large practice effects and their unfortunate interaction with medication and DBS status.

Altogether, the data clearly show that PD patients are impaired in serial prediction. In addition, most behavioural and brain imaging results substantiate our assumption that these serial prediction deficits are independent of the patients' general cognitive abilities but have an intimate relation to motor loop dysfunction. This interpretation is further supported by the second investigated aspect that will be presented in the following section.

3.1.2 Internally guided predictions are more affected than externally guided predictions after withdrawal of medication

The second focus of our research was to investigate if PD patients show more serial prediction deficits when they are forced to use internally driven processing that is facilitated by the SMA. Based on the assumption that the mesial motor loop is most affected in PD, we expected a drop of performance in the SPT+ compared to the SPT0 condition in comparison to healthy controls (hypothesis 2.1a) and after intermission of treatment (hypothesis 2.1b).

All participants were less likely to correctly identify deviant sequences during the SPT+ than during the SPT0 in all three studies. Unexpectedly, there was no significant interaction of group membership and task version in the behavioural and fMRI study (hypothesis 2.1a), that is, controls showed a similar decrease in performance in the SPT+ as patients "on" medication. In the behavioural study, patients "on" medication only performed worse than controls in the SPT0, but not the SPT+ task. On the contrary, in the PET study half of the patients could not accomplish the SPT+ while healthy controls performed sufficiently well. The patients' inability to succeed in the SPT+ possibly resulted from a combination of severe motor loop affection and the fact that they were measured "off" medication even when their DBS was turned on. These results indicate that the effect of missing stimuli in SPT+ trials critically depends on the level of preserved motor loop function. Thinking one step further, the SMA function of most medicated patients in the first two studies probably was still sufficient to fulfil the increased internal processing requirements. In line with this assumption, patients in the behavioural study were less probable to give correct responses in the SPT+ after withdrawal of medication (hypothesis 2.1b). Furthermore, in the fMRI study better performance of patients in the SPT+ was related to a higher level of SMA activity during this task. Higher performance rates were

additionally associated with an increase in SMA activity during the SPT+ compared to the SPT0 despite withdrawal of medication. That is, the more patients could level up SMA activity although they were "off" medication, the more often they decided correctly about the sequences. Importantly, the ability to increase SMA activity despite intermission of medication was the higher, the less severe a patient's motor impairment was.

To conclude, we got mixed results regarding SPT+ performance that can be resolved by taking different gradients of mesial motor loop dysfunction into account. Hypoactivity of the SMA may not always have resulted in SPT+ deficits, because in some patients SMA activity was not degraded during the SPT+ compared to SPT0 but even elevated. Importantly, this interpretation suggests that SMA activity could be preserved in some patients despite intermission of treatment. This seems plausible when considering that the PM came into play after withdrawal of medication and possibly interacted with the SMA, as will be explained in the next section.

3.1.3 There is compensatory hyperactivity of the lateral premotor cortex with limited scope

The third aim of this work was to investigate the influence of the PM on serial prediction. Based on evidence of compensatory PM hyperactivity in motor tasks, we expected patients to show higher PM activity compared to healthy controls (hypothesis 3.1a) and after withdrawal of medication (hypothesis 3.1b), especially in the SPT+ condition. It was further hypothesised that, if PM hyperactivity represents a compensatory mechanism, the task performance of patients would be preserved despite SMA hypoactivity and PM activity should be positively related to performance scores (hypothesis 3.2).

Indeed, both brain imaging studies detected PM hyperactivity in the left hemisphere, but under different circumstances. In the fMRI study, no PM hyperactivity was found compared to healthy controls. However, the left PM was found to be specifically more active during SPT+ than during SPT0 performance in patients "off" compared to "on" medication, that is, when SMA function was important, but limited. Patients gave less correct responses in this situation, but their performance may have decreased even more without PM involvement, as indicated by significant positive correlations of performance and PM activity. Individuals under normal medication performed better in the SPT+ if they exhibited higher levels of PM activity. Furthermore, higher PM activity was correlated with success in both serial prediction tasks after omission of medication. These associations demonstrate that PM hyperactivity did not simply index the patients' motor loop dysfunction but probably effectively helped in both internally

and externally driven processing of sequential information. The observed PM involvement can thus be interpreted as compensatory mechanism.

Nevertheless, this strategy seems to be variable and dependent on individual patient characteristics. First, it seemingly did not come into play to the same extend in the behavioural study, where patients performed worse in the SPT+ version after withdrawal of medication. Second, patients in the PET sample showed more, but less effective PM engagement. Probably due to proceeded motor loop affection, patients exhibited hyperactivity of the left PM compared to controls and "off" compared to "on" DBS even in the SPT0. Intraindividually, higher activity of the PM was related to better serial prediction performance, but interindividually, patients with less PM involvement were high performers. These correlations should be interpreted with caution because of the small sample size. Still, they shed light on possible limitations of compensatory PM involvement that are also evident in the poor SPT+ performance of this more severely affected sample of patients. Future studies should therefore investigate if the compensatory effect of PM involvement depends on sufficient residual capacity of the mesial motor loop and if the SMA is directly provided with additional PM input. As PM projections are not only part of the motor loop, but also of the dorsolateral prefrontal loop, the compensational effect of the PM may also be achieved via the latter circuit. This question can be resolved by directly testing the connectivity of the putamen, SMA and PM in PD patients at different disease stages.

Furthermore, the prefrontal areas' contribution should be investigated in more detail, as PM hyperactivity did not occur independent of prefrontal activity. In the fMRI study, the right dorsolateral prefrontal cortex was found to accompany PM hyperactivity. Patients in the PET study showed extensive bilateral hyperactivity in the prefrontal cortex compared to controls. These results are particularly interesting because studies on PD cognition commonly find the opposite pattern, i.e., prefrontal hypoactivity in PD patients. On the one hand, this supports our conclusion that serial prediction deficits were most probably caused by affection of the motor loop independent of prefrontal dysfunction which would be marked by prefrontal hypoactivity. On the other hand, the observation of prefrontal hyperactivity points in a new direction: To what extend can the prefrontal cortex support premotor function in different stages of the disease? This issue will be discussed in the context of the interaction of premotor and prefrontal dysfunction in PD (see chapter 3.2.3). Beforehand, the implications of motor loop dysfunction as the neural underpinning of serial prediction deficits will be discussed to work out the contribution of the basal ganglia and premotor areas to cognitive tasks in PD.

3.2 Contribution of the motor loop to cognitive deficits in Parkinson's disease

The theme of prediction deficits has been recurring throughout the PD literature in the context of motor planning and execution. Flowers (1978) proposed that PD patients are more reliant on currently available sensory information than healthy participants, because they make less use of predictions when controlling their actions. Since then, multiple studies of ocular motor functions (Bronstein & Kennard, 1985; Crawford, Goodrich, Henderson, & Kennard, 1989; Helmchen et al., 2012; O'sullivan et al., 1997) and serial motor learning (e.g., Clark et al., 2014; Siegert, Taylor, Weatherall, & Abernethy, 2006; Smith & McDowall, 2004) found that PD patients benefit less from predictive serial information. For example, one study found that patients were impaired in learning sequential information in order to predict target locations (Jackson, Jackson, Harrison, Henderson, & Kennard, 1995). Our results show that prediction deficits also occur in processing serial visual information independent of motor execution and that these difficulties are related to changes of activity in the motor loop. Why exactly are PD patients impaired in serial prediction? Which cognitive difficulties might patients face because of motor loop affection that are so far unnoticed? These questions will be approached in the following by describing in detail how serial prediction deficits are related to dysfunctions of the basal ganglia and the premotor areas (chapter 3.2.1), by exploring the general contribution of the motor loop's structures to cognition in PD patients (chapter 3.2.2), and by discussing the juncture of prefrontal and premotor loops in cognitive tasks (chapter 3.2.3).

3.2.1 Serial prediction deficits in Parkinson's disease

What is difficult about serial prediction for patients with PD? The SPT requires to learn serial contingencies between consecutive stimuli and to use this information to track sequence violations. In other words, participants have to identify improbable events in the context of the current trial based on the preceding sensory input. Notably, sequence learning and prediction are not necessarily separate functions but may rather be result of the same underlying principle facilitated by the motor loop. For example, if a participant has to figure out that there is a recurring order of medium, large and small circles, it is the continuous comparison and weighting of predicted and incoming sensory states that allows for the formation of hypotheses regarding the most probable sequential structure in the first place. Therefore, learning of a sequential pattern must involve a comparison of actual input and input to be expected on the

basis of former experience, i.e., making predictions and utilizing prediction errors for the adjustment of further predictions.

As described in the introduction of this work, the basal ganglia are perfectly designed to bind sensory stimuli and motor responses together that regularly follow one another (Berns & Sejnowski, 1998; Graybiel, 1998) so that in cooperation with the premotor and motor cortex actions can be readily selected based on the given context and learning history (Redgrave et al., 2010; Wu & Hallett, 2005). Our results suggest that the motor loop enables not only the representation of sensorimotor dependencies but also maps the temporal dependencies of consecutive sensory events, which allows to predict recurring sensory input. This is not surprising when acknowledging that the premotor cortex is not exclusively concerned with sensorimotor processing. Although the premotor areas are classically conceptualised to carry out action selection, planning and preparation, these functions are only part of their repertoire. As shown by the work of Schubotz and von Cramon (Schubotz, 2004, 2007; Schubotz & von Cramon, 2003), the premotor areas do represent information in motor terms, i.e., in reference to sensorimotor transformations, but nevertheless process sequential patterns in general if they unfold in the range of seconds. This is not only the case because actions are sequential in nature, but also because all dynamic features of our environment can be action relevant, so that even abstract changes of sensory properties trigger premotor responses (Schubotz and von Cramon, 2002b).

Considering that premotor areas map dynamic sensory information, how exactly can perceptions be predicted via the motor loop? What processes do the premotor areas and the putamen contribute to serial prediction, respectively? Notably, basal ganglia function cannot be easily distinguished from cortical involvement, especially when drawing on studies with PD patients. The parkinsonian state is characterised by deteriorated output of the basal ganglia to its cortical partners so that the whole information cycle within the cortico-basal ganglia-thalamo-cortical loops is disturbed (Turner & Desmurget, 2010; Wichmann & DeLong, 2016). Circumventing this confound, Turner and Desmurget (2010) reviewed studies that recorded local neural activity or tested focal lesions in the basal ganglia. They point out that learning of new movement sequences is severely impaired after lesioning the output structures of the basal ganglia, whereas the execution of over-learned or sensory guided sequential movements is slowed and hypometric, but otherwise intact. Therefore, it seems more accurate to characterise basal ganglia processing as a mechanism that supports learning and retrieving sequential associations, while the cortex stores sequential knowledge. Accordingly, Nachev, Kennard and Husain (2008) reviewed several lines of research on the SMA and suggested that its general

function is to map conditional dependencies of actions, amongst them sequential information. Single cell recordings also illustrate a primary role of the SMA in representing sequence information during the performance of learned serial movements (Shima & Tanji, 2000).

The interaction of the putamen and the SMA during serial prediction can be exemplified in different frameworks emphasising different functional aspects of the basal ganglia. Bischoff-Grethe, Crowley and Arbib (2002) propose that during the execution of a motor sequence the putamen helps the SMA to manage the temporal dimension of the sequence. The basal ganglia inform the cortex about the next motor state to be performed via the direct pathway, while the indirect pathway withholds the upcoming state as long as the current movement is in progress. As soon as the movement is finished, the SMA switches to the next state that typically was previously inhibited by the indirect pathway. If the interplay of the direct and indirect pathway is disturbed, information is not passed through with accurate timing and motor execution is stagnant and delayed, resulting in bradykinesia. Interpreting our results in this framework, PD patients might be impaired during serial prediction because the temporal coordination of processing current and upcoming states breaks down. As a consequence, representations of transitions between stimuli might overlap in the temporal domain and impede a clear representation of the stimulus order. Thus, PD patients might be especially impaired during prediction without continuous serial input, because it is more difficult to determine the timepoint at which to expect the next sensory input and thus to build a proper internal representation of the sequence. This interpretation is supported by literature that establishes the SMA and basal ganglia as important drivers of time perception and time processing in the range of seconds (e.g., Meck, Penney, & Pouthas, 2008).

From another perspective, prediction deficits might be less a temporal problem but rather the result of a reduced ability of the basal ganglia to filter simultaneous cortical information and to enforce specific cortical activity. Graybiel (1998) proposed that the basal ganglia's architecture allows to detect recurring patterns of cortical input within the plethora of competing cortical information and to distinguish "real" neuronal patterns from incidental co-occurrences. This capacity gives rise to cortical representations of sequences, because information about inner and outer states gets associated with states that repeatedly succeed within a time window up to several seconds. Indeed, most classical and more recent proposals converge on the assumption that a "filtering process" during learning, that equates to a "selection and amplifying process" during the retrieval of memorised patterns, probably is the core computation provided by the basal ganglia pathways (Beeler et al., 2013; Florio et al., 2018; Grillner, Robertson, & Stephenson-Jones, 2013; Hikosaka, Ghazizadeh, Griggs, &

Amita, 2018; Redgrave et al., 2010). A study that directly tested the effect of stimulus predictability on striatal and cortical activity revealed that the degree of striatal trial-by-trial prediction error activity regulated the connectivity of visual and premotor areas and thus mediated the influence of surprising stimuli on premotor activity (den Ouden, Daunizeau, Roiser, Friston, & Stephan, 2010). Therefore, when the balance of activity in the indirect and direct pathway is disturbed, the basal ganglia cannot efficiently support building associations between consecutive stimuli and thus new sequences cannot be accurately represented in the cortex.

Based on these concepts, serial prediction deficits of PD patients could be modelled as follows: During serial prediction, the structure of a new trial is unknown in the beginning. Information about the relevant stimulus property, object size, and its changes is represented in the PM in terms of sensorimotor transformations, namely expansion and contraction movements of the mouth or hand (Schubotz, 2007). This information enters the putamen via the motor loop next to various information about the status of the body and environment and previous states. If dopamine levels are adequate, task irrelevant input is blocked via the indirect pathway so that only relevant information about changes in stimulus size is transferred to the SMA via the direct pathway. Consequently, transitions between consecutive stimuli and the position of each stimulus within the sequence can be represented in the SMA. This developing sequence representation constitutes the basis for predictions of upcoming stimuli and allows to notice sequence violations at the end of a trial by comparing expected to actual input. Of course, in both healthy controls and PD patients, filtering relevant information and detecting recurring patterns is more difficult in the task version with missing stimulus information. When the filtering capacity of the basal ganglia is severely disturbed because of the manifesting dopaminergic shortage after withdrawal of medication, the performance of PD patients drops significantly, especially in this task version. However, if the SMA is not too severely affected, hyperactivity of the PM can partly overcome the inefficient basal ganglia processing, possibly because it provides direct access to the relevant stimulus dimension whose monitoring can be implemented via the SMA. This interpretation accounts for our finding that sufficient SMA function is a prerequisite for good serial prediction performance and necessary for successful compensation via increased activity of the PM. Notably, the left PM, which was found to be hyperactive in our studies, is more involved in learning new motor sequences while the right PM is rather activated during later learning stages (Schubotz, 2004). It will be discussed in the following section which cognitive or perceptual tasks might also depend on sufficient motor loop function.

3.2.2 Other cognitive deficits related to motor loop dysfunction

Are there any difficulties in PD related to motor loop affection that have been overlooked so far? Based on the serial prediction results and the functions of the motor loop discussed above, it can be assumed that PD patients are impaired in all tasks that require to process and predict dynamically changing sensory information. These deficits should be twofold: First, the basal ganglia's filtering mechanism that supports building sequence representations in the SMA should be disturbed. Therefore, patients should learn new serial patterns at lower rates than healthy controls. Second, patients should be impaired in the automatic retrieval of previously acquired knowledge about specific patterns because the selection and enforcing of sequence representations via the basal ganglia is weakened. These impairments should be the more pronounced the more the SMA is involved under healthy conditions (i.e., the higher the predictability of the processed patterns is), but the less severe, the easier the mapping of sensory parameters via the compensating PM is.

These assumptions apply to all movements, as actions involve predictions of future sensory states including proprioceptive, but also visual, tactile and auditory information (Wolpert & Flanagan, 2001). Accordingly, PD patients are impaired in implicitly learning serial movement patterns and have difficulties during the execution of automatic movements (see chapter 1.2.2) but are less impaired under visual or auditory guidance (see chapter 1.3.3). Independent of motor output, the detection and monitoring of predictable changes in visual, auditory and proprioceptive information should also be impaired. Indeed, PD patients are less sensitive in their conscious perception of proprioceptive signals, e.g., they recognise passive limb movement later than healthy controls (Konczak et al., 2009). This deficit may be related to the decreased capability of the basal ganglia to detect continuous patterns in sensory input. In the visual domain, motor loop dysfunction should generally affect the processing of predictable patterns in the environment including movement trajectories of objects and animals. Indeed, an impairment of visuospatial functions is a common aspect of MCI (see chapter 1.1.2) that affects all stages from altered retinal to higher cortical processing and includes worsened motion perception (Weil et al., 2016). The neural causes of visual deficits are diverse and to the author's knowledge no study so far directly investigated the neural underpinnings of deteriorated motion perception in PD patients. Nevertheless, recent studies found that PD patients are impaired in recognising biological motion (Jaywant, Shiffrar, Roy, & Cronin-Golomb, 2016; Kloeters et al., 2017). Furthermore, patients segment actions more variably than

healthy controls after medication withdrawal (Schiffer et al., 2015) which points to a role of the motor loop in higher level motion perception and action observation.

The motor loop is also involved in processing the temporal structure of auditory input and thus contributes to the perception of rhythm, music and speech. Accordingly, PD patients are not only impaired in generating rhythmic movements, but also show deficits in perceiving and discriminating complex rhythms (Grahn, 2009). Interestingly, these deficits are pronounced in beat-based rhythms, confirming the assumption that difficulties should increase with higher predictability of the stimulus patterns. Furthermore, two studies found patients to be impaired in recognising the emotional expression of music excerpts (Lima, Garrett, & Castro, 2013; van Tricht, Smeding, Speelman, & Schmand, 2010). These problems were independent of declarative cognitive impairment and may have, at least in part, depended on the inability to generate an internal representation of the music's temporal structure. Likewise, several studies found that PD patients are impaired in analysing prosodic intonation and affect (e.g., Ariatti, Benuzzi, & Nichelli, 2008; Breitenstein, Van Lancker, Daum, & Waters, 2001; Lloyd, 1999; Pell, 1996). Therefore, it was proposed that the motor loop is involved in extracting temporal features of speech and by this means supports language perception (Kotz, Schwartze, & Schmidt-Kassow, 2009). Independent of a specific sensory domain, PD patients need bigger time differences than healthy controls to perceive two events as separate (Artieda, Pastor, Lacruz, & Obeso, 1992) and show deficits in the estimation of short time intervals (Pastor, Artieda, Jahanshahi, & Obeso, 1992; Rammsayer, & Classen, 1997).

All this evidence confirms that the analysis and prediction of sensory information based on its serial and temporal structure is impaired in PD. Importantly, the capability to build and rapidly retrieve representations of task relevant temporally ordered conditional dependencies is the basis of many cognitive tasks. In a recent study, Hanakawa, Goldfine and Hallett (2017) investigated the mutual neural correlates of motor and cognitive slowing in PD. Participants either performed cued serial finger movements, imagined these movements or calculated corresponding numerical transformations. By manipulating the frequency of cue presentations, the neural basis of speeded processing in the three tasks was analysed in healthy participants and PD patients. Amongst other areas, healthy participants showed frequency related activity in the SMA, PM and putamen in all conditions. During motor execution, the parietal and primary motor cortex were involved and activation within the motor loop was more caudal opposed to a more rostral activity combined with prefrontal engagement during the calculation task. Nevertheless, the areas in the putamen and thalamus targeted by PM input showed similar frequency dependent activity during all conditions. Accordingly, PD patients were less able to

successfully increase their processing speed and showed decreased striatal and PM activity across all tasks. These results demonstrate an involvement of the motor loop and specifically the PM in all tasks that require sequential processing, even when abstract cognitive operations are performed. Moreover, Trempler et al. (2018) found that higher putamen volume of healthy controls and PD patients was related to better discrimination of relevant and irrelevant events during sequence processing. Another recent study investigated the contribution of the basal ganglia in a perceptual decision making task that required participants to learn associations of abstract images with one of three button presses (Hiebert et al., 2019). The putamen was found to mediate response-selection decisions in both healthy controls and PD patients and was hypoactive in patients after withdrawal of medication. Accordingly, a recent review highlights the contribution of the striatum during perceptual decision making by accumulating sensory evidence for different response alternatives (Huda, Goard, Pho, & Sur, 2018). The authors emphasise that motor and cognitive components are closely intertwined and basic substrates of cognition such as attention probably build on action selection mechanisms. Two meta-analytic studies that parcellated the PM based on connectivity patterns indeed revealed that its ventral and rostral part participate in music and speech comprehension, visual attention and go-nogo tasks, or mental rotation, visual and semantic discrimination, the Wisconsin Card Sorting Test, the Tower of London task and working memory tasks such as the n-back and Sternberg task, respectively (Genon et al., 2017, 2018).

Taken together, the motor loop has an often-unnoticed influence on a variety of cognitive tasks. Recent results complement former studies (see chapter 1.4.2) and demonstrate that sequential processing, set shifting and decision making depend on the motor loop. Therefore, medial premotor and striatal dysfunction most probably contribute to PD patients' impairments in cognitive tasks that require learning, selecting and predicting dynamically changing, but rather simple, conditional dependencies of actions or sensory events. Depending on the task and stage of the disease, the PM may also be subject to pathological decline and thus add to cognitive deficits, or it may provide a compensatory resource, as found in our studies. On the one hand, Kehagia and colleagues (2010) classified deficits in visuospatial functions, mental rotation, visual recognition memory and conditional associative learning as one aspect of MCI that is often found to be independent of classical executive impairment and dopaminergic medication. These functions resemble the list of rostral and ventral PM functions described by Genon and co-workers (2017, 2018), pointing to possible PM related dysfunctions in some patients. On the other hand, we found compensatory PM activity during serial prediction. Notably, this PM hyperactivity was accompanied by prefrontal hyperactivity,

probably because the PM is part of the motor and the dorsolateral prefrontal loop and can serve as an interface to prefrontal activity (Abe & Hanakawa, 2009). Therefore, just as the premotor cortex should not be neglected when discussing cognitive impairments, prefrontal involvement will be discussed in the following. To better understand and differentiate the neural underpinnings of cognitive difficulties and possible compensatory mechanisms in PD, a classical perspective and the present level of knowledge on the interplay of premotor and prefrontal activity will be presented.

3.2.3 Interaction of premotor and prefrontal hyperactivity

Classical analyses of compensatory prefrontal functions in PD patients, then referred to as global or general cognitive resources, were based on observations that patients are impaired in performing multiple tasks at the same time (Benecke et al., 1986; Castiello & Bennett, 1997). It was also noticed that PD patients are more affected when a cognitive task requires internal control compared to when guiding external input is available. For example, Brown and Marsden (1988a) compared performance in the Wisconsin Card Sorting Test to a task that required set shifting based on external cues and found that PD patients were only impaired in the former. Similarly, PD patients performed worse than healthy controls only in an un-cued version of the Stroop test, but not in a version that specified the currently relevant stimulus dimension (Brown & Marsden, 1988b). Several authors explained the dual task and internal control difficulties as an indirect effect of basal ganglia dysfunction. It was proposed that PD patients have to make use of effortful cognitive strategies during tasks that healthy participants perform automatically, and therefore fail when more attentional resources are needed in dual tasks or because of lacking external guidance (Berardelli et al., 2001; Brown & Marsden, 1991; Dirnberger & Jahanshahi, 2013; Woodward et al., 2002; Wu, Hallett, & Chan, 2015). Indeed indicating that patients employ more cognitive resources, some studies have shown increased prefrontal activity of PD patients during sequential motor tasks (Martin et al., 2019; Matt et al., 2017; Mentis et al., 2003; Nakamura et al., 2001; Wu & Hallett, 2005) and the Wisconsin Card Sorting Test (Monchi et al., 2004; Monchi, Petrides, Mejia-Constain, & Strafella, 2006).

In older populations, a shift of activity to prefrontal areas is a common observation (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010) also during motor tasks (Berchicci, Lucci, Pesce, Spinelli, & Di Russo, 2012). To interpret prefrontal engagement that may either indicate ineffective and unfocussed processing or a compensatory mechanism (Barulli & Stern, 2013), the patients' performance as well as the normal activity in healthy

participants must be considered. If new regions are found that normally are not involved, the activation pattern can represent a change in the neuronal implementation of the task as reaction to pathological changes in the underlying network or indicate a switch in the patients' cognitive strategies (Price & Friston, 1999). During serial prediction, prefrontal areas are not engaged in young, healthy participants (see chapter 1.4.3). Our fMRI study demonstrated that this holds true in older participants, as a conjunction analysis including all participants did not find prefrontal activity while performing the serial prediction task. Therefore, the prefrontal activation in PD patients either indicates the spontaneous involvement of supplementary resources because of motor loop pathology, or a shift from automatic serial processing to more consciously controlled strategies, or a combination of both. The event-related analysis revealed that increased activity of the right prefrontal cortex in Brodmann's areas 8/9 and the anterior cingulate cortex co-occurred with PM hyperactivity. Thus, the prefrontal cortex was only activated in concert with the PM that effectively supported task performance. Furthermore, the peak of prefrontal hyperactivity was located near compensatory activity during motor execution found in a recent study with early stage PD patients (Matt et al., 2017). This supports an interpretation of the prefrontal engagement as effective adaptation to reduced medial motor loop function. Accordingly, a recent study examined network changes during self-selected and externally cued movements and showed that preserved performance during external cueing was associated with enhanced effective connectivity between the prefrontal cortex and the PM after medication withdrawal (Michely et al., 2015). Furthermore, the influence of prefrontal activity on the SMA was increased under medication in all conditions and resulted in increased finger tapping speed, directly demonstrating that prefrontal activity constitutes a compensatory mechanism.

However, in case of our PET study, extensive prefrontal activity in PD patients was accompanied by a decrease in performance and a failure to perform the more difficult version of the serial prediction task. The patients in this more severely affected sample probably could not effectively recruit the motor loop and therefore possibly changed their strategy to an effortful conscious mode. Therefore, the processing probably needed more cognitive resources to allow working memory or language supported representations of the sequential structure. This may have resulted in the massive, but ineffective bilateral hyperactivity of the prefrontal cortex extending from Brodmann's area 46 to area 10.

These results demonstrate that the interplay of premotor and prefrontal activity depends on the stage of the disease and medication status and may have different effects, even during the same task. A few other studies found similar interactions between SMA, PM and prefrontal

activity and task performance (Mentis et al., 2003; Nakamura et al., 2001). In these studies, PD patients expressed heightened prefrontal activity to achieve a level of motor sequence learning equal to healthy controls. However, when task demands increased, healthy controls engaged prefrontal areas more efficiently and PD patients performed worse than controls despite prefrontal hyperactivity. Taken together, these results imply that prefrontal areas can compensate deficient motor loop processing, either via connections to the (rostral) premotor cortex or the (rostral) SMA, or via prefrontal basal ganglia loops. However, at some point in the disease's progress, motor loop dysfunction probably becomes dominant and cannot be compensated by prefrontal activity anymore, resulting in inefficient prefrontal hyperactivity.

Notably, these observations do not contradict the multitude of studies that found cognitive impairment to be associated with hypoactivity of the prefrontal cortex in tasks such as the Stroop test, the Tower of London task, working memory tests or verbal memory tasks (see chapter 1.4.1). These deficits typically emerge in later stages of the disease (Owen et al., 1992; Owen, Iddon, Hodges, Summers, & Robbins, 1997), in parallel to progressing deterioration of the anterior putamen and caudate nucleus, and thus when the dorsolateral and other prefrontal loops are affected (Cheesman et al., 2005; Lewis et al., 2003; Polito et al., 2012; Rinne et al., 2000) subsequent to the affection of the posterior putamen and the motor loop (Grahn et al., 2008; Kish et al., 1988). Therefore, prefrontal hyperactivity might be an indicator of mainly motor loop driven tasks, dissociating it from cognitive tasks that are rather characterised by prefrontal *and* premotor hypoactivity compared to healthy controls. For example, healthy participants employ the dorsolateral prefrontal cortex and the premotor cortex during n-back working memory tasks (Owen, McMillan, Laird, & Bullmore, 2005) and the Tower of London Task (Nitschke, Köstering, Finkel, Weiller, & Kaller, 2017). Consequently, the affection of both the motor and dorsolateral prefrontal loop in progressed PD stages probably results in poor cognitive task performance and concurrently decreased premotor and prefrontal activity. However, it is beyond the scope of this work to evaluate the specific contribution of the motor loop in cognitive tasks that involve prefrontal areas. Some ideas for studies on this topic will be presented in the following chapter in which the results of this work will be taken as a basis to outline possible rehabilitation strategies for PD patients and future directions for research.

3.3 Implication and prospects

The presented literature and our findings demonstrate that motor and cognitive representations are intertwined. To complement classical descriptions of PD, more integrative concepts should be applied that offer a comprehensive approach to motor and cognitive functions. As argued in the following, this would support the development of more effective strategies for the rehabilitation of PD patients and could inspire future research. Accordingly, the clinical implications of our results (chapter 3.3.1) and recommendations for further research on serial prediction and cognitive impairments of PD patients in general (chapter 3.3.2) will be presented in this chapter.

3.3.1 Clinical implications

To consider the impact of motor loop dysfunction on serial prediction opens new perspectives on some every-day problems of PD patients. For example, patients make more safety errors during driving than healthy controls (Stolwyk, Charlton, Triggs, Iansek, & Bradshaw, 2006; Uc et al., 2006). Driving requires monitoring a car's movement relative to stationary and other moving objects in the surrounding. Thus, PD patients might be unsafe drivers not only because of bradykinesia or dual tasking deficits, but also because the prediction of dynamic patterns and fast perceptual decision making processes are impaired. Indeed, one study found that safety errors were independent of the general cognitive impairment of patients, but related to performance in the Trail Making Test (Uc et al., 2006) which involves sequential processing and engages a fronto-parietal network including the premotor cortex (Zakzanis, Mraz, & Graham, 2005). Motor loop dysfunction might also effect social interactions, for example by impairing the kinaesthetic representation of the own body, the perception of others' movements and the understanding of emotional colouring in speech and music (see chapter 3.2.2).

These motor loop dependent problems can possibly be ameliorated by therapies that intend to target motor functions. First, appropriate medication that minimises motor loop dysfunction indeed improves most cognitive functions in early stages of the disease (Kehagia, 2010). Second, action observation and motor imagery probably support motor functions (Abbruzzese, Avanzino, Marchese, & Pelosin, 2015), and might also aid the cognitive aspects of motor loop activity. Third, physical exercise reduces motor impairment, and interestingly recent studies showed that cognitive functions benefit from high intensity physical training programs (Cruise et al., 2011; Morberg, Jensen, Bode, & Wermuth, 2014), treadmill training

(Picelli et al., 2016), dancing (de Natale et al., 2017; Hashimoto, Takabatake, Miyaguchi, Nakanishi, & Naitou, 2015) and aerobic exercises (Duchesne et al., 2015). The impact of physical exercise on cognition might at least partly be caused by higher motor loop efficiency and improved PM and prefrontal compensatory involvement.

A recent review emphasised that motor, cognitive and motivational aspects interact and claimed that all should be considered in the rehabilitation of PD patients (Ferrazzoli et al., 2018). In general, it would be beneficial to acknowledge that the motor and cognitive status of PD patients are interrelated, as further corroborated by recent experimental (Dahdal et al., 2016; Moustafa et al., 2016; Wiratman et al., 2017) and clinical studies (Chung et al., 2018; Monastero et al., 2018; Pedersen, Larsen, Tysnes, & Alves, 2017). The implications of these insights for future studies on PD will be outlined in the following section.

3.3.2 Ideas for future research

This work complements previous research that focussed on the contribution of prefrontal loops and the mesolimbic dopaminergic pathway to cognition in PD. To extend our results, which are limited in some respects, further studies on serial prediction should be implemented. First, the samples in this thesis were of small to medium size, so that further studies with bigger samples are needed to verify our results and directly investigate the connectivity between the basal ganglia, the SMA, PM and prefrontal cortex. Second, our assumption that compensatory hyperactivity is limited because of progressing motor loop dysfunction is plausible based on the current data but must be confirmed by testing PD patients in different stages within one study design. Third, this work only included PD patients of the akinetic-rigid or mixed subtype without other cognitive impairments than serial prediction deficits. Patients with manifest prefrontal cognitive impairment or other PD phenotypes, for example patients with late disease onset and fast progression of cognitive impairment (Halliday & McCann, 2010), require further research on the interaction of premotor and prefrontal areas.

Furthermore, our findings raise new questions regarding the engagement of the motor loop in other cognitive tasks than serial prediction. Thus, upcoming research should examine the interplay of premotor and prefrontal areas in commonly used cognitive tasks more closely. Especially tests that are used to measure cognitive impairments in PD such as the Trail Making Test, the Wisconsin Card Sorting Test and the Tower of London task, could be investigated based on concepts that consider the interaction of premotor and prefrontal areas in working memory and other cognitive functions (e.g., Abe & Hanakawa, 2009).

Already pointing in this direction, the perspectives on the premotor cortex and the basal ganglia seem to have broadened recently. For example, Huda and colleagues (2018) highlight that the dorsal putamen is involved in perceptual decision making and notice that a 'growing body of work indicates that fundamental substrates of cognition, such as attention, deeply engage and might even arise from mechanisms of action selection.' (p. 2). Other concepts generally question a strict separation of motor, perceptual and cognitive functions (Haber, 2003; Hurley, 2001), span domains by focussing on the neural implementation of specific information processes independent of content (Friston et al., 2012; Nachev, Kennard, & Husain, 2008), or apply a multi-system view on PD that puts more emphasis on the interaction of brain networks including the cerebellum (Caligiore et al., 2016; Wu & Hallett, 2013).

Complementary to more integrative theories that might reduce one-sided research, further studies are needed that implement innovative tasks like the SPT to uncover the neural underpinnings of specific cognitive processes. By this means, the mechanisms responsible for different types of cognitive impairment could be further differentiated, in accordance with the complexity of PD and its pathological mechanisms.

3.4 Conclusions

Although the profile of cognitive impairments in PD is heterogenous, a contribution of the motor loop to at least some aspects of MCI has long been widely neglected in PD literature. Closing this gap, our studies show that motor loop dysfunction causes serial prediction deficits, i.e., PD patients cannot learn and predict recurring sensory patterns as easily and efficiently as healthy controls. These deficits are aggravated when the motor loop is dysfunctional after medication withdrawal or severely affected in progressed disease stages, especially when sequential information is not presented continuously so that the stimulus order has to be internally represented by the SMA. Nevertheless, compensatory PM hyperactivity and possibly co-occurring prefrontal activity can prevent poor serial prediction performance despite missing stimulus information, if the motor loop is not too heavily impaired.

These results and other recent studies indicate that motor loop dysfunction contributes to cognitive impairments in PD during tasks that involve the prediction of dynamic patterns, or more generally speaking, the processing of temporally ordered dependencies between several sensory or motor states. These deficits probably range from the perception of own movements and observed motion and to the awareness of emotional aspects of music and prosody. Presumably, a disbalance of the direct and indirect pathway causes these deficits by impeding

information filtering mechanisms of the putamen. Consequently, consecutive states within a sequence or a pattern are not accurately associated, and thus internal representations in the SMA cannot be formed or retrieved efficiently. Probably because the SMA is more dependent on basal ganglia input than the PM, the latter can provide compensatory information about dynamic stimulus properties. When prefrontal loops are still intact in early stages of the disease, the PM may also transmit helpful input from the prefrontal cortex. Accordingly, the interplay of premotor and prefrontal areas in PD should be investigated more thoroughly in upcoming studies.

In general, this thesis and the whole body of work by Schubotz and von Cramon imply that future research should revise the classical concept of premotor areas as being purely motor centred. Recognising the importance of the motor loop for cognitive deficits might allow the development of better treatments and rehabilitation strategies for PD patients. Taking one step in this direction, our work offers a new perspective on the contribution of the motor loop to cognition and a glimpse on the complex interplay of deficits and compensatory forces in PD.

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5 APPENDIX

5.1 List of figures

5.2 List of abbreviations

ACA	anterior cingulate area
DBS	deep-brain stimulation
DLFPC	dorsolateral prefrontal cortex
EC	entorhinal cortex
FEF	frontal eye fields
fMRI	functional magnetic resonance imaging
GABA	gamma-amino-butyric-acid
GPi	globus pallidus pars interna
GPe	globus pallidus pars externa
HC	hippocampal cortex
ITG	inferior temporal gyrus
LOF	lateral orbitofrontal cortex
M1	primary motor cortex
MCI	mild cognitive impairment
MDpl	medialis dorsalis pars paralamellaris
MDmc	medialis dorsalis pars magnocellularis
MDpc	medialis dorsalis pars parvocellularis
PD	Parkinson's disease
PET	positron emission tomography
PM	lateral premotor cortex
PMv	ventral lateral premotor cortex
PPC	posterior parietal cortex
SC	somatosensory cortex
SMA	supplementary motor area

SNr	substantia nigra pars reticulata
SPT	serial prediction task
SPT0	serial prediction task version without missing stimuli
SPT+	serial prediction task version with missing stimuli
STN	subthalamic nucleus
STG	superior temporal gyrus
VAmc	ventralis anterior pars magnocellularis
Vapc	ventralis anterior pars parvocellularis
VLm	ventralis lateralis pars medialis
VLo	ventralis lateralis pars oralis
X	area X of Olszewski

5.3 Declaration

I herewith declare that this thesis is my own work and that I have used only the sources listed. No part of this thesis has been accepted or is currently being submitted for any other degree or qualification at this university or elsewhere.

Klara Hagelweide Düsseldorf, July 2019