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Dopamine modulation of spatial navigation memory in Parkinson's disease

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ABSTRACT

Striatal dopamine depletion is a key pathophysiological feature of Parkinson's disease (PD) causing motor and nonmotor symptoms. Research on nonmotor symptoms has mainly focused on frontostriatal functions. However, dopamine pathways ascending from the ventral tegmental area also innervate hippocampal structures and modulate hippocampal-dependent functions, such as spatial memory. Using a virtual spatial navigation task, we investigated dopaminergic modulation of spatial memory in PD patients in a crossover medication ON/OFF design. We examined medication effects on striatal- and hippocampal-dependent spatial memory by either replacing a location cue in the environment or enlarging its spatial boundary. Key results indicate that in contrast to prior evidence for younger adults, PD patients, like their age-matched controls, rely more on striatal cue-based than hippocampal spatial learning. Medication facilitated striatal-dependent cue-location learning, whereas medication benefit in hippocampal boundary-related spatial memory depended on prior experience with the task. Medication effects on spatial memory were comparable to and independent of benefits on motor symptoms. These findings shed new light on dopaminergic modulation of hippocampal-striatal functions in PD.

1. Introduction

Finding ways around the environment to reach particular destinations for carrying out actions that may achieve specific goals are quintessential aspects of human daily activities. Spatial learning and memory are subserved by the hippocampal-striatal circuitry (see Moser et al., 2008 for review), a network that is also affected in Parkinson's disease (PD). However, spatial navigation functions have not been the focus of research on PD-related cognitive symptoms and were so far investigated only very scarcely (e.g., Aksan et al., 2015; Uc et al., 2007). The present study aims at filling this gap, with a focus on relating effects of dopamine (DA) dysfunction and medication to spatial navigation performance in PD.

The pathophysiology of PD involves interactions between genetic, cellular, and environmental mechanisms that yield consequences on the homeostasis of substantia nigra pars compacta (SNc) and lead to degeneration of nigrostriatal DA (Halliday et al., 2011; Obeso et al., 2010; Sulzer, 2007) as well as disturbances in other transmitters, such as the noradrenergic and cholinergic systems (see Gratwicke et al., 2015; Halliday et al., 2014 for reviews). The multifactorial causes for cell loss

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in SNc notwithstanding, nigrostriatal DA deficiency is a key neuropathological feature of PD. Earlier evidence from postmortem studies indicates that acute loss of DA neurons in the SNc could range from about 50% to 90% depletion within the first decade after disease onset (e.g., Fearnley and Lees, 1991). In early PD, striatal DA degeneration follows a spatiotemporal dorsal to lateral-ventral gradient, with dorsal striatal DA terminals of the SNc (caudate and putamen) being more affected than the ventral tegmental area (VTA)-innervated ventral striatum (nucleus accumbens). In the course of the disease, DA loss further proceeds to the mesolimbocortical DA system (Agid et al., 1993; Kish et al., 1988). Symptomwise, PD is a multifaceted neurodegenerative disorder that manifests itself in motor, cognitive, and psychiatric symptoms. The cardinal motor symptoms (tremor, bradykinesia, rigor, and postural instability) are mainly manifestations of DA deficiency in the putamen, whereas DA depletions in caudate and ventral striatum might contribute to cognitive impairments. These nonmotor symptoms further constraint the patients' daily functions and quality of life (Chaudhuri and Schapira, 2009; Löhle et al., 2009).

Thus far, research about effects of medication on cognitive symptoms of PD has mostly focused on cognitive dysfunctions that can be attributed to DA deficiency mediated through the frontostriatal loop (e.g., Ko et al., 2013; see de la Fuente-Fernández, 2012 for a review), such as cognitive flexibility, executive control, and motivation of actions (Aarts et al., 2014; Frank et al., 2007; Vriend et al., 2015; Willemssen et al., 2011; see Kehagia et al., 2010a; Robbins and Cools, 2014 for reviews). Given that DA depletion in the striatum follows a dorsal to ventral gradient and given that an inverted-U function relates the levels of DA signaling and prefrontal cognitive functions (Arnsten, 1998; Li et al., 2001; Li and Sikström, 2002; Mattay et al., 2003; Vijayraghavan et al., 2007; see Cools and D'Esposito, 2011 for review), medication effects on cognition could be complex. Current evidence from pharmacological studies in PD patients reveals mostly beneficial effects of DA enhancing medication (e.g., levodopa or D2 receptor agonists) on performance in tasks that demand executive control, cognitive flexibility, or working memory (see Kehagia et al., 2010b for review). However, dosage levels necessary for improving cognitive flexibility supported by the dorsal striatum may overdose (i.e., impair) ventral striatal functions, such as reward processing (e.g., Aarts et al., 2014; Cools et al., 2001). Furthermore, session order in crossover designs (cf. Garrett et al., 2015) could also moderate DA medication effects on cognition.

As for cognitive functions that are subserved by the medial temporal lobe structures (e.g., visuospatial processing and episodic memory), existing findings for effects of DA medications in PD patients are equivocal and seem not to be systematically related to medication status (Kehagia et al., 2010b; Poletti and Bonuccelli, 2013). The inconsistencies in medication effects may, in part, reflect the complex dosage-response relations. Indeed, like effects on prefrontal cognitive functions, a recent pharmacological study in healthy older adults showed that although levodopa was beneficial for hippocampal episodic memory, the effect followed an inverted-U shaped dose-dependent relation (Chowdhury et al., 2012). Furthermore, other neurotransmitter systems (i.e., cholinergic, noradrenergic, and glutamatergic systems) may also be involved in affecting PD patients' medial temporal lobe functions, particularly in PD patients who also show symptoms of dementia (Calabresi et al., 2013; Gratwicke et al., 2015; Kehagie et al., 2010b). So far, the question as to whether DA medications targeting motor symptoms in PD might also affect spatial navigation—an important daily cognitive function implicating the hippocampal-striatal circuitry—is still open.

1.1. Spatial learning and memory in PD: beyond frontostriatal cognitive symptoms

Given that the hippocampal-striatal circuitry plays a key role in spatial navigation, striatal DA degeneration may also affect navigation performance in PD. However, cognitive functions that implicate interactions between the hippocampal formation and striatal DA modulation have so far rarely been investigated in PD with only few exceptions (e.g., Aksan et al., 2015; Uc et al., 2007). Other than modulating cognitive functions through the frontostriatal pathway, DA signaling originating from neurons in the VTA also modulates long-term potentiation (LTP) in the hippocampus and affects hippocampal-dependent plasticity and memory functions (Grace et al., 2007; Lisman and Grace, 2005; Lisman et al., 2011). In animal studies, DA receptor activations or deactivations by agonists or antagonists, respectively, facilitate or block hippocampal LTP (Li et al., 2003; Otmakhova and Lisman, 1996, 1998). Of note, attenuations of LTP in CA1 hippocampal neurons have also been shown in neurotoxic (e.g., 6-hydroxydopamine-induced nigral and VTA lesions in rats) or transgenic models (e.g., mice expressing truncated human α-synuclein) of PD, with negative functional consequences on hippocampal-dependent memory and learning that could, in turn, be reversed by levodopa treatments (e.g., Costa et al., 2012; see also Calabresi et al., 2013 for review). In humans, a greater hippocampal DA D2 receptor binding potential is associated with superior episodic memory (Takahashi et al., 2007). A recent pharmacological study in healthy older adults also reported a dose-dependent effect of levodopa in enhancing episodic memory persistence of even weakly encoded events, supporting DA's role in modulating hippocampal memory consolidation (Chowdhury et al., 2012).

Regarding spatial navigation, findings from animal lesion studies (Miyoshi et al., 2012; Packard et al., 1989) as well as human behavioral (Doeller and Burgess, 2008; Schuck et al., 2013; Wiener et al., 2013) and brain imaging studies (Bohbot et al., 2004; Doeller et al., 2008; Moffat et al., 2007; Schuck et al., 2015; Wolbers et al., 2007) show that the hippocampus, entorhinal cortex, and striatum play important roles in spatial learning. Of particular interest, whereas evidence from rodent single cell recording studies suggests that complex memory representations of spatial layouts of the environment are primarily subserved by hippocampal place cells (O'Keefe and Dostrovsky, 1971) as well as entorhinal grid cells (Hafting et al., 2005) and head direction cells (Taube et al., 1990; see Moser et al., 2008 for review), memories of stimulus-response associations between visual cues and locations are mainly supported by striatal processes (e.g., Miyoshi et al., 2012; Packard et al., 1989; see Mizumori et al., 2004 for review).

Substrates for these two facets of spatial learning have more recently also been observed in a human functional imaging study (e.g., Doeller et al., 2008): hippocampal activity was associated with boundary-related learning of spatial layouts, whereas landmark/location cue-based learning correlated with activities in the striatum. In a similar vein, there is also evidence suggesting that navigation strategies that rely on allocentric place information primarily implicate hippocampal spatial representations, whereas strategies that rely on cue-based learning involve the striatum (e.g., McDonald and White, 1994). Moreover, evidence from human aging research indicates that the usual, nonpathological processes of aging compromise hippocampal-dependent allocentric strategies, resulting in older adults' greater reliance on extrahippocampal, striatal-dependent cue-based navigation strategies (e.g., Harris et al., 2012; Konishi and Bohbot, 2013; Moffat et al., 2007; Nicolle et al., 2003; Wiener et al., 2013).

Early pharmacological studies of DA modulation of spatial navigation in rodents also lend support for the dissociation of these

two aspects of spatial learning and their modulation via the dopaminergic system. Striatal injection of DA receptor agonists (e.g., amphetamine, D1 and D2 receptor agents) facilitated performance in the win-stay radial maze and in the cued water maze task, which mainly involved the formation of stimulus-response associations between cues and locations but had no effects on learning spatial layouts. In contrast, hippocampal injections of DA agonists only selectively enhanced the performance in the win-shift radial maze and in the spatial water maze task, which involved spatial cognitive mappings, such as representations of recently visited maze locations and their relations to distal extramaze cues (Packard and Teather, 1998; Packard and White, 1991; Packard et al., 1994). Besides dopaminergic modulation, evidence from early animal research also showed that the cholinergic and glutamatergic systems are also involved in memory functions subserved by the hippocampal-striatal circuitry (Diez del Guante et al., 1991; Packard et al., 2001; Prado-Alcala, 1985).

Although spatial deficits have been suggested in mouse models of PD (De Leonibus et al., 2007), to date there is surprisingly little research about PD patients' spatial navigation abilities. In the rare cases in which navigation-related abilities in PD patients were investigated, the studies mostly explored effects of visual inputs on movement deficits that are related to directional veering (Davidsdottir et al., 2008) or internal self-motion cues (Paquette et al., 2011). There are also a few behavioral studies showing PD patients' deficits in route and traffic sign following during actual driving (Aksan et al., 2015; Uc et al., 2006, 2007). Earlier studies by Pillon et al. (1996, 1997, 1998) described impaired memory for spatial locations in PD patients relative to controls but the impairment was mainly considered as frontostriatal attentional deficits. Whereas basic neuroscience knowledge about mechanisms for hippocampal spatial representation and striatal cue-location learning is well established (see Moser et al., 2008), PD has not yet been used as a model disorder to better understand how the dopaminergic pathophysiology of PD and DA medications targeting motor and nonmotor symptoms may influence these two aspects of spatial navigation.

1.2. Study aim and hypotheses

Taken together, the aim of this study was to shed new light on DA modulation of processes implicating spatial navigation in PD. Specifically, we investigated the effects of DA medication by comparing spatial learning performance in PD patients ON and OFF medication in a virtual navigation paradigm (cf. Doeller et al., 2008; Schuck et al., 2013, 2015). In light of striatal DA depletion being a key feature of PD pathophysiology (Fearnley and Less, 1991, see Pavese and Brooks, 2009 for review), we expected better navigation performance under DA medication in PD patients. Given that DA depletion in PD directly involves nigrostriatal neurons in early disease stages, whereas pathology-related abnormalities of DA signaling in other extrastriatal regions emerge in more advanced disease stages (e.g., Kaasinen et al., 2000), we expect the effects of DA medication to be apparent in striatal-dependent aspects of navigation performance. In light of the literature indicating that striatal DA signaling also modulates the hippocampal circuitry (Goto and Grace, 2005; Grace et al., 2007), DA medication might also potentially affect hippocampus-dependent spatial navigation. However, given that hippocampal-dependent spatial learning is computationally more demanding and subjected to aging-related impairments (cf. Schuck et al., 2013, 2015), effects of medication on this aspect of spatial learning may be moderated by other factors, such as prior experience and familiarity with the task.

2. Methods

2.1. Participants

Thirty-four PD patients (aged 41–74 years) and 34 healthy controls (aged 45–75 years) gave informed consent to participate in the study as approved by the local ethic committee of the TU Dresden (EK 259072011). PD participants were recruited at the Movement Disorders Outpatient Center at the Department of Neurology of the University Clinic at the TU Dresden, as well as from local neurologists in Dresden city and surrounding suburbs. Healthy controls were recruited in Dresden by means of flyers and announcements in public institutions (including local senior recreation centers and during blood donation initiatives of the German Red Cross). Control subjects were matched to the PD patients in terms of age (±5 years), gender, education level, smoking status, and handedness. PD patients were at the initial and early stages of the disease (Hoehn and Yahr scale: 1–3; additional inclusion and exclusion criteria are given in Table 1).

All PD patients were under an at least 3-month stable dopaminergic treatment at the time of admission to the study. The patients were classified according to Gelb et al. (1999) and staged according to Hoehn and Yahr (1967) (modified criteria). In a randomized 2-session crossover design, PD patients were tested twice within 4 weeks with counter-balanced order of DA medication (ON and OFF). All assessments took place in the morning. When ON medication, PD patients were under their prescribed antiparkinsonian medications. Altogether 23 PD patients took DA agonists alone or in combination with monoamine oxidase type B (MAO-B) or *N*-methyl-D-aspartate (NMDA) inhibitors or both. The remaining 11 PD patients took L-DOPA in combination with DA agonists and/or MAO-B inhibitors and/or NMDA inhibitors. Levodopa dose equivalency (LED) was calculated for all PD patients (cf. Tomlinson et al., 2010). In the OFF medication condition, patients were asked to omit their prescribed PD medication from 8 PM of the previous day until the end of the assessments which were carried out between 7:30 AM and 1 PM. on the following day. Control subjects were screened for psychiatric disorders during the last 12 months

Table 1
Inclusion and exclusion criteria for study participation

Criteria	Controls	PD
Inclusion	■ Control subject fulfills matching criteria (cf. sample) ■ German native speaker	■ Parkinson's disease according to Gelb et al. (1999) ■ Stable dopaminergic medication for ≥3 mo ■ Patient can tolerate OFF-session over night ■ German native speaker
Exclusion	■ MoCA ≤24 ■ Recent diagnosis of psychiatric disorders ■ Lifetime diagnosis of neurological disorders ■ Psychotropic medications	■ Hoehn and Yahr stage >3 ■ MoCA ≤24 ■ Lifetime diagnosis of other neurological disorders ■ Nondopaminergic psychotropic medications (except antidepressants) ■ Deep brain stimulation

Key: OFF, OFF medication; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease patients.

Table 2
Demographic and clinical sample characteristics

Variables	Controls (n = 34)	PD-ON-starters (n = 18)	PD-OFF-starters (n = 16)	Test statistic (df)	*p*-value
Demographic data					
Male (n)	25	13	12	$\chi^2_{(2)} = 0.1$	0.94
Right-handed (n)	32	17	14	$\chi^2_{(2)} = 0.8$	0.67
Smokers (n)	6	2	1	$\chi^2_{(2)} = 1.3$	0.52
Age (y)	59.4 (8.0)	61.3 (8.8)	56.9 (7.1)	$F_{(2,65)} = 1.3$	0.28
Education (y)	10.9 (1.1)	11.1 (1.0)	10.8 (1.1)	$F_{(2,65)} = 0.4$	0.70
Clinical data					
PD duration (y)	N/A	5.3 (3.3)	7.3 (5.5)	$t_{(24.3)} = -1.3$	0.22
LED (mg)	N/A	490.5 (380.3)	682.9 (478.0)	$t_{(28.6)} = -1.3$	0.21
UPDRS-III-ON	N/A	16.3 (6.9)	15.7 (5.3)	$t_{(31.4)} = 0.3$	0.78
UPDRS-III-OFF	N/A	19.7 (6.6)	19.9 (7.8)	$t_{(29.7)} = -0.1$	0.95
MoCA	27.9 (1.3)	27.5 (2.0)	28.1 (1.4)	$F_{(2,65)} = 0.6$	0.56

Values represent n or mean (SD).
Education refers to the number of school years. PD duration refers to the number of years since disease diagnosis.
Key: df, degrees of freedom; LED, L-Dopa equivalent dose; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease patients; PD-OFF-starters, PD patients OFF medication at session 1; PD-ON-starters, PD patients ON medication at session 1; SD, standard deviation; UPDRS-III-ON, Unified Parkinson's Disease Rating Scale, Part III (motor evaluation), assessed ON medication; UPDRS-III-OFF; Unified Parkinson's Disease Rating Scale, Part III (motor evaluation) assessed OFF medication.

according to the Composite International Diagnostic Interview (CIDI German version; Wittchen and Pfister, 1997). Depression symptoms were further rated using the Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg, 1979). Table 2 shows the demographic and clinical characteristics of the PD and control samples. One-way analyses of variance of between-group differences comparing PD patients at the first session (i.e., PD patients starting ON vs. OFF medication at session 1, henceforth termed PD-ON-starters and PD-OFF-starters) and healthy controls revealed no difference with respect to age, cognitive status (Montreal Cognitive Assessment; Nasreddine et al., 2005), and education level. χ^2 test of independence detected no difference in the distributions of gender or smoking behavior between groups. Independent *t* tests comparing PD-ON- and PD-OFF-starters also revealed no difference in PD medication dosage (LED) and motor dysfunction (Unified Parkinson's Disease Rating Scale—Part III: motor evaluation; UPDRS-III; Fahn et al., 1987).

2.2. Virtual reality spatial navigation task and procedure

We modified a computerized virtual reality spatial navigation task (cf. Doeller et al., 2008; Schuck et al., 2013, 2015) using UnrealEngine2 Runtime software (Epic Games; http://udn.epicgames.com). Distance is expressed in virtual meter (vm), with 1 vm being equal to 62.5 program defined units. The task consisted of encoding, learning, and retrieving locations of different objects in a 3D rendering of an open circular arena with a grassy field that was surrounded by a low stone wall. A 360-degree panoramic image of a landscape with mountains, clouds, and the sun was also visible behind the boundary that was marked by the stone wall. These distal cues were projected at infinity, so that parallax cannot be used to determine one's exact location in the arena; they were, however, informative for directional orientations (cf. Hartley et al., 2004). Participants navigated in the first-person view on the grassy field to search for visual objects. An intraenvironment location cue (i.e., a traffic cone) was set at a fixed location during the encoding and learning trials. The scenes of the environment were presented on the computer screen and participants navigated through the virtual environment using a joystick. The virtual position (x- and y-coordinates) of the participants were sampled every 100 ms. Before the experiment, participants were given a brief training to familiarize them with operating the joystick to navigate in the virtual environment. After the training, the actual experiment started with the encoding and learning phase, which were then followed by a transfer phase (see Fig. 1). Participants received detailed instructions before each of these phases.

During the initial encoding trials, participants were instructed to pick up four everyday objects (e.g., a hat, a ball, and so forth) that were presented one after the other on the grass field in the circular arena. Participants were asked to remember each object's location. When participants felt sufficiently confident about the location of a given object, they collected the object by virtually walking over it and then proceeded to the next object. After initial encoding of the positions of the objects, three learning trials started. In each learning trial, each of the four objects was presented on the screen for 4 seconds as a probe for the search. After each probe, the participants' task was to navigate to the memorized location of the probed object and to press a button once they thought they had reached the memorized object location. After the participants' response, the object appeared in its correct location. The participants then used the joystick to navigate to the correct location to pick up the object. In this way, the participants could use the difference between their memorized position and the correct object location as a feedback to allow further learning of the correct object locations. The four objects were probed one at a time in a pseudorandomized order in a learning trial. The three learning trials were followed by the transfer trials.

In the transfer phase, either the boundary of the circular arena (i.e., the stone wall) or the intra-arena location cue (i.e., position of the traffic cone) was manipulated independently. Specifically, in the boundary enlargement condition the distance from the center of the arena to the stone wall (i.e., the radius of the circular boundary) was expanded by 20% (from 80 vm to 96 vm, thus resulting in an increase of 32 vm of the diameter), whereas the (allocentric) position of the location cue was not changed. In the location cue shift condition, the position of the location cue was shifted away from its original location by about 30 vm, whereas the boundary remained unchanged. These manipulations allowed us to assess, respectively, the sensitivity of spatial memory to changes in boundary or cue location information. Each object location was probed in each of the two transfer conditions in orders that were counterbalanced between subjects. Altogether, the experiment took around 30–45 minutes. The participants performed the task in two sessions (between-session interval ranged from 2 to 4 weeks), with the order of medication status (ON/OFF) counterbalanced across the two sessions.

Evidence from animal (O'Keefe and Burgess, 1996) and human (Hartley et al., 2004) studies shows that spatial learning is sensitive to geometric properties of the environment (e.g., distances to a

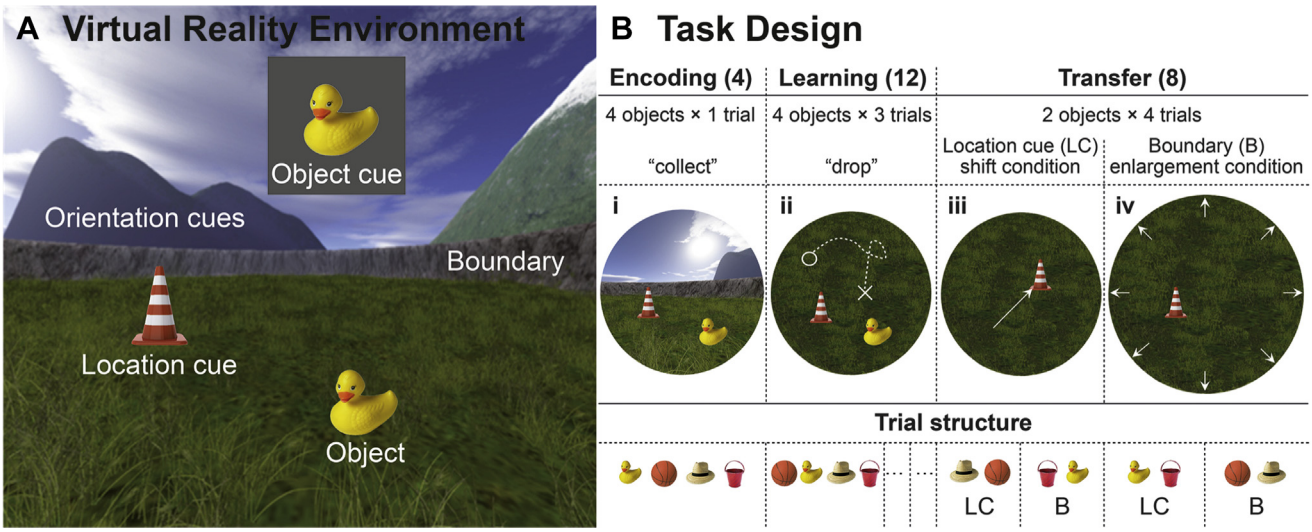

Fig. 1. Schematic diagram of the task environment (A) and task design with 3 phases and an example trial structure (B). (A) The virtual environment consisted of a circular grass plane surrounded by a stone wall (boundary [B]). A traffic cone (location cue [LC]) was placed on the grass. Mountains, clouds, and the sun (orientation cues) were projected to infinity behind the stone wall. During learning and transfer trials a cue (object cue) was presented in the top middle of the screen, indicating which object's location had to be retrieved. (B) (i) During the encoding phase, 4 objects were presented one at a time, and subjects were instructed to memorize their locations. Subjects continued to the next object by collecting the current object. (ii) In the learning phase, each of the 4 objects was cued 3 times at pseudorandom order. Subjects were instructed to navigate to the memorized object location. By pressing a button, subjects could drop the objects and received feedback about the correct object location (e.g., the rubber dug was shown again at its actual location). The transfer phase comprised the (iii) locations cue shift (LC) and (iv) boundary enlargement (B) condition that were presented in LC-B-LC-B sequence. During the transfer phase, subjects were also instructed to navigate to the memorized location of the cued object (each object cued once in each condition) but no feedback was provided anymore.

boundary). Results from an earlier study using square- or rectangular-shaped arenas found that people used information about the nearby boundary to mark the positions of objects in the environment. This sensitivity to boundary information is particularly apparent when the spatial arena is expanded (Hartley et al., 2004). More recently, we applied manipulations similar to those used in the present study in a sample of healthy younger and older adults and could show that during object search younger adults navigated outward after boundary enlargement, indicating their sensitivity to boundary expansion. In comparison, healthy older adults were less sensitive to the manipulation (Schuck et al., 2015). Beyond descriptive patterns of search orientations, the sensitivity of spatial memory to boundary or location cue can be quantified in terms of deviations of search orientations between the participants' performance and predictions derived from models relying on these two aspects of information (see methods below in Section 2.2.1). In the present study, we will test to what extent DA medication may affect PD patients' navigation performance in terms of sensitivity to location cue shift and boundary enlargement.

2.2.1. Measures of navigation performance

Three measures of navigation performance were derived from the data: distance error during the learning phase and sensitivities to boundary or location cue information during the transfer phase. Spatial memory of object locations during the learning phase was indexed by computing the Euclidian distance (in vm) between the actual object location and the memorized location (i.e., location remembered by the participant). A larger distance error (in vm) thus indicates worse spatial memory.

To quantify the sensitivity of navigation performance to either boundary or location cue, behavioral data from the transfer phase were compared to predictions of 2 simple geometric models (Schuck et al., 2015) that used either information about the radial expansion of the arena (boundary model) or the replacement of the location cue (location model). These simplified models were adapted from an earlier boundary vector model of hippocampal place cell firings (Burgess & O'Keefe, 1996) that considered four directions in squared environments to integrate the multitude of directions in circular environments (see supplementary information in Schuck et al., 2015 for further details of the relevant algebraic geometry). In a nutshell, here the boundary model corresponds to a geometric transformation of each object position (p) to a predicted memorized position ($\tilde{p}_m$) after the boundary enlargement, according to the change in radius (Δr) in a radial direction:

$$\tilde{p}_m = \left(1 \pm \frac{\Delta r}{r^2}|p|\right)p \quad (1)$$

The location model posits that the distance between cue and location is kept constant even when the position of the cue is shifted (translated) by an arbitrary translation vector (v). To capture performance after the displacement of the location cue, the location model assumes that the memorized location ($\tilde{p}_m$) will be shifted in the same direction as the shifted location cue. Specifically, if the distance of an object position p to the location cue (LC) is described by the translation vector: $v = p_{LC} - p$, then the memorized location in the transfer phase that is predicted by the location model will have the same distance v from the shifted location cue position. Hence, the direction and distance between each object and the location cue will be the same before and after the shift:

$$\Delta_{LC} = \left|v\right| \text{ and } \theta_{LC} = \tan^{-1}\left(\frac{y_v}{x_v}\right). \quad (2)$$

The empirical data from the transfer conditions were compared to predictions of the boundary or location cue model by first calculating the expected memorized position for each object after boundary enlargement or location cue displacement as described previously. In a second step, the predicted directional shifts after the environmental changes for each object derived from the two models were then computed as the angle of the vector that connect the predicted memorized position,($\tilde{p}_m$), and the object's original location, (p). The observed directional shifts after environmental

changes in the behavioral data were computed as the angle of the vector connecting the observed position in the transfer condition ($\tilde{p}_o$) and the original object locations (p). The sensitivity of memory performance to boundary or location cue was then evaluated as the degree of mismatch between the observed data and the directional shifts predicted by the two models, respectively. A larger mismatch between the observed behavior and predictions by the boundary or location cue model would, respectively, indicate that the behavior is less sensitive to computations based on either of the two types of information.

2.3. Data analyses

All statistical analyses were performed using R packages (version 0.98.945) in RStudio (www.rstudio.com). Baseline sample characteristics of PD-ON-starters, PD-OFF-starters, and healthy control subjects were analyzed using the Student *t* test (2-tailed with Welch's approximation of the degrees of freedom in case of unequal variances) or analysis of variance with *F* statistic for continuous variables and the Pearson χ^2 test for categorical variables (see Table 2). Other analyses were conducted with linear mixed-effect models using maximum-likelihood estimation with single subjects as random intercept. Effect sizes are given as intraclass correlation coefficients (ICC; cf. Maxwell et al., 1981).

Linear mixed-effect models were conducted using lme from the nlme package in R (Pinheiro et al., 2015). For the crossover analysis, the following two factors were used throughout all models (see Supplementary Table 1 in the supplemental material for other details): the within-subject factor medication (referring to ON/OFF medication status) and the within-subject factor session (indicating two assessment sessions i.e., S1/S2). The medication-by-session interaction in this case would reflect an effect of session order, also known as carry-over effect, which indicates differential effects at the two sessions (S1/S2) depending on session 1 medication status (i.e., whether PD patients started the study ON or OFF medication). Recently, it has been suggested that session order in crossover designs may be an inherently interesting moderator of DA effects on cognition (Garrett et al., 2015). Given that DA availability in the frontal-striatal circuitry supports cognitive plasticity and thereby may affect learning (see Cools, 2006 for review), a carry-over effect from session 1 to 2 involving an interaction between the within-subject factor session and the between-subject factor treatment group (defined by medication status in session 1 i.e., PD-ON- vs. PD-OFF-starters) might be expected (cf. Garrett et al., 2015).

Separate analyses were conducted for data obtained from the learning and the transfer phases. For the learning phase, we conducted a 2 (medication) × 2 (session) × 3 (trial) within-subject model. The learning phase involves three learning trials; therefore, besides the factors of medication and session, an additional within-subject factor of trial was added to the model to analyze potential within-subject improvements in task performance over learning trials. For data from the transfer phase, we conducted a 2 (medication) × 2 (session) × 2 (condition) within-subject model. The within-subject factor condition was added to refer to manipulations of location cue shift or boundary enlargement. In case of significant 2- or 3-way interactions with session, post hoc analysis were conducted for both test sessions separately with treatment group (PD-ON-starters vs. PD-OFF-starters) as between-subject factor and trial or condition as within-subject factor in a mixed-effect model design. For comparisons with healthy control participants whose navigation performance was assessed in session 1 only, we conducted mixed-effect models with group (PD-ON-starters, PD-OFF-starters, and healthy controls) as between-subject factor and trial (learning phase) or condition (transfer phase) as the within-subject factor. For comparison analyses with healthy controls, the respective models were conducted with type 3 sum of squares tests to control for potential confounding of effects of unequal sample sizes (cf. Shaw and Mitchell-Olds, 1993), given the sample size differences between the groups at session 1 (PD-ON-starters n = 18, PD-OFF-starters n = 16, and healthy controls n = 34). Furthermore, to check for potential confounding effects, all model analyses were also repeated with age and gender as covariates. Additionally, in the sample of PD patients, depression rating (Montgomery-Asberg Depression Rating Scale score), LED, and motor dysfunction (UPDRS-III score) assessed while ON medication were also checked as additional covariates. None of these covariates had an effect on the observed main effects or interactions (all $ps > 0.1$). Thus, results reported in the following sections were based on models without covariates (see details of models provided in Supplementary Table 1). Normal distribution of all models' residuals was confirmed using the Shapiro-Wilk test (*W* statistic) and visual inspection (Q-Q plots). The statistical significance level (α) was set to 0.05 for all analyses.

Furthermore, to compare the relative effects of DA medication on motor symptoms and spatial learning, performance gains with medication were also analyzed. Specifically, the percentage of DA treatment gains in cognitive function (i.e., spatial navigation performance in the learning and transfer phase) and motor function (i.e., UPDRS-III) were computed as (OFF − ON)/OFF × 100 and are expressed in percentage (%).

3. Results

3.1. Learning phase

Results of the linear model with medication (ON/OFF), session (S1/S2), and trial (1–3) as within-subject factors yielded a significant main effect of medication ($F_{(1,159)} = 5.8$; $p = 0.02$; $M_{(ON)} = 43.5$ vm; $M_{(OFF)} = 47.6$ vm; ICC = 0.19) and session ($F_{(1,159)} = 8.3$; $p = 0.005$; $M_{(S1)} = 47.9$ vm; $M_{(S2)} = 43.2$ vm; ICC = 0.22). No further main effects or interactions were observed (all $ps > 0.5$). Together the two main effects indicate that dopaminergic medication and learning over the two repeated test sessions improved location memory (i.e., reduced differences in vm between the actual target location and the remembered object location) in PD patients. Given the absence of a medication × trial or medication × trial × session interaction, there is no evidence that DA medication affected learning across the three trials within both sessions (see Fig. 2A and B).

Furthermore, performances of PD patients were compared with healthy controls who were only assessed once in session 1. Results of the linear mixed-effect model of session 1 with group (PD-ON-starters, PD-OFF-starters, healthy controls) as between-subject factor and trial (1–3) as within-subject factor showed that PD patients did not perform differently than the healthy controls ($F_{(2,65)} = 0.3$; $p = 0.76$; ICC = 0.09). Furthermore, the effect of learning trial was not significant ($F_{(2,130)} = 2.9$; $p = 0.06$; ICC = 0.21), as the case in the crossover analysis of the PD patients.

3.2. Transfer phase

Results of the linear model with medication (ON/OFF), session (S1/S2), and condition (LC shift/B enlargement) as within-subject factors revealed significant main effects of medication ($F_{(1,95)} = 23.4$; $p < 0.0001$; ICC = 0.45), session ($F_{(1,95)} = 11.6$; $p = 0.001$; ICC = 0.33) and condition ($F_{(1,95)} = 303.8$; $p < 0.0001$; ICC = 0.87) as well as a medication × session × condition interaction ($F_{(1,95)} = 5.8$; $p = 0.02$; ICC = 0.24). Because the 3-way interaction could indicate a carry-over effect, further post hoc analyses with treatment group (PD-ON-starters/PD-OFF-starters) as between-subject factor and

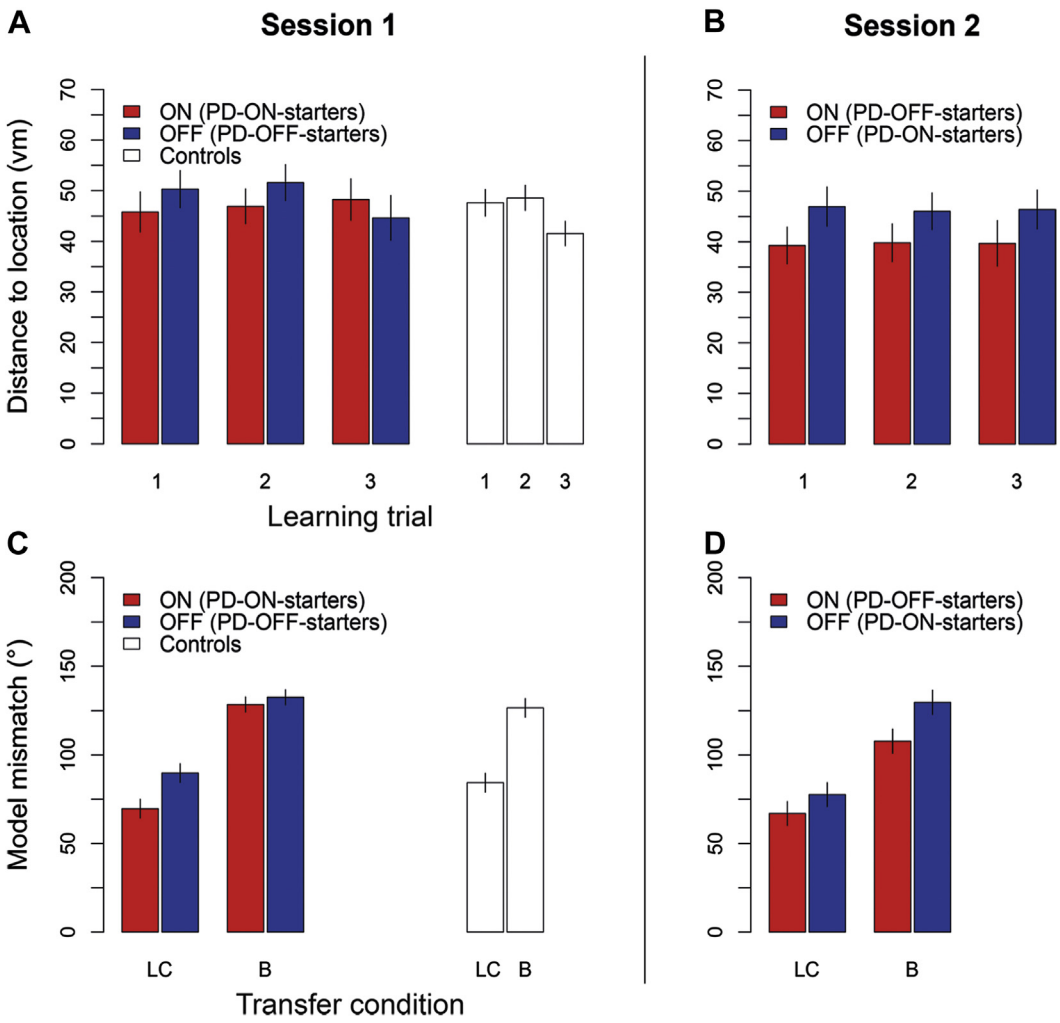

Fig. 2. Effects of DA medication on PD patients' spatial memory performance. (A and B) Distance between memorized location and actual object location in the learning phase comparing PD-ON-starters, PD-OFF-starters, and healthy controls at session 1 (A) and comparing PD-ON-starters versus PD-OFF-starters at session 2 (B). (C and D) Direction angle deviations between observed direction vector and model predicted vector after location cue shift (LC) or boundary enlargement (B) comparing PD-ON-starters, PD-OFF-starters, and healthy controls at session 1 (C) and comparing PD-ON-starters versus PD-OFF-starters at session 2 (D). Higher y-values indicate worse performance. Medication status (but not treatments group) is color-coded equally in both sessions and PD groups (i.e., red is ON and blue is OFF). Error bars are standard errors of the mean (SE). Abbreviations: DA, dopamine; PD, Parkinson's disease. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

condition (LC shift/B enlargement) as within-subject factor were therefore computed for both sessions separately. In session 1, results showed significant main effects of treatment group ($F_{(1,32)} = 4.1$; $p = 0.05$; ICC = 0.34) and condition ($F_{(1,32)} = 225.1$; $p < 0.0001$; ICC = 0.94), as well as a treatment group × condition interaction ($F_{(1,32)} = 5.5$; $p = 0.03$; ICC = 0.38; see Fig. 2C). Accordingly, the medication benefit as assessed between PD-ON- and PD-OFF-starters at session 1 was significant in the LC condition ($t_{(28.5)} = 3.2$; $p = 0.004$; $M_{(ON)} = 69.6°$; $M_{(OFF)} = 89.7°$) but not in the B condition ($t_{(30.5)} = 0.6$; $p = 0.57$; $M_{(ON)} = 128.4°$; $M_{(OFF)} = 132.5°$). This indicates that, without prior experience with the task, DA medication specifically enhances LC-dependent but not B-dependent spatial memory in session 1. In contrast, results from session 2 revealed main effects of treatment group ($F_{(1,32)} = 4.8$; $p = 0.04$; ICC = 0.36) and condition ($F_{(1,32)} = 121.4$; $p < 0.0001$; ICC = 0.89) but no significant treatment group × condition interaction ($p = 0.2$; see Fig. 2D), indicating similar medication effects in both conditions in session 2 when the task was already familiar. Considering these effects from a different perspective, in PD-ON-starters the potential learning effect in session 2 could be counteracted by the withdrawal of medication benefit. Therefore, no significant performance difference could be observed in the PD-ON-starters between the two sessions ($p = 0.09$). PD-OFF-starters, who benefitted from both prior task experience in session 1 and DA medication effect in session 2, improved in both the LC shift ($t_{(15)} = 3.1$; $p = 0.007$; $M_{(S1)} = 89.7°$; $M_{(S2)} = 66.9°$) and the B enlargement condition ($t_{(15)} = 4.3$; $p = 0.0006$; $M_{(S1)} = 132.5°$; $M_{(S2)} = 107.8°$) from session 1 to session 2.

Performances of the PD patients in the two conditions during the transfer phase were also compared with those of the healthy controls at session 1. Results of the linear mixed-effect model with group (PD-ON-starters, PD-OFF-starters, healthy controls) as between-subject factor and condition (LC shift/B enlargement) as within-subject factor yielded again a significant main effect of condition ($F_{(1,65)} = 195.6$; $p < 0.0001$; ICC = 0.87) but an only marginally significant group × condition interaction ($F_{(2,65)} = 2.5$; $p = 0.09$; ICC = 0.27). Given that a treatment group × condition interaction was observed in the PD patients at session 1, we followed up the latter trend further. The only effect of interest was that PD-ON-starters performed better than PD-OFF-starters

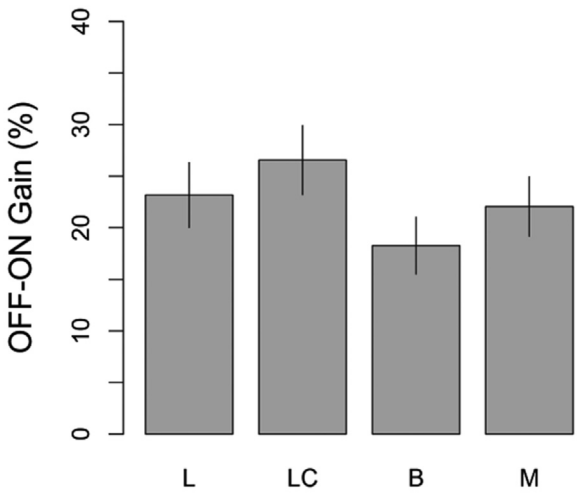

Fig. 3. Medication effects on gain scores (computed as (OFF − ON)/OFF × 100) of PD patients' motor dysfunction (M; measured by the Unified Parkinson's Disease Rating Scale—Part III motor scale), spatial navigation performance in the learning phase averaged across the 3 trials (L), and the transfer phase conditions (LC—location cue, B—boundary). Error bars are standard errors of the mean (SE). Abbreviation: PD, Parkinson's disease.

($t_{(28.5)} = 3.2$; $p = 0.003$) and healthy controls ($t_{(35.1)} = 2.2$; $p = 0.03$) in the LC condition ($M_{(PD\text{-}ON)} = 69.6°$; $M_{(PD\text{-}OFF)} = 89.7°$; $M_{(C)} = 84.3°$). In the B condition, there was no difference between the groups ($p = 0.8$).

3.3. Treatment gains in cognitive versus motor functions

Furthermore, to further evaluate the effects of DA medication on spatial learning in relation to medication effects on motor symptoms, the percentage of treatment gains (computed as (OFF − ON)/OFF × 100, expressed in %) for the navigation task in the learning phase (averaged over all three trials), the transfer phase (LC vs. B condition), and for motor dysfunction (UPDRS-III) are plotted in Fig. 3. The analysis of potential difference in treatment gain showed no significant difference between the improvements in motor function and the improvements in all three spatial navigation measures (spatial learning, LC-related, and B-related spatial memory; all $ps > 0.6$), reflecting comparable degrees of medication benefit for motor function and spatial learning. Of note, all previously reported statistical analyses were also computed with the UPDRS-III score ON medication as covariate and all observed main effects and interactions of the learning and transfer phase remained unaffected when controlling for motor symptoms.

4. Discussion

Using a virtual reality spatial navigation task, we investigated spatial navigation in PD patients and the effects of DA medication on two facets of spatial memory. Main results of our study can be summarized in three aspects. First, DA medication improved spatial navigation performance in PD patients. Moreover, effects of the medication benefit were comparable to and independent of motor effects. Second, DA medication benefits differed between types of spatial memory and sessions. Without prior experience with the task, medication facilitated navigation performance only in the LC condition in session 1; however, medication benefits were comparable in both the LC and B conditions in the later session for those patients who could already familiarize with the task in the prior session and received medication in session 2. In other words, whereas PD-ON-starters in session 2 did not show further benefit of having done the task once already, because the potential learning effect could be counteracted by the withdrawal of medication from them in session 2, PD-OFF-starters in session 2 showed better performance for both striatal LC-dependent and hippocampal B-related spatial memory, presumably benefitting both from DA medication and having prior task experience from session 1. Third, PD patients did not perform worse than healthy controls.

During the learning phase, when ON dopaminergic medication PD patients remembered the spatial locations of the to-be-learned objects more precisely (i.e., the distances between the remembered and the actual target locations were smaller) than when they were OFF medication. Results from the transfer phase were particularly informative for further specifying medication benefits on the two facets of spatial learning. The transfer phase assessed navigation performance after changes in the spatial environment (i.e., either shifting the LC or enlarging the B) that reflected striatal-dependent cue-based learning or hippocampal-dependent learning of spatial layouts. Mismatches in directional angles between observed performance and model-based predictions were smaller for striatal-dependent cue-based learning than for hippocampal-dependent B learning in all participants. This finding is in line with previous evidence for age-related differences in spatial navigation (Schuck et al., 2015, 2013; Wiener et al., 2013): In contrast to younger adults who primarily relied on memory of spatial layouts during navigation, PD patients, similar to older adults, relied more on location cue information than representations of spatial layouts during navigation.

Based on the animal literature, deficits in hippocampal spatial learning and memory in older age can, at least in part, be attributed to aging-related neuroanatomical alterations in the hippocampus (Raz et al., 2005) and to aging-related decline in the specificity of hippocampal place cell firing during navigation (Barnes et al., 1983; Rosenzweig and Barnes, 2003). Cumulating evidence suggests that interactions between the hippocampus and the dopaminergic system are implicated in cognitive deficits in PD (see Calabresi et al., 2013 for review). The hippocampus receives dopaminergic input along the VTA-hippocampal loop (Lisman and Grace, 2005) and the ventral striatum (Rinaldi et al., 2012). Relative to healthy younger adults, deficient striatal DA signaling as in the case of aging and PD may thus be a further contributing factor to compromised hippocampal spatial representations and deficits in related memory functions because of attenuated DA modulation of hippocampal LTPs (Lisman and Grace, 2005; Lisman et al., 2011).

Of particular interest are results regarding effects of medication on the two facets of spatial learning. The benefit of DA medication on striatal cue-based spatial memory was observed in both sessions, irrespective of prior experience. Previous findings emphasize the roles of the caudate nucleus in location cue-based spatial learning in the present task (Doeller et al., 2008; Schuck et al., 2013, 2015), during route following (Hartley et al., 2003), or response strategy learning when navigating in a virtual maze task (Iaria et al., 2003). In healthy aging, consistent with our findings, extra-hippocampal, striatal cue-based navigation strategies are generally preferred over hippocampus-dependent strategies during spatial navigation (e.g., Harris et al., 2012; Konishi and Bohbot, 2013; Moffat et al., 2007; Nicolle et al., 2003; Wiener et al., 2013). Aside from the normal aging-related global DA degeneration (e.g., Bäckman et al., 2006; Suhara et al., 1991), which might in part be related to the shift in navigation strategies in older age, the dorsal striatum (including the caudate nucleus) is further affected by pathology-related DA depletion already during early PD (Damier et al., 1999; Hirsch et al., 1988; Pham et al., 2012; Reyes et al., 2013). Increasing DA signaling in the dorsal striatum of PD patients should therefore facilitate dorsal striatum subserved cognitive functions such as location cue-based spatial learning and

memory, as was readily observed in this study. In comparison, a medication effect in facilitating boundary-related spatial memory could only be observed in session 2 in PD patients who had some prior experience with the task already in session 1. In line with evidence from animal research, the hippocampal, allocentric navigation strategies also depend on the interaction between the nucleus accumbens of the ventral striatum and the hippocampus. Specifically, this interaction is modulated by phasic DA release and D1 receptor activity; accordingly D1 agonists have been shown to facilitate spatial performance (Goto and Grace, 2005). Taken together, our results indicate although DA medication is beneficial for spatial learning in early PD in general, medication yields benefit for the striatal-dependent location cue-based learning more readily, whereas benefit for the hippocampal-dependent learning of spatial layout seems to be conditioned on prior experience with the task. This finding is in line with a commonly held view of hippocampal-dependent spatial learning being computationally more demanding than striatal-dependent location cue-based learning (e.g., Bohbot et al., 2012; Schuck et al., 2015; Wiener et al., 2013). Of practical clinical relevance, it should be noted that the observed medication effects on both aspects of spatial navigation performance are comparable to and independent of medication effect on improved motor function.

The performance of healthy controls did not differ significantly from those of PD patients OFF medication, indicating that PD patients OFF medication did not show greater impairments in spatial navigation than healthy age-matched controls. On the one hand, the more gradual but less specific attenuation of DA modulation in various striatal and extrastriatal regions (Li and Rieckmann, 2014 for review) may affect spatial learning in the healthy age-matched controls (45–75 years). On the other hand, PD patients under medication receive an ongoing DA treatment, which may boost cognitive functions such as striatum-dependent spatial memory to a similar or even beyond the performance level of age-matched controls (for similar effects on frontal-striatal functions cf. Cools et al. (2010) reporting comparable or even superior working memory performance in PD patients OFF medication compared with healthy controls depending on task demands and cf. Frank et al. (2004) showing comparable performance of PD patients OFF medication and healthy controls during frontal-striatal probabilistic reinforcement learning). It should also be kept in mind that aging-related declines in dopaminergic modulation in various striatal and extrastriatal regions were presumably also ongoing in the age-matched controls and that PD patients had only a temporary (over night) withdrawal from their regular DA medication in the OFF condition, which does not provide a full washout of the dopaminergic medication effect. Moreover, because of the restricted matching criteria for the healthy controls resulting in a rather selective control group, future studies that also include longer medication OFF periods for PD patients are needed to further investigate performance equivalence or difference in spatial navigation between PD patients and healthy age-matched controls. Furthermore, this finding should be considered in light of the fact that the PD patients in our study were all still in early stages of the disease. Spatial navigation performance of early stage PD in the hippocampal condition may still be comparable to matched healthy controls given that the age-related degeneration of the hippocampus (e.g., Raz et al., 2005; Rosenzweig and Barnes, 2003) affects both healthy controls and PD patients of the same age and given the evidence also for compensatory recruitment of hippocampal circuitry in PD (e.g., Beauchamp et al., 2008; Moody et al., 2004).

Given findings suggesting that DA neurons in the VTA are less vulnerable than neurons in SNc to early PD-related degeneration (Damier et al., 1999; Hirsch et al., 1988; Pham et al., 2012; Reyes et al., 2013), questions as to whether aging-related hippocampal (e.g., Raz et al., 2005; Rosenzweig and Barnes, 2003) and global dopaminergic degeneration (e.g., Bäckman et al., 2006; Suhara et al., 1991) may be similar or exceed the effect of pathology in early PD with respect to spatial navigation should be subjected to further research. Relatedly, epidemiological evidence suggests that aging is a key risk factor for developing PD; however, whether the mechanisms of age-related decline in DA function associated with usual aging (see Li and Rieckmann, 2014 for review) and those associated with DA neuron degeneration in PD are distinct (Fearnley and Lee, 1991; Kish et al., 1992), related, or even common (Collier et al., 2011) are still not well understood and remain very much a topic of debate. Future pharmacoimaging studies comparing DA medication effects in healthy younger and age-matched controls with naïve (untreated) as well as progressed PD patients OFF and ON medication during tasks involving the frontostriatal and hippocampal-striatal pathways would be instrumental to gain further insights into the underlying mechanisms.

5. Conclusions

Our main findings of DA medication effects on different aspects of spatial navigation performance in PD patients provide new insights into nonmotor symptoms of PD, particularly cognitive impairments. The results reported here extend studies on implications of dysfunctional striatal DA signaling and DA medication effects on frontostriatal cognitive functions (i.e., cognitive flexibility, executive control, and motivation; Aarts et al., 2014; Frank et al., 2007; Vriend et al., 2015; see also Robbins and Cools, 2014 for review) to processes relying on the hippocampal-striatal circuitry. So far, prior studies on cognitive impairments in PD involving striatal and medial temporal regions have mainly focused on motor sequence learning (e.g., Beauchamp et al., 2008; Moody et al., 2004; Schendan et al., 2013) and mental rotation ability (e.g., Amick et al., 2006) instead of abilities of spatial learning and memory. Here, we showed that DA medication improved striatal location cue-based and hippocampal boundary-related spatial navigation in PD patients and that spatial memory improvements were comparable to and independent of medication effects on motor symptoms. The overall DA medication benefit in the striatal navigation condition can be expected in light of DA depletion in PD mainly involving nigrostriatal neurons in early stages (e.g., Kaasinen et al., 2000). Given that the PD patients included in this study were not advanced PD cases (Hoehn and Yahr scale 1–3), benefits of DA medication in the hippocampal condition might be related to a strengthening of limbic-ventral striatal pathway (cf. Grace et al., 2007). These results provide further evidence on the role of the hippocampal-striatal circuitry and the DA system in spatial learning and memory.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at the online version at http://dx.doi.org/10.1016/j.neurobiolaging.2015.10.019.

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