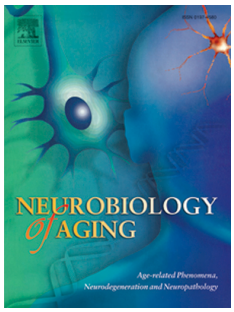
Accepted Manuscript



Dopamine Modulation of Spatial Navigation Memory in Parkinson's Disease

Franka Thurm, Nicolas W. Schuck, Mareike Fauser, Christian F. Doeller, Yuliya Stankevich, Ricarda Evens, Oliver Riedel, Alexander Storch, Ulrike Lueken, Shu-Chen Li

PII: S0197-4580(15)00523-0

DOI: 10.1016/j.neurobiolaging.2015.10.019

Reference: NBA 9419

To appear in: *Neurobiology of Aging*

Received Date: 13 April 2015

Revised Date: 15 October 2015

Accepted Date: 23 October 2015

Please cite this article as: Thurm, F., Schuck, N.W., Fauser, M., Doeller, C.F., Stankevich, Y., Evens, R., Riedel, O., Storch, A., Lueken, U., Li, S.-C., Dopamine Modulation of Spatial Navigation Memory in Parkinson's Disease, *Neurobiology of Aging* (2015), doi: 10.1016/j.neurobiolaging.2015.10.019.

Dopamine Modulation of Spatial Navigation Memory in Parkinson's Disease

Franka Thurm[a,*], Nicolas W. Schuck[b], Mareike Fauser[c], Christian F. Doeller[d], Yuliya Stankevich[e], Ricarda Evens[e], Oliver Riedel[e,†], Alexander Storch[c,f], Ulrike Lueken[e,†,§] and Shu-Chen Li[a,g,*,§]

(Revision of manuscript No. NBA-15-272R1 for review in *Neurobiology of Aging*)

[a] Department of Psychology, Chair of Lifespan Developmental Neuroscience, TU Dresden, 01062 Dresden, Germany
[b] Princeton Neuroscience Institute, Princeton University, Princeton, NJ 08540, USA
[c] Division of Neurodegenerative Diseases, Department of Neurology, TU Dresden, 01307 Dresden, Germany
[d] Radboud University, Donders Institute for Brain, Cognition and Behaviour, 6500 HB Nijmegen, the Netherlands
[e] Institute for Clinical Psychology and Psychotherapy, Department of Psychology, TU Dresden, 01187 Dresden, Germany
[f] German Center for Neurodegenerative Diseases (DZNE) Dresden, 01307 Dresden, Germany
[g] Center for Lifespan Psychology, Max Planck Institute for Human Development, 14195 Berlin, Germany

* *Corresponding authors:*
Department of Psychology, Chair of Lifespan Developmental Neuroscience,
TU Dresden, D-01062 Dresden, Germany
Tel.: +49 351 46334162; Fax: +49 351 46342194
Address correspondences to Franka Thurm (franka.thurm@tu-dresden.de) or
Shu-Chen Li (shu-chen.li@tu-dresden.de)

[§] *Shared last authors.*

[†] *Present addresses:*
OR is currently at the Leibniz Institute for Prevention Research and Epidemiology, Department of Clinical Epidemiology, 28359 Bremen, Germany;
UL is currently at the Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, 97080 Würzburg, Germany
AS is currently at the Department of Neurology, Rostock University Medical Center, 18147 Rostock, Germany

Authors' e-mail addresses:
CFD: christian.doeller@donders.ru.nl; RE: ricarda.evens@tu-dresden.de; MF: mareike.fauser@uniklinikum-dresden.de; SCL: shu-chen.li@tu-dresden.de; UL: Lueken_U@ukw.de; OR: riedel@bips.uni-bremen.de; NS: nschuck@princeton.edu; YS: yuliya.stankevich@tu-dresden.de; AS: alexander.storch@med.uni-rostock.de; FT: franka.thurm@tu-dresden.de

ABSTRACT

Striatal dopamine depletion is a key pathophysiological feature of Parkinson's disease (PD) causing motor and non-motor symptoms. Research on non-motor symptoms has mainly focused on fronto-striatal 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 cross-over 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 navigation in the striatal location cue condition, whereas medication benefit in hippocampal boundary-related spatial memory depended on prior experience with the task. Effects on spatial memory were comparable to and independent of motor effects. These findings shed new light on dopaminergic modulation of hippocampal-striatal functions in PD.

(170 words; Max. 170 words)

Keywords:

Spatial navigation; Striatum; Hippocampus; Parkinson's disease; Dopamine; Aging

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 current study aims at filling this gap, with a focus on relating effects of dopamine 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 dopamine (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 death 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 & Lees, 1991). In early PD, striatal DA degeneration follows a spatio-temporal 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, dopamine loss further proceeds to the mesolimbocortical DA system (Agid, et al., 1993; Kish et al., 1988). Symptom-wise, 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 non-motor symptoms further constraint the patients' daily functions and quality of life (Chaudhuri & 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 fronto-striatal 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 & 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 & Sikström, 2002; Mattay et al., 2003; Vijayraghavan et al., 2007; see Cools & 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 dopamine enhancing medication (e.g., levodopa or D2 receptor agonists) on performance in tasks that demand executive control, cognitive flexibility or working memory (see Kehagie 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), and session order in cross-over designs (cf. Garrett et al., 2015) might further moderate dopamine 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 & 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 fronto-striatal cognitive symptoms

Given that the hippocampal-striatal circuitry plays a key role in spatial navigation, striatal dopamine degeneration may also affect navigation performance in PD. However, cognitive functions that implicate interactions between the hippocampal formation and striatal dopamine 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 fronto-striatal 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 & Grace, 2005; Lisman, et al., 2011). In animal studies, dopamine receptor activations or deactivations by agonists or antagonists, respectively, facilitate or block hippocampal LTP (Li et al., 2003; Otmakhova & 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 dopamine 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 dopamine'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 & 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 & Dostrovsky, 1971) and entorhinal grid cells (Hafting et al., 2005) as well as 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, while 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 & White, 1994). Moreover, evidence

from human aging research indicates that the usual, non-pathological 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 & 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 dopamine 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 & White, 1991; Packard et al., 1994; Packard & Teather, 1998). 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 fronto-striatal 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 been used as a model disorder yet to better understand how the dopaminergic pathophysiology of PD and DA medications targeting motor and non-motor symptoms may influence these aspects of spatial navigation.

1.2. Study aim and hypotheses

Taken together, the aim of this study was to shed new light on dopamine modulation of processes implicating spatial navigation in PD. Specifically we investigated the effects of dopamine 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 & Less, 1991, see Pavese & 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 signalling 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 dopamine signaling also modulates the hippocampal circuitry (Goto & 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 & Yahr scale: 1-3; additional inclusion and exclusion criteria are given in Table 1).

---- Insert Table 1 about here ----

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 two-session cross-over design, PD patients were tested twice within four 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 anti-Parkinsonian medications. Altogether 23 PD patients took DA agonists alone or in combination with MAO-B or 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 8:00 p.m. of the previous day until the end of the assessments which were carried out between 7:30 a.m. and 1:00 p.m. on the following day. Control subjects were screened for psychiatric disorders during the last 12 months according to the Composite International Diagnostic Interview (CIDI German version; Wittchen & Pfister, 1997). Depression symptoms were further rated using the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & 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, MoCA; Nasreddine et al., 2005), and education level. *Chi*^{2} (χ^2)-test of independence also 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).

---- Insert Table 2 about here ----

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 intra-environment 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 Figure 1). Participants received detailed instructions prior to each of these phases.

---- Insert Figure 1 about here ----

During the initial encoding trials, participants were instructed to pick up four everyday objects (e.g., a hat, a ball, etc.) 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. Following 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 pseudo-randomized 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), while 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, while the boundary remained unchanged. These manipulations, henceforth boundary (B) or location-cue (LC) conditions, allowed us to assess, respectively, the sensitivity of spatial memory to changes in boundary or cue location. 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 to 45 minutes. The participants performed the task in two sessions (between-session interval ranged from 2-4 weeks), with the order of medication status (ON/OFF) counter-balanced across the two sessions.

Evidence from animal (O'Keefe & 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 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 current study in a sample of healthy younger and older adults and could show that during object search younger adults navigated outwards 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 boundary or location cue 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 the location cue, behavioral data from the transfer phase were compared to predictions of two simple geometric models (Schuck et al., 2015) that utilized 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 in order 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 ($\tilde{\mathbf{p}}_m$) after the boundary enlargement, according to the change in radius (Δr) in a radial direction:

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

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 ($\boldsymbol{v}$). To capture performance after the displacement of the location cue, the location model assumes that the memorized location ($\tilde{\mathbf{p}}_m$) 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 is described by the translation vector: $\boldsymbol{v} = \boldsymbol{p_{LC}} - \boldsymbol{p}$, then the memorized location in the transfer phase that is predicted by the location model will have the same distance $\boldsymbol{v}$ from the shifted location cue position. Hence, the direction and distance between each object and the location cue, given below, will be the same before and after the location cue shift:

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

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 above. 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, ($\tilde{\mathbf{p}}_m$), 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 ($\tilde{\mathbf{p}}_o$) 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 boundary or locational cue 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 boundary or location cue 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's *t*-test (two-tailed with Welch's approximation of the degrees of freedom in case of unequal variances) or analysis of variance (ANOVA) with *F*-statistic for continuous variables and the Pearson Chi^2 (χ^2)-test for categorical variables (see Table 2). Other analyses were conducted with linear mixed effect models using maximum-likelihood (ML) estimation with single subjects as random intercept. Effect sizes are given as intra-class 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 cross-over analysis, the following two factors were used throughout all models (see Table S1 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 cross-over designs may be an inherently interesting moderator of dopamine effects on cognition (Garrett et al., 2015). Given that dopamine 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 cue-location shift or boundary enlargement. In case of significant two- or three-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 in order to control for potential confounding of effects of unequal sample sizes (cf. Shaw & 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 (MADRS 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 Supplemental Table S1). 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, in order 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; $M_{(T1)}$ = 47.9 vm; $M_{(T2)}$ = 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 virtual meters (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 dopamine medication affected learning across the three trials within both sessions (see Figure 2A,B).

Furthermore, performances of PD patients were compared to 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 cross-over analysis of the PD patients.

3.2. Transfer Phase

Results of the linear model with Medication (ON/OFF), Session (S1/S2), and Condition (location cue shift/boundary 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). Since the three-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 Condition (location cue shift /boundary 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 Figure 2C). Accordingly, the medication benefit as assessed between PD-ON- and PD-OFF-starters at session 1 was significant in the location cue condition ($t_{(28.5)}$ = 3.2; p = 0.004; $M_{(ON)}$ = 69.6°; $M_{(OFF)}$ = 89.7°) but not in the boundary 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 location cue-dependent but not boundary-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 Figure 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 session1 and DA medication effect in session 2, improved in both the location cue shift ($t_{(15)} = 3.1$; $p = 0.007$; $M_{(S1)} = 89.7°$; $M_{(S2)} = 66.9°$) and the boundary 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 to 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 (location cue shift/boundary 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 ($t_{(28.5)} = 3.2$; $p = 0.003$) and healthy controls ($t_{(35.1)} = 2.2$; $p = 0.03$) in the location cue condition ($M_{(PD\text{-}ON)} = 69.6°$; $M_{(PD\text{-}OFF)} = 89.7°$; $M_{(C)} = 84.3°$). In the boundary condition there was no difference between the groups ($p = 0.8$).

---- Insert Figure 2 about here ----

3.3. Treatment gains in cognitive versus motor functions

Furthermore, in order 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 3 trials), the transfer phase (location cue vs. boundary condition), and for motor dysfunction (UPDRS-III) are plotted in Figure 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, location cue-related and boundary-related spatial memory; all *p*s > 0.6), reflecting comparable degrees of medication benefit for motor function and spatial learning. Of note, all above 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.

---- Insert Figure 3 about here ----

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 location cue condition in session 1; however, medication benefits were comparable in both the location cue and boundary 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 location cue-dependent and hippocampal boundary-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 location cue or enlarging the boundary) 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 boundary learning in all

participants. This finding is in line with previous evidence for age-related differences in spatial navigation (Schuck et al., 2013, 2015; 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 cues 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 & 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 & 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, due to attenuated DA modulation of hippocampal LTPs (Lisman & 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, extrahippocampal, striatal cue-based navigation strategies are generally preferred over hippocampus-dependent strategies during spatial navigation (e.g., Harris et al., 2012; Konishi & 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 dopamine 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 & 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 upon 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 & 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 to 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, due to 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., Rosenzweig & Barnes, 2003; Raz et al., 2005) 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 ageing-related hippocampal (e.g., Rosenzweig & Barnes, 2003; Raz et al., 2005) 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 dopamine function associated with usual aging (see Li & Rieckmann, 2014 for review) and those associated with dopamine neuron degeneration in PD are distinct (Fearnley & 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 pharmaco-imaging 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 fronto-striatal 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 non-motor symptoms of PD, particularly cognitive impairments. The results reported here extend studies on implications of dysfunctional striatal DA signaling and DA medication effects on fronto-striatal 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 & 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; Schendan et al., 2013; Moody et al., 2004) 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 dopamine 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 & 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 dopamine system in spatial learning and memory.

Acknowledgements

The work was supported in part by the German Research Foundation (DFG) through the Collaborative Research Center (CRC 940 "Volition and Cognitive Control) to Project C4 (PIs: UL, OR and AS) at the TU Dresden, Germany. Part of the data collection was also supported by a BMBF grant Q1GQ1313 to SCL as well as the regular position budget of the Chair of Lifespan Developmental Neuroscience at TU Dresden. CFD is supported by grants from the European Research Council (ERC-StG 261177) and the Netherlands Organisation for Scientific Research (NWO-Vidi 452-12-009).

Disclosure Statement

Conflicts of interest: none

References

Aarts E, Nusselein AA, Smittenaar P, Helmich RC, Bloem BR, Cools R. Greater striatal responses to medication in Parkinson's disease are associated with better task-switching but worse reward performance. Neuropsychologia. 2014 Sep;62:390-7.

Agid Y, Ruberg M, Javoy-Agid F, Hirsch E, Raisman-Vozari R, Vyas S, et al. Are dopaminergic neurons selectively vulnerable to Parkinson's disease? Adv Neurol. 1993;60:148–64.

Aksan N, Anderson SW, Dawson J, Uc E, Rizzo M. Cognitive functioning differentially predicts different dimensions of older drivers' on-road safety. Accid Anal Prev. 2015 Feb;75:236-44.

Amick MM, Schendan HE, Gains G, Cronin-Golomb A. Frontostriatal circuits are necessary for visuomotor transformation: mental rotation in Parkinson's disease. Neuropsychologia. 2006;44(3):339-49.

Arnsten AFT. Catecholamine modulation of prefrontal cortical function. Trends Cogn Sci. 1998 Nov 1;2:436-47.

Baloyannis SJ, Costa V, Baloyannis IS. Morphological alterations of the synapses in the locus coeruleus in Parkinsion's disease. J Neurol Sci. 2006;248:35-41.

Bäckman L, Nyberg L, Lindenberger U, Li S-C, Farde L. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci Biobehav Rev. 2006;30(6):791-807.

Barnes CA, McNaughton BL, O'Keefe J. Loss of place specificity in hippocampal complex spike cells of senescent rat. Neurobiol Aging. 1983;4(2):113-9.

Beauchamp MH, Dagher A, Panisset M, Doyon J. Neural substrates of cognitive skill learning in Parkinson's disease. Brain Cogn. 2008 Nov;68(2):134-43.

Bohbot VD, Iaria G, Petrides M. Hippocampal function and spatial memory: evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe rescetions. Neuropsychology. 2004 Jul;18(3):418-25.

Bohbot VD, McKenzie S, Konishi K, Fouquet C, Kurdi V, Schachar R, et al. Virtual navigation strategies from childhood to senescence: evidence for changes across the lifespan. Front Aging Neurosci. 2012 Nov 15;4:28.

Burgess N, O'Keefe J. Neuronal computations underlying the firing of place cells and their role in navigation. Hippocampus. 1996;6(6):749-62.

Calabresi P, Castrioto A, Di Filippo M, Picconi B. New experimental and clinical links between the hippocampus and the dopaminergic system in Parkinson's disease. Lancet Neurol. 2013 Aug;12(8):811-21.

Calabresi P, Picconi B, Parnetti L, Di Filippo M. A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. Lancet Neurol. 2006;5:974-983.

Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 2009 May;8(5):464-74.

Chowdhury R, Guitart-Masip M, Bunzeck N, Dolan RJ, Düzel E. Dopamine modulates episodic memory persistence in old age. J Neurosci. 2012;32:14193-204.

Collier TJ, Kanaan NM, Kordower JH. Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human pimates. Nat Rev Neurosci. 2011 Jun;12(6):359-66.

Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev. 2006;30(1):1-23.

Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex. 2001 Dec;11(12):1136-43.

Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry. 2011 Jun 15;69(12):e113-25.

Cools R, Miyakawa A, Sheridan M, D'Esposito M. Enhanced frontal function in Parkinson's disease. Brain. 2010 Jan;133(Pt 1):225-33.

Costa C. Sgobio C, Siliquini S, Tozzi A, Tantucci M, Ghiglieri V. et al. Mechanisms underlying the impairment of hippocampal long-term potentiation and memory in experimental Parkinson's disease. 2012. Brain. 135;1884-99.

Damier P, Hirsch EC, Agid Y, Graybiel AM. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain. 1999 Aug;122(Pt 8):1437-48.
Davidsdottir S, Wagenaar R, Young D, Cronin-Golomb A. Impact of optic flow perception and egocentric coodinates on veering in Parkinson's disease. Brain. 2008 Nov;131(Pt 11):2882-93.
de la Fuente-Fernández R. Frontostriatal cognitive staging in Parkinson's disease. Parkisons Dis. 2012;2012:561046.
De Leonibus E., Pascucci T, Lopez S, Oliverio A, Amalric M, Mele A.Spatial deficit in a mouse model of Parkinson disease. Psychopharmacology. 2007 Nov;194(4):517-25.
Diez del Guante MA, Cruz-Morales SE, Prado-Alcala RA. Time-dependent effects of cholinergic blockade of the striatum on memory. Neurosci Lett. 1991;122:79-82.
Doeller CF, Burgess N. Distinct error-correcting and incidental learning of location relative to landmarks and boundaries. Proc Natl Acad Sci U S A. 2008 Apr 15;105(15):5909-14.
Doeller CF, King JA, Burgess N. Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. Proc Natl Acad Sci U S A. 2008 Apr 15;105(15), 5915-20.
Dubois B, Ruberg M, Javoy-Agid F, Ploska A, Agid Y. A subcortico-cortical cholinergic system is affected in Parkinson's disease. Brain Res. 1983; 288:213-18.
Fahn S, Elton RL, UPDRS program members. Unified Parkinsons Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease, vol 2. Florham Park, NJ: Macmillan Healthcare Information; 1987. p. 153-163.
Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain. 1991 Oct;114(Pt 5):2283-301.
Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation and medication in Parkinsonism. Science. 2007 Nov 23;318(5854):1309-12.
Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science. 2004 Dec 10;306(5703):1940-3.
Garrett DD, Nagel IE, Peuschhof C, Burzynska AZ, Marchner J, Wiegert S, et al. Amphetamine modulates brain signal variability and working memory in younger and older adults. Proc Natl Acad Sci U S A. 2015 Jun 16;112(24):7593-8.
Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol. 1999 Jan;56(1):33-9.
Goto Y, Grace AA. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat Neurosci. 2005 Jun;8(6):805-12.
Grace AA, Floresco SB, Goto Y, Lodge DJ. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci. 2007 May;30(5):220-7.
Gratwicke J, Jahanshahi M, Foltynie T. Parkinson's disease dementia: a neural networks perspective. Brain. 2015 Jun;138(Pt 6):1454-76.
Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. Microstructure of a spatial map in entorhinal cortex. Nature. 2005 Aug 11;436(7052):801-6.
Halliday G, Lees A, Stern M. Milestones in Parkinson's disease--clinical and pathologic features. Mov Disord. 2011 May;26(6):1015-21.
Halliday G, Leverenz JB, Schneider JS, Adler CH. The neurobiological basis of cognitive impairment in Parkinson's disease. Mov Disord. 2014 Apr 15;29(5):634-50.
Harris MA, Wiener JM, Wolbers T. Aging specifically impairs switching to an allocentric navigational strategy. Front Aging Neurosci. 2012 Nov 1;4:29.
Hartley T, Maguire EA, Spiers HJ, Burgess N. The well-worn route and the path less travelled: distinct neural bases of route following and wayfinding in humans. Neuron. 2003 Mar 6;37(5):877-88.
Hartley T, Trinkler I, Burgess N. Geometric determinants of human spatial memory. Cognition. 2004 Nov;94(1):39-75.
Hirsch E, Graybiel AM, Agid YA. Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. Nature. 1988 Jul 28;334(6180):345-8.
Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967 May;17(5):427-42.
Iaria G, Petrides M, Dagher A, Pike B, Bohbot VD. Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. J Neurosci. 2003 Jul 2;23(13):5945-52.

Kaasinen V, Någren K, Hietala J, Oikonen V, Vilkman H, Farde L, et al. Extrastriatal dopamine D2 and D3 receptors in early and advanced Parkinson's disease. Neurology. 2000 Apr 11;54(7):1482-87.

Kehagia A, Murray GK, Robbins TW. Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. Curr Opin Neurobiol 2010a Apr;20(2):1-6.

Kehagia A, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol. 2010b Dec;9(12):1200-13.

Kish SJ, Schannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idopathic Parkinson's disease: pathophysiologic and clinical implications. N Engl J Med. 1988 apr 7;318(14):870-80.

Ko JH, Antonelli F, Monchi O, Ray N, Rusjan P, Houle S., et al. Prefrontal dopamine receptor abnoormalities and executive functions in Parkinson's Disease. Hum Brain Mapp. 2013 Jul;34(7):1591-604.

Konishi K, Bohbot VD. Spatial navigation strategies correlate with gray matter in the hippocampus of healthy older adults tested in a virtual maze. Front Aging Neurosci. 2013 Feb 20;5:1.

Li S, Cullen WK, Anwyl R, Rowan MJ. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. Nat Neurosci. 2003 May;6(5):526-31.

Li S-C, Rieckmann A. Neuromodulation and aging: implications of aging neuronal gain control on cognition. Curr Opin Neurobiol. 2014 Dec;29:148-58.

Li S-C, Siktröm S. Integrative neurocomputational perspectives on cognitive aging, neuromodulation and representation. Neurosci Biobehav Rev. 2002 Nov;26(7):795-808.

Li S-C, Lindenberger U, Sikström S. Aging cognition: from neuromodulation to representation. Trends Cogn Sci. 2001 Nov 1;5(11): 479-486.

Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron. 2005 Jun 2;46(5):703-13.

Lisman JE, Grace AA, Duzel E. A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. Trends Neurosci. 2011 Oct;34(10):536-47.

Löhle M, Storch A, Reichmann H. Beyond tremor and rigidity: non-motor features of Parkinson's disease. J Neural Transm. 2009 Nov;116(11):1483-92.

Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A. 2003 May 13;100(10):6186-91.

Maxwell SE, Camp CJ, Arvey RD. Measures of Strength of association: a comparative examination. J Appl Psychol. 1981 Oct;66(5):525-34.

McDonald RJ, White NM. Parallel information processing in the water maze: Evidence for independent memory systems involving dorsal striatum and hippocampus. Behav Neural Biol. 1994 May;61(3):260-70.

Miyoshi E, Wietzikoski EC, Bortolanza M, Boschen SL, Canteras NS, Izquierdo I., et al. Both the dorsal hippocampus and the dorsolateral striatum are needed for rat navigation in the Morris water maze. Behav Brain Res. 2012 Jan 1;226(1):171-8.

Mizumori SJ, Yeshenko O, Gill KM, Davis DM. Parallel processing across neural systems: implications for a multiple memory system hypothesis. Neurobiol Learn Mem. 2004 Nov;82(3):278-98.

Moffat SD, Kennedy KM, Rodrigue KM, Raz N. Extrahippocampal contributions to age differences in human spatial navigation. Cereb Cortex. 2007 Jun;17(6):1274-82.

Montgomery S, Asberg M. A new depression scale designed to be sensitive to change. Brit J Psychiatry. 1979 Apr;134:382-9.

Moody TD, Bookheimer SY, Vanek Z, Knowlton BJ. An implicit learning task activates medial temporal lobe in Patients with Parkinson's disease. Behav Neurosci. 2004 Apr;118(2):438-42.

Moser EI, Kropff E, Moser M-B. Place cells, grid cells, and the brain's spatial representation system. Annu Rev Neurosci. 2008;31:69-89.

Nasreddine ZS, Philips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9.

Nicolle MM, Prescott S, Bizon JL. Emergence of a cue strategy preference on the water maze task in aged C57B6 x SJL F1 hybrid mice. Learn Mem. 2003 Nov-Dec;10(6):520-4.
Obeso JA, Rodriguez-Oroz MC, Goetz CG, Marin C, Kordower JH, Rodriguez M, et al. Missing pieces in the Parkinson's disease puzzle. Nat Med. 2010 Jun;16(6):653-61.
O'Keefe J, Burgess, N. Geometric determinants of the place fields of hippocampal neurons. Nature. 1996; 381_425-428.
O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rats. Brain Res. 1971 Nov;34(1):171-5.
Otmakhova NA, Lisman JE. D1/D5 dopamine receptor activation increases the magnitude of early long-term potentiation at CA1 hippocampal synapses. J Neurosci. 1996 Dec 1;16(23):7478-86.
Otmakhova NA, Lisman JE. D1/D5 dopamine receptors inhibit depotentiation at CA1 synapses via cAMP-dependent mechanism. J Neurosci. 1998 Feb 15;18(4):1270-9.
Packard MG, Cahill L, McGaugh JL. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. Proc Natl Acad Sci U S A. 1994 Aug;91:8477-81.
Packard MG, Hirsh R, White MN. Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. J Neurosci. 1989 May;9(5):1465-72.
Packard MG, Teather LA. Amygdala modulation of multiple memory systems: hippocampus and caudate-putamen. Neurobiol Learn Mem. 1998 Mar;69(2):163-203.
Packard MG, Vecchioli SF, Schroeder JP, Gasbarri A. Task-dependent role for striatum metabotrophic glutamate receptors in memory. Learn Mem. 2001 Mar-Apr; 8(2):96-103.
Packard MG, White NM. Dissociation of hippocampus and caudate nucleus memory systems by posttraining intracerebral injection of dopamine agonists. Behav Neurosci. 1991 Apr;105(2):295-306.
Paquette C, Franzén E, Jones GM, Horak FB. Walking in circles: navigation deficits from Parkinson's disease but not from cerebellar ataxia. Neuroscience. 2011 Sep 8;190:177-83.
Pavese N, Brooks DJ. Imaging neurodegeneration in Parkinson's disease. Biochim Biophys Acta. 2009 Jul;1792(7):722-9.
Pham AH, Meng S, Chu QN, Chan DC. Loss of Mfn2 results in progressive, retrograde degeneration of dopaminergic neurons in the nigrostriatal circuit. Hum Mol Genet. 2012 Nov 15;21(22):4817-26.
Pillon B, Deweer B, Vidailhet M, Bonnet AM, Hahn-Barma V, Dubois B. Is impaired memory for spatial location in Parkinson's disease domain specific or dependent on "strategic" processes? Neuropsychologia. 1998 Jan;36(1):1-9.
Pillon B, Ertle S, Deweer B, Bonnet AM, Vidailhet M, Dubois B. Memory for spatial location in "de novo" parkinsonian patients. Neuropsychologia. 1997 Mar;35(3):221-8.
Pillon B, Ertle S, Deweer B, Sarazin M, Agid Y, Dubois B. Memory for spatial location is affected in Parkinson's disease. Neuropsychologia,. 1996 Jan;34(1):77-85.
Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team. nlme: Linear and nonlinear mixed effects models. R package version 3.1-120. Available from: http://cran.r-project.org/web/package=nlme; 2015.
Poletti M, Bonuccelli U. Acute and chronic cognitive effects of levodopa and dopamine agonists on patients with Parkinson's disease: a review. Ther Adv Psychopharmacol. 2013 Apr;3(2):101-13.
Prado-Alcala RA. Is cholinergic activity of the caudate nucleus involved in memory? Life Sci. 1985 Dec;37(23):2135-42.
Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex. 2005 Nov;15(11):1676-89.
Reyes S, Fu Y, Double KL, Cottman V, Thompson LH, Kirik D, et al. Trophic factor differentiate dopamine neurons vulnerable to Parkinson's disease. Neurobiol Aging. 2013 Mar;34(3):873-86.
Rinaldi A, Oliverio A, Mele A. Spatial memory, plasticity and nucleus accumbens. Rev Neurosci. 2012;23(5-6):527-41.
Rinne JO, Lönnberg P, Marjamäki P, Rinne UK. Brain muscarinic receptor subtypes are differently affected in Alzheimer's and Parkinson's disease. Brain Res. 1989 Apr;483(2):402-6.
Robbins TW, Cools R. Cognitive deficits in Parkinson's disease: a cognitive neuroscience perspective. Mov Disord. 2014 Apr 15;29(5):597-607.

Rosenzweig ES, Barnes CA. Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. Prog Neurobiol. 2003 Feb;69(3):143-79.

Shaw RG. Mitchell-Olds T. ANOVA for unbalanced data: an overview. Ecology. 1993 Sep;74(6):1638-45.

Schendan HE, Tinaz S, Maher SM, Stern CE. Frontostriatal and mediotemporal lobe contributions to implicit higher-order spatial sequence learning declines in aging and Parkinson's disease. Behav Neurosci. 2013 Apr;127(2):204-21.

Schuck NW, Doeller CF, Schjeide B-M, Schröder J, Frensch PA, Bertram L, et al. Aging and KIBRA/WWC1 genotype affect spatial memory processes in a virtual navigation task. Hippocampus. 2013 Oct;23(10):919-30.

Schuck NW, Doeller CF, Polk TA, Lindenberger U, Li S-C. Human aging alters neural computation and representation of space. Neuroimage. 2015 Aug 15;117:141-50.

Suhara T, Fukuda H, Inoue O, Itoh T, Suzuki K, Yamasaki T, et al. Age-related changes in human D1 dopamine receptors measured by positron emission tomography. Psychopharmacology. 1991;103(1):41-5.

Sulzer D. Multiple hit hypotheses for dopamine neuron loss in Parkinson's disease. Trends Neurosci. 2007 May;30(5):244-50.

Takahashi H, Kato M, Mayashi M, Okubo Y, Takano A, Ito H, et al. Memory and frontal lobe functions; possible relations with dopamine D2 receptors in the hippocampus. Neuroimage. 2007 Feb 15;34(4):1643-9.

Taube JS, Muller RU, Ranck JB Jr. Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. J Neurosci. 1990 Feb;10(2):420-35.

Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010 Nov 15;25(15):2649-53.

Uc EY, Rizzo M, Anderson SW, Sparks JD, Rodnitzky RL, Dawson JD. Impaired navigation in drivers with Parkinson's disease. Brain. 2007 Sep;130(Pt 9):2433-40.

Uc EY, Rizzo M, Anderson SW, Sparks J, Rodnitzky RL, Dawson JD. Impaired visual search in drivers with Parkinson's disease. Ann Neurol. 2006 Oct;60(4):407-13.

Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci. 2007 May;10(3):376-84.

Vriend C, Gerrits NJ, Berendse HW, Veltman DJ, van den Heuvel OA, van der Werf YD. Failure of stop and go in de novo Parkison's disease – a functional magnetic resonance imaging study. Neurobiol Aging. 2015 Jan;36(1):470-5.

Wiener JM, de Condappa O, Harris MA, Wolbers T. Maladaptive bias for extrahippocampal navigation strategies in aging humans. J Neurosci. 2013 Apr 3;33(14):6012-7.

Willemssen R, Falkenstein M, Schwarz M, Müller T, Beste C. Effects of aging, Parkinson's disease, and dopaminergic medication on response selection and control. Neurobiol Aging. 2011 Feb;32(2):327-35.

Wittchen HU, Pfister H. [DIA-X interviews: manual for screening procedures and interview]. DIA-X-Interviews: Manual für Screening Verfahren und Interview. Frankfurt: Swets & Zeitlinger; 1997. German.

Wolbers T, Wiener JM, Mallot HA, Büchel C. Differential recruitment of hippocampus, medial prefrontal cortex, and the human motion complex during path integration in humans. J Neurosci. 2007 Aug 29;27(35):9408-16.

Table 1

Table 1. Inclusion and exclusion criteria for study participation

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

MoCA – Montreal Cognitive Assessment; OFF – off medication; PD – Parkinson's disease patients.

Table 2

Table 2. Demographic and clinical sample characteristics

	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 (years)	59.4 (8.0)	61.3 (8.8)	56.9 (7.1)	$F(2,65) = 1.3$	0.28
Education (years)	10.9 (1.1)	11.1 (1.0)	10.8 (1.1)	$F(2,65) = 0.4$	0.70
Clinical data					
PD duration (years)	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

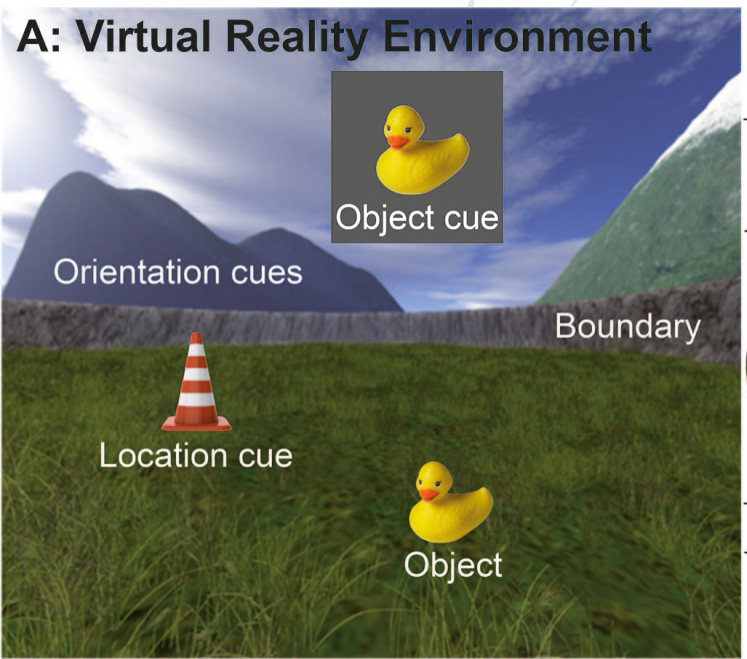
Values represent n or mean (SD). LED – L-Dopa equivalent dose; MoCA – Montreal Cognitive Assessment; PD – Parkinson's disease patients; PD-OFF-starters – PD patients OFF medication at session 1; PD-ON-starters – PD patients ON medication at session 1; UPDRS-III-ON – Unified Parkinson's Disease Rating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

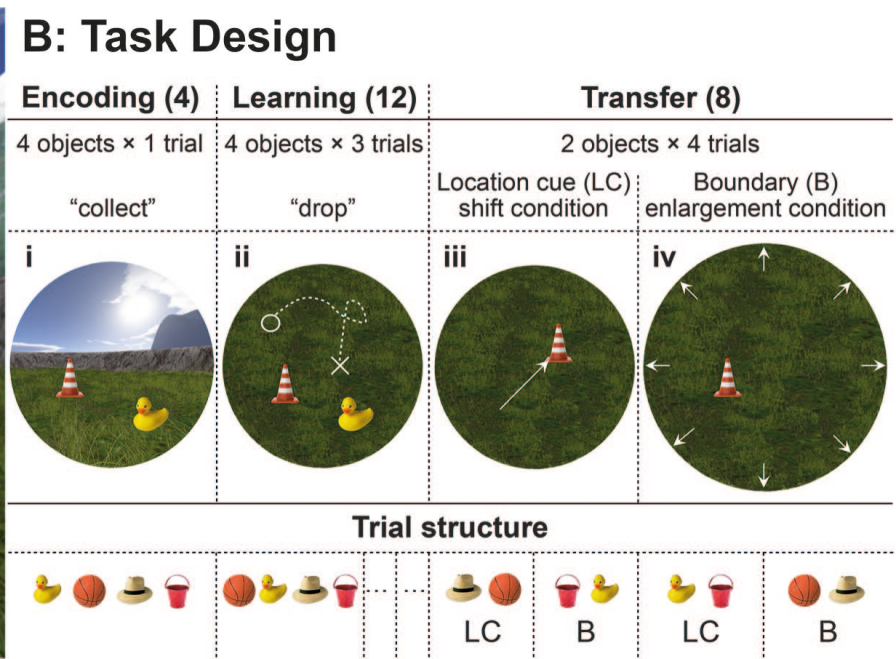
Figure Captions

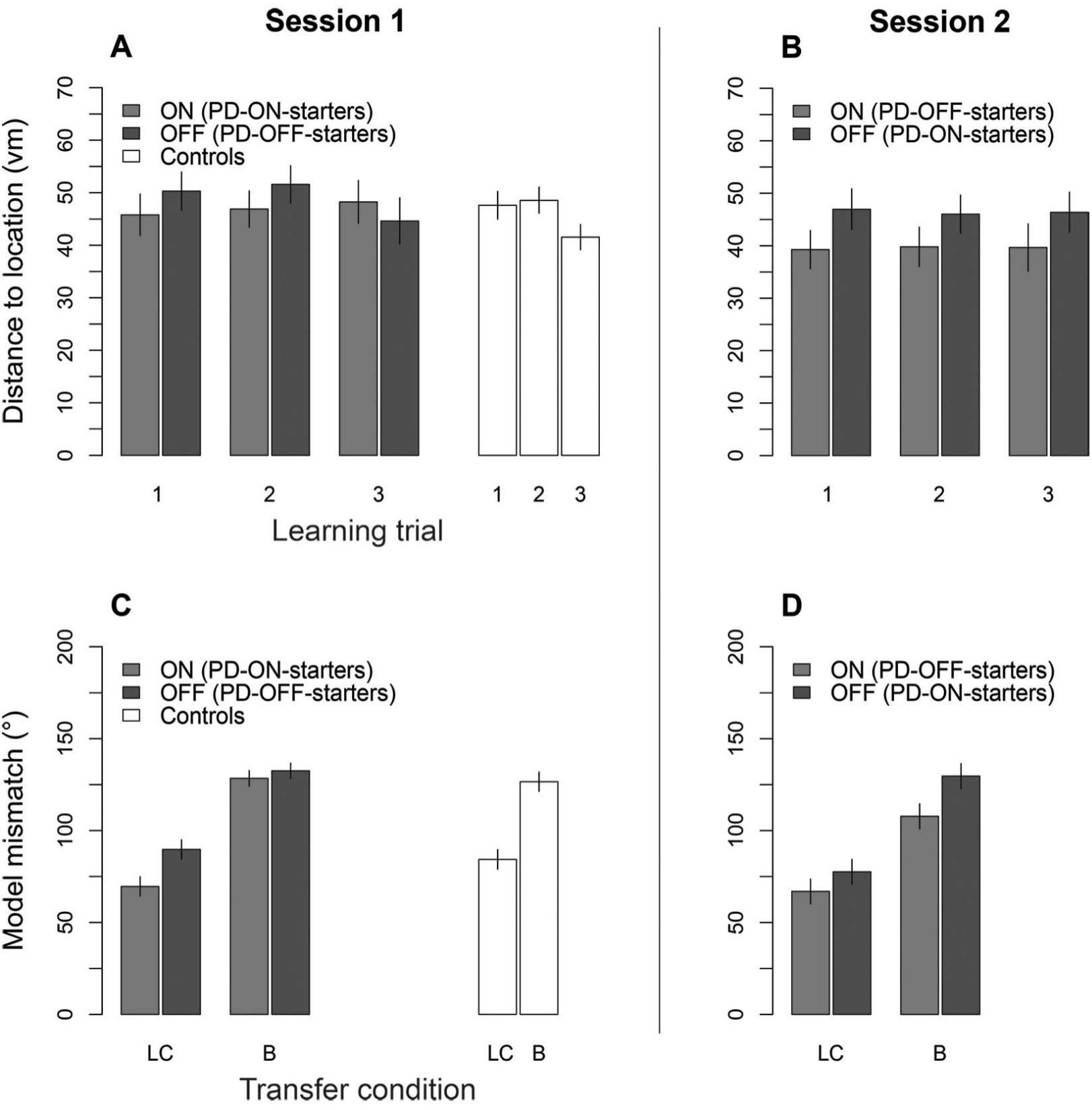
Figure 1. Schematic diagram of the task environment (A) and task design with 3 phases and an example trial structure (B). A: The virtual environment consisted of a circular grass plane surrounded by a stone wall (Boundary). A traffic cone (Location cue) was placed on the grass. Mountains, clouds, and 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.

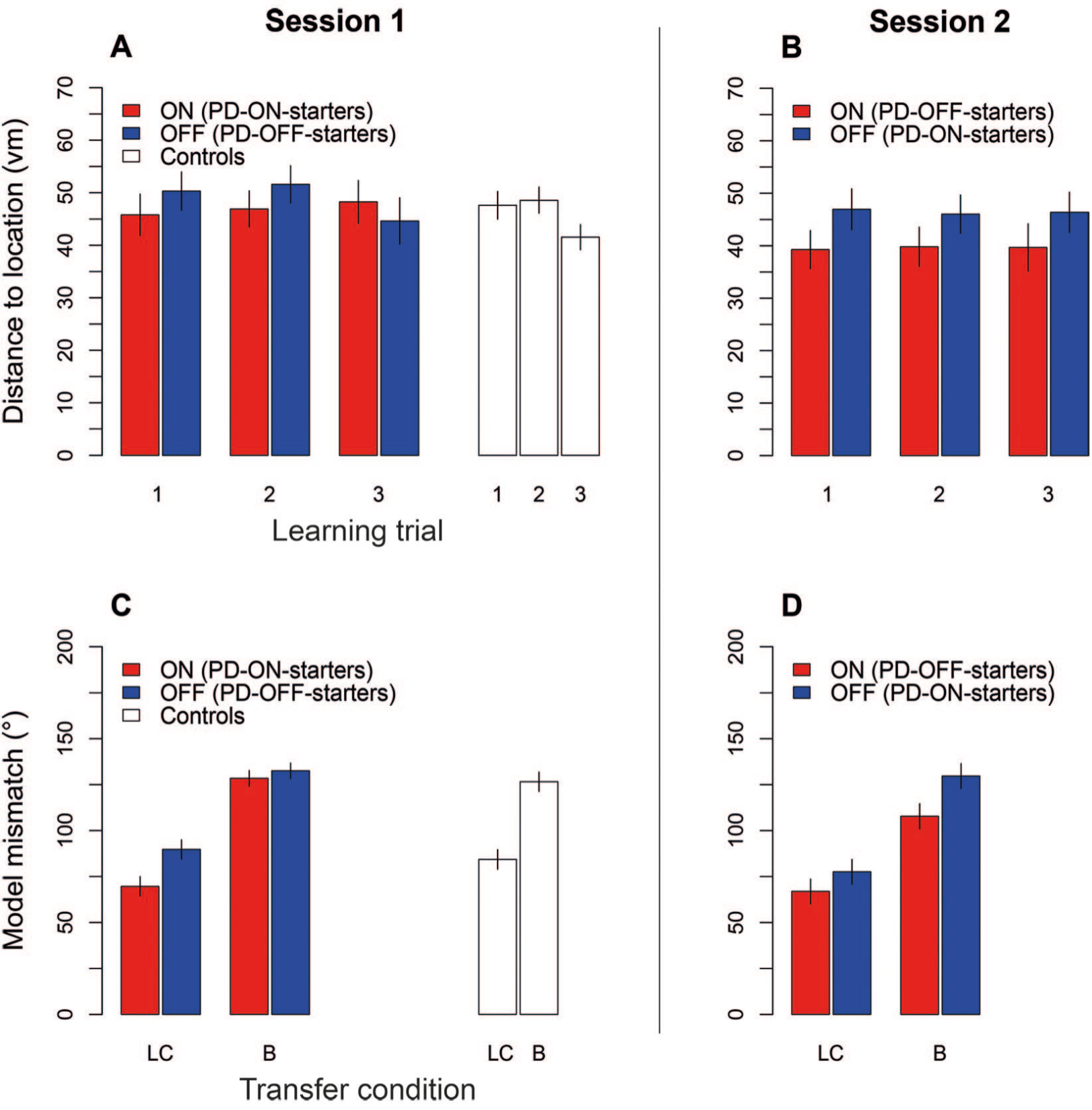
Figure 2. Effects of DA medication on PD patients' spatial memory performance. A-B: Distance between memorized location and actual object location in the learning phase comparing PD-ON-starters, PD-OFF-starters, and healthy controls at session 1 (A) and comparing PD-ON-starters versus PD-OFF-starters at session 2 (B). C-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 – ON; blue – OFF). Error bars are standard errors of the mean (SE).

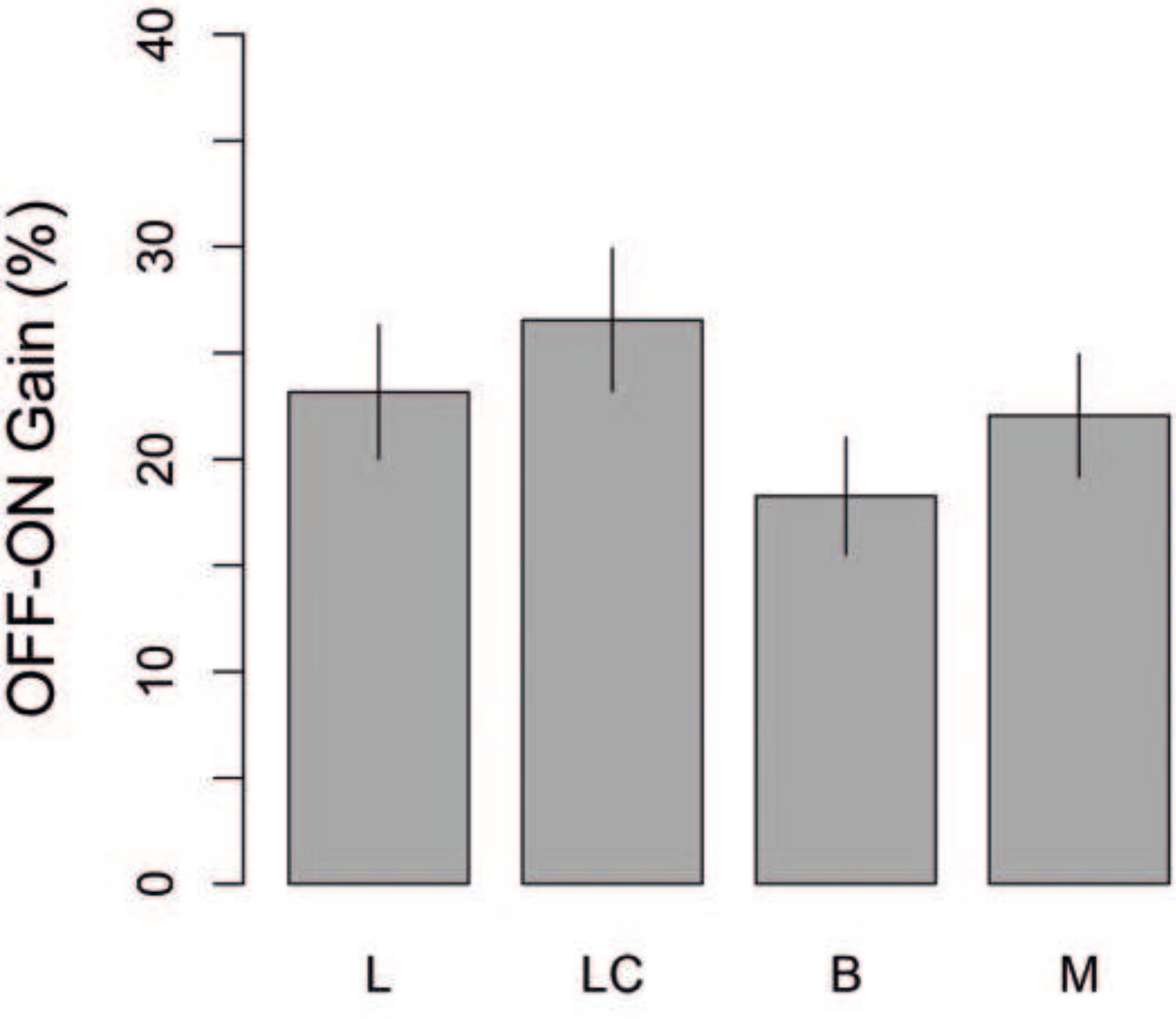
Figure 3. Medication effects on gain scores (computed as OFF – ON/OFF*100) of PD patients' motor dysfunction (M; measured by the UPDRS-III motor scale), spatial navigation performance in the learning phase averaged across the 3 trials (L), and the transfer phase conditions (LC – Location cue, B – Boundary). Error bars are standard errors of the mean (SE).






Session 1
A
ON (PD-ON-starters)
OFF (PD-OFF-starters)
Controls
Distance to location (vm)
0
10
20
30
40
50
60
70
1
2
3
1
2
3
Learning trial
Session 2
B
ON (PD-OFF-starters)
OFF (PD-ON-starters)
1
2
3
C
ON (PD-ON-starters)
OFF (PD-OFF-starters)
Controls
Model mismatch (°)
0
50
100
150
200
LC
B
LC
B
Transfer condition
D
ON (PD-OFF-starters)
OFF (PD-ON-starters)
LC
B


Session 1
A
ON (PD-ON-starters)
OFF (PD-OFF-starters)
Controls
Distance to location (vm)
0
10
20
30
40
50
60
70
1
2
3
1
2
3
Learning trial
Session 2
B
ON (PD-OFF-starters)
OFF (PD-ON-starters)
1
2
3
C
ON (PD-ON-starters)
OFF (PD-OFF-starters)
Controls
Model mismatch (°)
0
50
100
150
200
LC
B
LC
B
Transfer condition
D
ON (PD-OFF-starters)
OFF (PD-ON-starters)
LC
B


OFF-ON Gain (%)
0
10
20
30
40
L
LC
B
M

Faculty of Mathematics and Natural Sciences

Department of Psychology, Section of Lifespan Developmental Neuroscience

Technische Universität Dresden, 01062 Dresden

Dr. Franka Thurm
Telefon: 0351 463-39192
Telefax: 0351 463-42194
E-Mail: franka.thurm@ tu-dresden.de

2015-10-14

To
Peter R. Rapp
Editor-in-Chief/Section Editor

Neurobiology of Aging

Highlights for the revised and resubmitted manuscript with the title:
"Dopamine Modulation of Spatial Navigation Memory in Parkinson's Disease"

- Hippocampal-striatal spatial navigation was assessed in a virtual reality task.
- Dopamine medication improves spatial memory in Parkinson's disease (PD) patients.
- PD patients and controls rely more on striatal than hippocampal spatial learning.
- Medication effect on hippocampal spatial learning is moderated by task familiarity.
- Dopamine medication benefits were comparable to and independent of motor effects.

Postadresse (Briefe)
Technische Universität Dresden
Fakultät Mathematik/Naturwissenschaften
Fachrichtung Psychologie
01062 Dresden

Postadresse (Pakete u.ä.)
Technische Universität Dresden
Fakultät Mathematik/Naturwissenschaften
Fachrichtung Psychologie
Helmholtzstraße 10
01069 Dresden

Besucheradresse
DRE.PUNCT, Zimmer A 233
Zellescher Weg 17
Tiefgarage und
Aufzug vorhanden

www.psychologie.tu-dresden.de