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Dopamine differentially modulates medial temporal lobe activity and behavior during spatial navigation in young and older adults

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ABSTRACT

Aging is associated with changes in spatial navigation behavior. In addition to an overall performance decline, older adults tend to rely more on proximal location cue information than on environmental boundary information during spatial navigation compared to young adults. The fact that older adults are more susceptible to errors during spatial navigation might be partly attributed to deficient dopaminergic modulation of hippocampal and striatal functioning. Hence, elevating dopamine levels might differentially modulate spatial navigation and memory performance in young and older adults. In this work, we administered levodopa (L-DOPA) in a double-blind within-subject, placebo-controlled design and recorded functional neuroimaging while young and older adults performed a 3D spatial navigation task in which boundary geometry or the position of a location cue were systematically manipulated. An age by intervention interaction on the neural level revealed an upregulation of brain responses in older adults and a downregulation of responses in young adults within the medial temporal lobe (including hippocampus and parahippocampus) and brainstem, during memory retrieval. Behaviorally, L-DOPA had no effect on older adults' overall memory performance; however, older adults whose spatial memory improved under L-DOPA also showed a shift towards more boundary processing under L-DOPA. In young adults, L-DOPA induced a decline in spatial memory performance in task-naïve participants. These results are consistent with the inverted-U-shaped hypothesis of dopamine signaling and cognitive function and suggest that increasing dopamine availability improves hippocampus-dependent place learning in some older adults.

1. Introduction

Being able to spatially orient oneself, to flexibly navigate and to remember the locations of places, route intersections or other landmarks in complex environments is essential for maintaining an independent lifestyle throughout old age. Successful spatial navigation requires a complex integration of egocentric cues, specifically external sensory information and internal self-motion-related signals, into reliable allocentric representations of space. Thus, spatial learning and memory are subserved by multiple brain systems, particularly the hippocampus and parahippocampus, the entorhinal cortex, the (dorsal) striatum, the retrosplenial complex and the posterior parietal cortex (cf. Baumann and Mattingley, 2021; Burgess, 2008; Chersi and Burgess, 2015). Furthermore, prefrontal contributions seem of specific relevance for prospective hippocampal place cell coding of locations and goals during spatial navigation (Ito, 2018; Martinet et al., 2011) and for flexibly switching between different navigation strategies or types of spatial learning (e.g. Malagon-Vina et al., 2018; Ragozzino et al., 1999a, 1999b).

A large body of empirical evidence based on animal work and human neuroimaging studies underscores parallel hippocampal and striatal contributions during spatial navigation. Whereas the striatum extracts information about spatial locations from intramaze cues (also termed landmarks) and movement sequences (e.g. Doeller et al., 2008; Hartley et al., 2003), the hippocampus relies on spatial information from boundaries and extramaze cues to compute complex allocentric representations of spatial environments (also referred to as cognitive maps,

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see O'Keefe and Nadel, 1978). Both systems support different types of spatial learning, namely, striatum-dependent stimulus-response (cue-location) learning and hippocampus-dependent place learning, with the latter being more flexible but also more resource-demanding (see e.g. Chersi and Burgess, 2015, for a review). In addition, with its projection to the hippocampus via the entorhinal cortex, the parahippocampus supports hippocampus-dependent spatial navigation by providing important information about visuo-spatial features of scenes, including egocentric boundary information (cf. Baumann and Mattingley, 2021).

Aging has global as well as region-specific detrimental effects on structure, function and neurotransmission in several brain regions implicated in spatial learning and memory, resulting in various deficits during spatial navigation (see Lester et al., 2017 for a review). Older adults' deficits in inferring spatial orientation and location seem to be strongly associated with aging-related alterations of the hippocampus, parahippocampus, and other medial temporal lobe structures (Lester et al., 2017). With increasing adult age, the specificity of hippocampal place cell firing decreases, whereas firing latency increases (Barnes et al., 1983; Hok et al., 2012; Rosenzweig and Barnes, 2003). Factors contributing to negative effects of aging on hippocampal learning and memory further include, among others, loss of functional synapses and plasticity, reduced neuromodulatory input from dopaminergic and other neurotransmitter systems and increasing imbalance between excitatory and inhibitory inputs (cf. Leal and Yassa, 2015; Lester et al., 2017). In line with these findings, we have previously shown that older adults shift towards relying more on intramaze cue-dependent compared to boundary-dependent spatial learning (Glöckner et al., 2021; Schuck et al., 2013) and recruit more striatal compared to hippocampal resources. In contrast, young adults' spatial learning shows stronger hippocampal than striatal involvement (Schuck et al., 2015). Similarly, others have reported that older compared to young adults are less capable of computing and utilizing spatial relations during navigation (e.g. Iaria et al., 2009; Moffat et al., 2006; Moffat and Resnick, 2002), show a preference for (egocentric) navigation strategies that are mainly subserved by extrahippocampal structures (Moffat et al., 2007; Wiener et al., 2013) and have deficits particularly in switching from egocentric to allocentric navigation strategies (see Colombo et al., 2017 for a review; Harris and Wolbers, 2012, 2014). Moreover, normal aging-related NMDA receptor loss in medial prefrontal regions might compromise the process of maintaining spatial locations in working memory (McQuail et al., 2016), and aggravate performance deficits during spatial learning and memory (see Colombo et al., 2017; Lester et al., 2017 for reviews). In addition, aging-related deficits in spatial navigation can also be linked to a suboptimal weighting of external sensory compared to internal self-motion cues during multisensory integration, possibly leading to noisier spatial representations in older age (Bates and Wolbers, 2014). One mechanism that links decreased cognitive performance to increased neural noise in older age is dopaminergic modulation (Li et al., 2001).

Among its other functions, the dopamine system also implicates spatial learning and memory. The hippocampus receives dopaminergic projections from the ventral tegmental area via the mesolimbic pathway. Recent evidence shows that dopamine is also released into the hippocampus via a second pathway, namely by noradrenergic neurons originating in the locus coeruleus (McNamara and Dupret, 2017). In contrast, the dorsal striatum is mainly innervated by nigrostriatal dopaminergic neurons originating in the substantia nigra pars compacta (Bjorklund and Dunnett, 2007). Mesolimbic dopaminergic neurons seem to be involved in creating and storing spatial representations of an environment (e.g. McNamara et al., 2014). More specifically, dopamine plays an important role in regulating long-term potentiation (see e.g. Lisman and Grace, 2005 for a review) and in stabilizing spatial representations such as new goal locations during hippocampus-dependent learning (e.g. Bethus et al., 2010). Moreover, elevating dopamine availability in the rodent hippocampus or striatum by injecting dopamine agonists into either brain region facilitates hippocampus- or striatum-dependent spatial learning, respectively (Packard et al., 1994; Packard and Teather, 1998; Packard and White, 1991). Taken together, the evidence indicates that the dopamine system modulates both types of spatial learning subserved by the hippocampus and the striatum.

Based on cross-sectional estimates, starting from early adulthood we lose approximately ten percent of our dopamine (e.g. D2) receptor density per decade, and the related decline in dopaminergic modulation of cognitive functions is assumed to be even accelerated in very old age (see e.g. Bäckman et al., 2010, 2006 for reviews), although there is evidence that age-related receptor density decline does not occur at an equal rate throughout the brain (Rieckmann et al., 2011; Seaman et al., 2019). Cumulative evidence indicates that deficient dopamine modulation might constrain performance in various cognitive domains, including working memory and episodic memory (see Li and Rieckmann, 2014 for a review; Nordin et al., 2021; Nyberg et al., 2016; Papenberg et al., 2014). In line with empirical (e.g. Vijayraghavan et al., 2007) and computational evidence (Li and Sikstrom, 2002) that relates dopamine level to memory performance, an inverted-U-shaped relationship between dopamine signaling and cognitive functioning has been hypothesized (see e.g. Bäckman et al., 2010, 2006; Cools and D'Esposito, 2011; Li and Rieckmann, 2014; Lindenberger et al., 2008 for reviews). Thus, older adults' cognitive performance deficits may be reduced by pharmacologically increasing their dopamine levels, whereas raising dopamine levels in younger adults might have negative consequences depending on task demands. For example, in a previous study we showed that older adults with Parkinson's disease are able to shift towards more boundary-related and presumably more hippocampus-dependent spatial navigation in a familiar task when receiving dopamine-enhancing drugs (Thurm et al., 2016). However, results of pharmacological studies investigating the effects of transient dopamine augmentation on cognitive functions subserved by striatal and hippocampal circuitries in healthy older age are mixed. For example, in older adults, dopamine precursor levodopa (L-DOPA) improved reward-based learning only in a subgroup of participants. Specifically, an L-DOPA-induced modulation of the reward prediction error signal in the ventral striatum (nucleus accumbens) was only observed in older adults with substantial L-DOPA-induced improvements in choice behavior, indicating considerable interindividual differences in dopamine effects on performance (Chowdhury et al., 2013). Chowdhury et al. (2012) also investigated whether L-DOPA might facilitate hippocampus-dependent episodic memory in older adults and found that dopamine enhancement at a medium dosage modulates later post-encoding processes that are relevant for stabilizing hippocampal memory representations. Regarding young adults, there is tentative evidence for a beneficial effect of the L-DOPA on striatum-dependent reward-based learning and decision-making in young adults (Pessiglione et al., 2006; Wunderlich et al., 2012). However, pharmacological effects on dopamine-relevant functions are less straightforward to predict, since at the peak of the inverted-U function other factors, such as task demands and cognitive loads, relative drug dose and individual differences in dopamine availability (Kroemer et al., 2019; Lee et al., 2019) may come more into play (cf. Cools and D'Esposition, 2011).

Taken together, the interplay between aging, dopamine modulation and cognitive function in general is complex. Regarding spatial navigation, in previous work we have separately shown that age (Schuck et al., 2015) and dopamine dysregulation in Parkinson's disease (Thurm et al., 2016) affect hippocampus- and striatum-dependent spatial learning and memory. In this functional brain imaging study, we therefore aimed at investigating potential effects of a within-subject, placebo-controlled L-DOPA intervention on spatial learning and memory in healthy young and older adults at the behavioral and brain level by using a computerized spatial navigation task (Doeller et al., 2008; Schuck et al., 2015; Thurm et al., 2016). Following the assumption of an inverted-U-shaped relation between dopamine signaling and cognition, we primarily hypothesized that behaviorally, L-DOPA will shift spatial learning performance of older adults more toward the performance of young adults

under placebo. In addition, with respect to performance indicators reflecting hippocampus- (boundary-) dependent versus striatum- (intramaze cue-) dependent spatial navigation derived from relevant transfer task conditions, we expected older adults to show improved processing of hippocampus- (relative to striatum-) dependent information during spatial learning when under L-DOPA compared to placebo. In terms of brain functions, we aimed to replicate the age group differences in brain activity during spatial navigation reported by Schuck et al. (2015), with an underrecruitment of hippocampal activity in older adults, relative to younger adults, during spatial memory retrieval. Relative to younger adults, we also hypothesized that older adults may rely more on striatum during spatial navigation. Further, we hypothesized that a potential intervention-induced increase in older adults' spatial learning performance and boundary sensitivity would be associated with increased medial temporal lobe activity under L-DOPA compared to placebo. Regarding young adults, studies so far mostly focused on prefrontal or frontostriatal function with some identifying positive effects (Pessiglione et al., 2006; Wunderlich et al., 2012) and other detrimental effects (Vo et al., 2016) of L-DOPA on cognitive performance. Thus, L-DOPA could either increase or decrease learning and memory during spatial navigation in the young. Finally, given high interindividual differences, we also explored the relations between potential L-DOPA-induced changes in spatial learning during the learning phase (i.e. in the standard environment) and in the individual's relative reliance on hippocampus- versus striatum-dependent navigation during the transfer phase (i.e. after either manipulating the geometry of either the boundary or the location cue).

2. Methods

2.1. Participants

Altogether 672 out of 5927 young (YA; 25–35 years) and older adults (OA; 65–75 years), who were recruited from a population-based database provided by the city registry of Dresden, Germany (between April 2017 and September 2020) completed the study telephone screening, out of which 485 were screening failures (194 YA and 291 OA) and 187 were included into the study. Participants were eligible to partake in the study if they (1) spoke German fluently (written and spoken), (2) had no diagnosed mental disorders within the past 12 months, (3) had no neurological disorders and never experienced a seizure in their lifetime, (4) did not take antidepressants or neuroleptics within the past 12 months, anxiolytics or hypnotics within the past two weeks or any other drug potentially affecting brain dopamine levels within three days prior to each study sessions, (5) had normal or corrected-to-normal vision, (6) were neither pregnant nor currently breastfeeding and (7) had no magnetic resonance imaging (MRI) or levodopa (L-DOPA) contraindications. Older adults received additional dementia screening via the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), with a cut-off score of 23 or higher as an inclusion criterion in order to reduce the MoCA false-positive rate (Carson et al., 2018). A flow of participants figure (Fig. S1) and additional information regarding sample recruitment can be found in the Supplementary Material. Written informed consent was obtained from eligible young and older adults before study participation. Participants received 100 Euro plus earnings based on performance in additional tasks also included in the test battery, resulting in a total payout ranging from ~ 118 – 196 Euro. The study was approved by the ethics committee of the Technische Universität Dresden (number: EK440202012) and was conducted in adherence to the revised Declaration of Helsinki.

After study inclusion, participants were randomized to receive L-DOPA either in the first or in the second fMRI session (i.e. L-DOPA/placebo or placebo/L-DOPA intervention order). The study thus used a within-subject, placebo-controlled double-blind crossover fMRI design. Randomization was stratified by age group and sex such that intervention order was counterbalanced within each of the resulting four subgroups. In addition, one fifth of the participants were randomized to a control group who received a placebo in both fMRI sessions (placebo/placebo group). Only participants who completed the spatial navigation task and followed the pharmacological intervention protocol in both fMRI sessions were included for data analyses. Altogether, 130 participants completed all study sessions. Of these, 18 participants were excluded from further analyses due to incomplete execution or omission of the spatial navigation fMRI task, technical fMRI scanning-related issues and/or prolonged nausea during and after the fMRI scanning procedures. Ten further participants were excluded based on their spatial navigation task performance (> 25% of probes in the learning and transfer phase were timeouts, or > 60% of the responses overlapped with cue presentation). The application of all inclusion and exclusion criteria resulted in a final sample of 82 participants who received L-DOPA either in the first or in the second fMRI session (L-DOPA/placebo or placebo/L-DOPA). Among these 45 were young adults (YA; mean age: 31.13 ± 3.03 years, range: 26–35, 29 male) and 37 were older adults (OA; mean age: 68.24 ± 2.65 years, range: 65–75, 31 male). The remaining 14 YA (mean age: 31.93 ± 3.22 years, range: 26–35, 9 male) and 6 OA (mean age: 69 ± 1.79 years, range: 67–72, 3 male participants) were in the placebo-placebo control group. Due to the small size of the final placebo/placebo group, data analysis focused on the intervention group that received L-DOPA on either of the two fMRI sessions. Information on the placebo/placebo group can be found in Supplementary Table S1.

Sex distribution and years of education did not differ between age groups. Baseline cognitive performance was assessed during the first behavioral session using three computerized tasks. The Spot-a-Word (SAW) task tests verbal knowledge and is a reliable correlate of crystallized intelligence, whereas the Identical-Pictures (IDP) task assesses perceptual speed as a brief but reliable indicator of fluid functions (Lindenberger and Baltes, 1997; Lindenberger et al., 1993). In addition, the Spatial Working Memory (SWM) task (Klingberg et al., 2002; Nagel et al., 2008) measures working memory of spatial location and serial order for low and high working memory load conditions. Older adults outperformed young adults in the SAW verbal knowledge task ($p < 0.001$) and showed age-appropriate decline compared to young adults with regard to perceptual speed of processing (IDP; $p < 0.001$) and working memory for spatial locations (SWM; $p < 0.001$), which is in line with previous age-comparative work (e.g. Glöckner et al., 2021; Li et al., 2004; Nagel et al., 2008; please refer to these references for more details on these tasks). Further study sample characteristics of the intervention group are summarized in Table 1 and (in more detail) in Table S2 (including the age group by intervention order interactions) in the Supplementary Material.

2.2. Study procedure and pharmacological intervention

Participants attended three (one behavioral and two pharmaco-fMRI) sessions, which took place on separate days. On all sessions, participants underwent an illicit drug screening (urine-based test; Kombi/DOA10-Schnelltest, MAHSAN Diagnostika, Reinbek, Germany) and two breath tests that monitored recent alcohol consumption (Alcotest 6510, Dräger, Lübeck, Germany) and carbon monoxide (CO) levels (Mikro 4 Smokerlyzer, Rochester, England) that indicate recent tobacco smoking. Participants were excluded from further study participation in case of a positive alcohol or drug screening. Heavy smokers who were not able to comply with the study protocol due to high pressure to smoke during a session were also excluded from further participation. Participants within both age groups did not differ between fMRI sessions regarding their CO levels (rank sign tests, p-values > 0.7). On session one, participants answered questionnaires about their health status and education and completed computerized behavioral tasks, including the Spot-a-Word (SAW), Identical-Pictures (IDP) and Spatial Working Memory (SWM) task as well as other tasks and further questionnaires that are not part of this work.

Table 1
Study sample characteristics, intervention order assignment and cognitive covariates of young and older adults in the intervention group.

	YA	OA	Test statistic	*p*-value
n	45	37		
Age (years)	31.13 ± 3.03	68.24 ± 2.65		
MoCA		26.68 ± 2.12		
Sex (female/male)	16/29	6/31	*OR* = 2.81	0.08
BMI (kg/m^2)	24.86 ± 3.83	27.11 ± 3.33	*W* = 519.5	<0.05
Education (years) [1]	16.94 ± 3.23	15.24 ± 3.81	*W* = 869.5	0.07
CO_{Breath}, session two (ppm)	1, *IQR* = 2	0, *IQR* = 1	*W* = 984	0.13
CO_{Breath}, session three (ppm)	1, *IQR* = 2.75	0, *IQR* = 1	*W* = 1038	<0.05
Intervention order				
L-DOPA starters	22	17	*OR* = 1.12	0.83
Placebo starters	23	20		
Baseline cognitive covariates:				
Spot-a-Word (correct responses) [2]	21.88 ± 3.96	26.06 ± 3.39	*W* = 321.5	<0.001
Identical-Pictures (correct responses) [2]	29.34 ± 5.66	21.31 ± 3.91	*W* = 1434.5	<0.001
Spatial-Working-Memory (accuracy) [3,4]				
Low load condition	96.79 ± 3.70	89.99 ± 8.36	*W* = 1232.5	<0.001
High load condition	89.01 ± 7.23	74.82 ± 11.98	*W* = 1327.0	<0.001

MoCA = Montreal Cognitive Assessment, BMI = body mass index, *OR* = odds ratio, CO_{Breath} = breath carbon monoxide level, ppm = parts per million, *IQR* = interquartile range, *W* = Wilcoxon rank sum statistic. Average values are expressed as the arithmetic mean ± standard deviation, except CO_{Breath} values, which are expressed as the median. Missing data sets: [1] n = 4 YA, n = 3 OA; [2] n = 1 OA; [3] n = 2 OA. Note: [4] The serial order memory subtest of the task is not reported due to ≥ 50% missing responses of n = 7 OA in the low working memory load condition and n = 15 OA in the high load condition.

Pharmacological intervention combined with task-fMRI was carried out on sessions two and three. To achieve sufficient L-DOPA absorption rates (Crevoisier et al., 2003; Tsui et al., 1989), we asked participants to abstain from eating protein-rich foods within twelve hours, and not to eat anything within eight hours prior to the beginning of these sessions, which took place in the morning. In order to reduce side effects of L-DOPA intake, participants received four butter biscuits (~ 120 kcal) upon arrival and three glucose tablets (~ 26 kcal) ten minutes prior to the drug intervention. To get familiar with the structure of the spatial navigation task, participants received a detailed explanation of the task procedure, followed by a training on a short version of the spatial navigation task that included all task phases, but featured a different environment with different objects compared to the scanner version. Participants took either 150 mg L-DOPA + 37.5 mg benserazide (Madopar, Roche, Grenzach-Wyhlen, Germany) or a placebo tablet 15 min before MR imaging. After participants completed structural and resting state scans and a task that is not part of the present work, they received a booster dose (either 75 mg L-DOPA + 18.75 mg benserazide or a placebo), 110 min after intake of the first tablet. Benserazide inhibits the conversion of L-DOPA to dopamine in the periphery thereby facilitating the dopamine increase in the brain, which in addition reduces potential side effects of Madopar. The spatial navigation task started 25 min after the booster dosage. The time gap between the two MRI sessions was at least 13 days and at most 45 days in the intervention group, while most participants (> 91%; mean = 17.18 ± 5.70 days) fell within a 14 to 28 days' range regarding their between-sessions gap. Ten minutes after booster administration, participants entered the MR scanner room where they were familiarized with navigating a virtual environment in a lying position, having a joystick placed upon their abdomen. To this end, participants completed another brief joystick training task in the lying position and the experimenter repeated the main task instructions to them. After participants felt sufficiently confident with the joystick setup in the scanner, the spatial navigation task was started (approximately 20 min after intake of the booster dose).

2.3. Spatial navigation task

We employed a modified version of a computerized spatial navigation task (Doeller et al., 2008; Schuck et al., 2013) that probes object location memory and assessed participants' reliance on intramaze cue- or boundary information for spatial memory by systematically manipulating the location of the intramaze cue or the width of the boundary (Glöckner et al., 2021; Schuck et al., 2015; Thurm et al., 2016). The task was created with UnrealEngine2 (Epic Games; https://docs.unrealengine.com/udk/Two/). The 3D spatial environment of the task consisted of a grass plane enclosed by a circular stone wall that functioned as a spatial boundary. The height of the stone wall allowed the view of mountains, clouds and the sun beyond its perimeter, which served as distal background orientation cues. However, these distal cues were projected at infinity, precluding the possibility of applying the principle of parallax for estimating distance and relative locations of objects within the circular arena. Participants navigated through this spatial environment in a first-person view, using a custom-made MR-compatible joystick while their positions (x, y coordinates) were sampled every 100 ms. While lying in the scanner, participants viewed the spatial environment via a set of mirrors mounted on top of the MR head coil, projecting images from a screen on the rear wall of the room. Distances within the arena were defined in virtual meters (one vm = 62.5 UnrealEngine2 units; diameter of boundary = 180 vm) and the only permanent object within the virtual environment was a traffic cone with a fixed location during spatial encoding and learning, that served as an intramaze location cue. The exact location of the intramaze cue and objects differed between sessions. The task involved three consecutive phases: an encoding phase, a learning phase and a transfer phase (see Fig. 1). In the initial encoding phase, participants were positioned close to the center of the circular arena and had to move towards the object location to pick it up by walking over it, thus completing an encoding run. We used two sets of five distinct objects (e.g. an alarm clock, a briefcase, a rubber duck etc.) that were counter-balanced between participants and MRI sessions. During the encoding phase, only one of the five objects was present in each run and after picking up the object, the participants started the next run with a different object, again at a location near the center of the arena, but with a random heading vector. In the subsequent learning phase, participants were instructed to consecutively return to the locations of each of the five objects seen during the initial encoding phase over six repetitions, resulting in a total of 30 runs in the learning phase. The order of the objects was pseudorandomized, such that within a sequence of five consecutive runs (constituting a trial), each object was presented exactly once. Each learning phase run started with the presentation of a 2D image (cue) of a given object

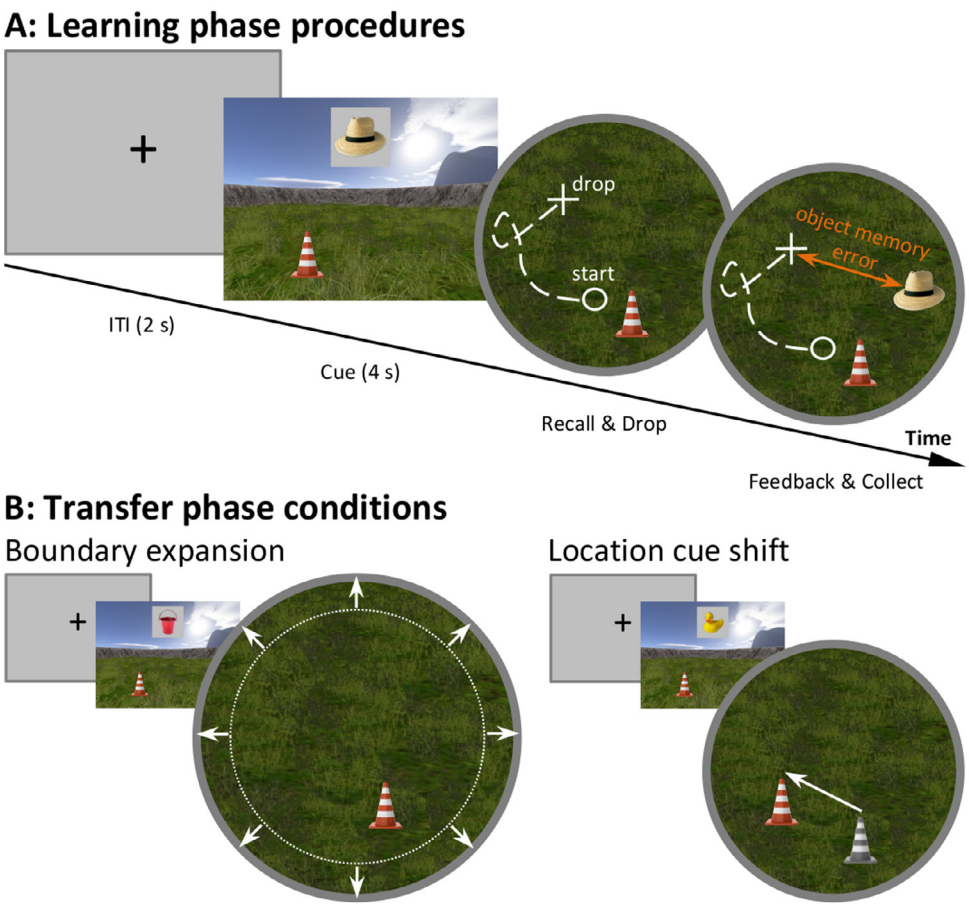

Fig. 1. Outline of the learning and transfer phase of the computerized spatial navigation task. (A) After an initial encoding phase in which participants were familiarized with the locations of five everyday objects in the circular arena, the learning phase began. A learning phase trial of five objects started with a gray screen, followed by the presentation of an object cue for the duration of 4 s. Participants were required to walk from their starting position (o) to the remembered position of the cued object (+) and "drop" it there via button press. After the object was dropped, feedback about its actual location was given and participants picked up the object. The learning phase included six trials and within a given trial, all five objects were presented once. (B) In the transfer phase, participants performed the same task as in the learning phase (without feedback) and additionally faced either one of two conditions: expansion of the stone wall boundary or shift of the location cue (participants were unaware of these manipulations). ITI = inter-trial interval.

displayed on a gray background in the upper half of participants' field of view for four seconds. Then, participants navigated towards the remembered location of the cued object and indicated its position via button press (object "drop"). Upon button press, the respective object appeared in its exact spatial location as presented in the initial encoding phase as a feedback. Participants could then use the discrepancy between the remembered and actual object position to update their object location memory. A learning phase run was completed after participants picked up the object again in its displayed, actual location, which initiated the next run starting from the position of the previously recalled (picked-up) object. When the participant's remembered object location was sufficiently accurate (i.e. within a 5 vm radius of the actual object position) the feedback "Perfect" was displayed in the center of participants' field of view for three seconds, directly followed by the next run. Within learning runs, the time from cue onset until object drop constitutes the "replace period", while the time from drop until pickup of the object at its correct location denotes the "feedback period". The transfer phase is the third and the last phase of the task, which included two independent conditions: boundary expansion and intramaze location cue shift. In the boundary expansion condition, the stonewall boundary was enlarged by 20%, resulting in a radius increase from 80 to 96 vm while the intramaze cue (a traffic cone) kept its position relative to the center of the arena. In the location cue shift condition, the traffic cone was shifted by 30 vm relative to its original position while the boundary size remained unchanged. Each experimental manipulation occurred ten times with two or three runs belonging to one condition appearing in a row, and every object appeared twice in each condition (overall sequence of objects was pseudorandom), resulting in 20 transfer phase runs in total (10 per condition). Participants were naïve to the boundary and location cue manipulations and were instructed to navigate to the remembered locations of cued objects, akin to the learning phase, but without receiving feedback about the actual object locations. During the learning and the transfer phase, participants navigated continuously from one run to the next. More specifically, the participants starting location and heading vector of each run within a trial equaled the end location and heading vector of the previous run. Apart from the five initial encoding runs, all runs had a timeout criterion of 70 s in the replace period. The duration of the replace period could vary between persons but was comparable between age groups (YA: mean = 26.16 ± 6.31 min, range = 13.65 – 48.32 min; OA: mean = 28.08 ± 6.51 min, range = 15.28 – 43.57 min).

2.4. MRI data acquisition

We recorded all MRI data using a 3 Tesla MAGNETOM Trio Tim whole body scanner (Siemens, Erlangen, Germany) at the Neuroimaging Center of the Technische Universität Dresden. Prior to echo planar imaging (EPI) acquisition, a gradient echo sequence was recorded to obtain a field map, which was used to correct for geometric distortions caused by static field inhomogeneities (TR: 532 ms, TE 1: 5.32 ms, TE 2: 7.78 ms, FOV: 192 × 192 mm, acquisition matrix: 64 × 64, number of slices: 48, voxel dimensions: 3 × 3 × 2.5 mm). Functional data were acquired using a T2*-weighted EPI sequence in a descending acquisition order (TR: 2360 ms, TE: 25 ms, FA: 80°, FOV: 192 × 192 mm, acquisition matrix: 64 × 64, number of slices: 48, voxel dimensions: 3 × 3 × 3 mm). For EPI acquisition, slices were tilted by −25° relative to the anterior-posterior commissure line. The same field map and EPI sequences were used in both MRI sessions. During the first MRI session, we additionally obtained a structural high-resolution 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) image (TR: 2400 ms, TE: 2.19 ms, FA: 8°, FOV: 272 × 272 mm, acqui-

sition matrix: 320 × 320, number of slices: 192, voxel dimensions: 0.85 × 0.85 × 0.85 mm) for normalization to template space.

2.5. Behavioral analyses of spatial learning and memory performance

Object location memory was assessed by calculating the Euclidean distance between actual and remembered object locations (termed "distance error") during the learning phase of the spatial navigation task; hence larger distances (in vm) signify worse memory performance. These "distance to location" data were analyzed using mixed-effects ANOVA models with the between-subject factors Age Group (YA or OA) and Intervention Order (L-DOPA Starters or Placebo Starters) and within-subject factors Intervention (L-DOPA or Placebo) and Learning Trial (1 to 6). We included the between-subject factor Intervention Order to account for the possibility that the mere order of drug application (participants received either L-DOPA in the first and placebo in the second session, or vice versa) might cause differences in behavioral outcome (cf. Garrett et al., 2015).

2.6. Boundary and location cue model of spatial navigation

In addition to assessing object location memory performance in the learning phase, we also applied two models to the data obtained from the two transfer conditions (i.e. boundary expansion and location cue shift) to analyze hippocampus- (boundary-) and striatum- (location cue-) dependent spatial learning (Schuck et al., 2015). In a nutshell, the boundary model assumes that enlarging the size of the boundary will alter object location memory to the degree that participants rely on boundary information (shifting the remembered object position radially outwards), while shifting the location cue (traffic cone) is assumed to change participants' memory according to their reliance on intramaze cue information in the location cue model (shifting the remembered object location in accordance with the location cue shift).

Specifically, the boundary model transforms each object position $\mathbf{p}$ (defined by x, y coordinates) to a predicted memorized position $\tilde{\mathbf{p}}_m$ with respect to the change in the radius (Δr) of the spatial environment:

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

The location cue model instead predicts a change in the object location memory along the same direction that the intramaze cue was shifted, meaning that the shift of the cue by the translation vector v_{LC} shifts the predicted remembered locations by that same vector. Hence, both models make assumptions about changes in remembered object locations either as a function of boundary expansion or intramaze location cue shift, respectively. These predictions were then compared to participants' behavior to assess individual and age-related differences in the reliance on boundary and location cue information. First, we calculated the angle that connects a participant's remembered location of a given object in the last learning phase trial $\mathbf{p}$ to the model's assumptions in the transfer phase $\tilde{\mathbf{p}}_m$. Then, we calculated the angle between the remembered location $\mathbf{p}$ in the learning phase to the remembered (observed) locations for the same objects in the transfer phase, $\tilde{\mathbf{p}}_o$. The vertex of each angle was the center of the circular arena. Finally, to compare the predicted direction changes (first angle, γ_m) to the observed direction changes (second angle, γ_o) we took the difference between the angles of the vectors ($\mathbf{p}$ - $\tilde{\mathbf{p}}_m$) and ($\mathbf{p}$ - $\tilde{\mathbf{p}}_o$):

$$\gamma_m - \gamma_o = \tan^{-1}\left(\mathbf{p} - \tilde{\mathrm{p}}_m\right) - \tan^{-1}\left(\mathbf{p} - \tilde{\mathrm{p}}_o\right) \quad (2)$$

The resulting values indicate a mismatch between individual behavior and the respective boundary and location cue model predictions, ranging from 0 to 180° Thus, a higher mismatch indicates lower sensitivity to boundary or location cue processing during spatial navigation. The same procedure was performed for each object. Every object occurred twice in each condition within the transfer phase. Therefore, we averaged angle-mismatch values across all five objects and their two occurrences within each condition. We analyzed these data in a mixed-effects ANOVA with the between-subject factors Age Group (YA or OA) and Intervention Order (L-DOPA Starters or Placebo Starters) and within-subject factor Condition (Boundary or Location Cue).

All analyses of behavior, including model-derived data from the spatial navigation task, were carried out using the R software environment (https://R-Project.org/). Linear models were calculated using the R package 'afex' (https://CRAN.R-project.org/package=afex). Mauchly tests of sphericity were calculated and Greenhouse-Geisser corrections of significance values were applied where appropriate. To estimate effect sizes we opted for generalized eta squared (η_G^2), since it allows to compare effects of within- and between-subject designs (Bakeman, 2005).

2.7. Functional MRI preprocessing and statistical analyses

Spatial preprocessing of imaging data was conducted with SPM 12 (Statistical Parametric Mapping; www.fil.ion.ucl.ac.uk/spm). First, we calculated voxel-displacement maps (VDM) from individual and session-specific field maps to correct for geometric distortions in EPI images. Then, functional images of both sessions were spatially realigned to the first image of the first session to correct for head motion and unwarped using the VDMs calculated in the previous step. Functional data were slice time corrected via SPM's Fourier phase shifting interpolation, using the middle slice as a reference. The individual structural T1-weighted image was co-registered to the mean EPI image of both sessions and then segmented into gray and white matter. These segmented images were used to normalize EPI images of both sessions to the standard space of the Montreal Neurological Institute (ICBM 152 MNI template) using SPM's DARTEL algorithm. We created age group-specific DARTEL templates to account for age-related differences in brain morphology. Finally, functional images of both sessions were resampled to their original acquisition resolution of 3 mm^3 voxels and spatially smoothed with an isotropic 8 mm full width at half maximum (FHWM) Gaussian kernel.

We carried out single-subject (first-level) blood-oxygen-level-depend (BOLD) analyses of the task's learning phase using SPM 12. To this end, we convolved fMRI time series' with the canonical hemodynamic response function (HRF) to include the following (unmodulated) regressors of interest in the design matrix: Cue, modeled as an event of the object-cue onset, Replace, modeled as a block that spans the duration between cue display and object drop, Feedback, modeled as a block for the period between object drop and collection of an object shown in its correct location, and ITI, model as an event for the display of a gray screen between blocks of objects. In addition, we created two further regressors for model-based analyses by parametrically modulating the Replace regressor with values indicating the mismatch between behavior and the boundary model ($Replace_{(boundary)}$) and the Feedback regressor with values indicating the mismatch between behavior and the location cue model ($Feedback_{(location\ cue)}$) as in Schuck et al. (2015). Since previous work by Doeller et al. (2008) has linked location cue learning to reinforcement processes, location cue model predictions were used to modulate the feedback phase, while the replace phase, which demands memory retrieval processes, was modulated by the predictions of the boundary model. To mitigate the effects of in-scanner head-movement we applied the following measures: inclusion of a Volterra expansion of the six motion parameters (Lund et al., 2005) and the censoring of scans affected by high levels of motion by including scan nulling regressors (Power et al., 2012; Siegel et al., 2014) as covariates of no interest in the design matrix. The Volterra expansion comprises linear and quadratic effects of the estimated motion parameters (from the spatial realignment step) and linear and quadratic effects of the first derivative of said parameters. Together this results in 24 covariates which are able to capture higher-order effects of motion, like spin-history effects (Friston et al., 1996). For motion censoring, we first calculated the framewise displacement (FD) of every volume of each individual's fMRI timeseries, which is a scalar value representing scan-to-scan deviations (i.e. sum of absolute translations and rotations). Then, we set the crite-

rion for excessive head motion to FD > 0.9 (cf. Siegel et al., 2014) and created scan nulling regressors that flagged affected scans, thereby excluding them from general linear model (GLM) estimation. Comparisons between L-DOPA and placebo trials showed no differences in FD head movement, neither for YA ($V = 519.5$, $p > 0.9$) nor for OA ($V = 342$; $p > 0.8$). As a final step for GLM estimation, functional data were high-pass filtered with a cut-off of 128 s and corrected for temporal autocorrelation using the AR(1) model.

Statistical contrasts on the first-level represented the main effects of the following regressors: Replace, $\text{Replace}_{(\text{Boundary})}$, Feedback and $\text{Feedback}_{(\text{location cue})}$. The contrast images of first-level analyses were submitted to second-level mixed design models with Intervention as a within-subject factor, and Age and Intervention Order as between-subject factors. In order to yield robust estimations of the repeated-measures factor, we opted for the Sandwich Estimator Toolbox (SwE; Guillaume et al., 2014; Guillaume and Nichols, 2015). SwE uses a non-iterative Ordinary Least Squares (OLS) model approach followed by the application of the so-called Sandwich Estimator, which accounts for within-subject correlations in repeated-measures data. For model estimation, we chose the modified SwE procedure with small sample size correction (type C2) and used the non-parametric Wild Bootstrap (WB) procedure with 999 iterations for cluster-level inference (t-scores). We calculated all main effects and interactions of the three above-mentioned factors. Results were examined at the cluster-level significance of $p < 0.05$ (family-wise error (FWE) corrected after applying a cluster-forming threshold of $p = 0.001$ at the WB step). Second-level results of unmodulated first-level effects (Replace and Feedback) were examined at the whole-brain level, whereas group results from model-based analyses were restricted to anatomical regions of interest (ROIs) of the hippocampus/parahippocampus for the $\text{Replace}_{(\text{Boundary})}$ and caudate nucleus for the $\text{Feedback}_{(\text{location cue})}$ model (cf. Schuck et al., 2015). Anatomical ROIs were taken from the AAL3 toolbox (Rolls et al., 2020).

2.8. Associations between L-DOPA-induced changes in the outcome measures of the learning and transfer phase

Although all participants received the same L-DOPA intervention, interindividual differences in drug response are to be expected within age groups, partly due to genetic predispositions (Evans and Johnson, 2001) that may potentially further interact with between age group differences in levodopa/benserazide pharmacokinetics (Contin et al., 1991). In addition, L-DOPA might affect individual spatial learning capacities in the initial phase of the task (i.e. in the original task environment where object locations are learned), which may in turn influence task behavior in the subsequent transfer phase (i.e. when the task environment is changed by either shifting the intra-maze location cue or expanding the boundary). This raises the question whether participants who show L-DOPA-related improvements in the behavioral outcome of the learning phase also improve with respect to the outcome measures of the transfer phase. Therefore, we explored the relationship between drug-induced modulations of object location learning and drug-related differences in boundary or location cue sensitivity in both age groups. To this end, for data from the learning phase, we first subtracted the distance error (in vm) of the last trial from the first trial (since higher values indicate worse performance and, hence, values should decrease over time) and divided the difference by the performance on the first trial (i.e. (T1 – T6)/T1) for each participant. These values were then z-standardized across participants of both age groups and transformed into T-scores (T-score = 10 × z-score + 50). Then, the values from the placebo session were subtracted from values from the L-DOPA session to derive an L-DOPA-induced learning effect for each participant. As for the L-DOPA induced effect on boundary- or location cue processing, assessed in the transfer phase, we subtracted the averaged mismatch values (between behavior and boundary or location cue model) in the L-DOPA session from those in the placebo session. These computations were done to have the scales of all three measures of L-DOPA-induced effects (i.e. spatial learning, boundary sensitivity and location cue sensitivity) in the same direction (i.e. higher values reflected L-DOPA-induced improvement). To test if the influence of L-DOPA on object location learning is concomitant with the drugs' influence on boundary or location cue sensitivity, we calculated Kendall's tau rank correlations between these measures separately for YA and OA. We chose to perform non-parametric Kendall's tau correlations because data on L-DOPA-induced changes in boundary sensitivity were not normally distributed in YA. Correlation coefficients were false discovery rate (FDR) corrected (Benjamini and Hochberg, 1995) where appropriate.

3. Results

3.1. Effects of age and L-DOPA on spatial learning and memory performance

Object location memory (distance error between remembered and correct object locations) was analyzed using a mixed-effects ANOVA with the between-subject factors Age Group (YA or OA) and Intervention Order (Placebo Starters or L-DOPA Starters) and the within-subject factors Intervention (Placebo or L-DOPA) and Learning Trial (1 to 6). Mean distance (in vm) to correct object location is shown in Fig. 2A. A main effect of Age Group ($F_{(1,78)} = 233.04$, $p < 0.001$, $\eta_G^2 = 0.59$) revealed overall better performance of young compared to older adults. We also observed a main effect of Trial ($F_{(5,390)} = 24.53$, $p < 0.001$, $\eta_G^2 = 0.02$), which showed memory improvement (reduced distance error) over the course of the learning phase. The significant Age Group × Trial interaction ($F_{(5,390)} = 6.00$, $p < 0.001$, $\eta_G^2 = 0.005$) indicated a steeper reduction of distance error in young relative to older adults. Moreover, the significant Intervention × Intervention Order interaction ($F_{(1,78)} = 15.51$, $p < 0.001$, $\eta_G^2 = 0.012$) constituted a cross-session learning effect with overall better memory performance in session two compared to session one ($\text{mean}_{(S1)} = 33.80$ vm, $\text{mean}_{(S2)} = 29.47$ vm, $t_{(78)} = 3.94$, $p < 0.001$). Finally, the analysis also yielded a significant but small Age Group × Trial × Intervention Order interaction ($F_{(5,390)} = 2.86$, $p = 0.02$, $\eta_G^2 = 0.002$). There were no further significant main effects or interactions, including no main effect of Intervention. To resolve the three-way interaction, we ran separate ANOVA models for YA and OA with Trial as within-subject factor and Intervention Order as between-subject factor. The results showed significant main effects of Trial in both age groups (YA: $F_{(5,215)} = 27.80$, $p = <0.001$, $\eta_G^2 = 0.10$; OA: $F_{(5,175)} = 7.87$, $p < 0.001$, $\eta_G^2 = 0.079$) as well as a Trial × Intervention Order interaction only in the young adults, indicating steeper learning in the Placebo compared to the L-DOPA Starter group ($F_{(5,215)} = 3.73$, $p = 0.003$, $\eta_G^2 = 0.015$). There were no further significant main effects or interactions in both ANOVAs.

Acknowledging the lack of statistical power for detecting a 4-way interaction, these results still tentatively hint towards an age group dependent influence of intervention order on L-DOPA-induced changes in navigation behavior. In a previous study, we were able to show that in conditions of dysfunctional dopamine modulation such as Parkinson's disease, the order of being ON versus OFF medication affects boundary sensitivity while performing a similar version of this navigation task (Thurm et al., 2016). Furthermore, a dopamine challenge seems to differentially affect working memory performance in young and older adults (Garrett et al., 2015). We therefore also further explored the full model – first separately for both age groups and in the second step separately for both starter groups. For the young adults, in addition to the above reported main effect of Trial and Trial × Intervention Order interaction, the full model also revealed a Intervention × Intervention Order interaction ($F_{(1,43)} = 20.22$, $p < 0.001$, $\eta_G^2 = 0.05$), whereas in older adults only the above reported main effect of Trial was shown. These results revealed that the cross-session learning effect (i.e. the Intervention × Intervention Order interaction) in the full model seems specific to the YA group ($\text{mean}_{(S1)} = 20.72$ vm, $\text{mean}_{(S2)} = 15.45$ vm, $t_{(43)} = 4.50$, $p < 0.001$) and that in OA only a within-session learning improvement

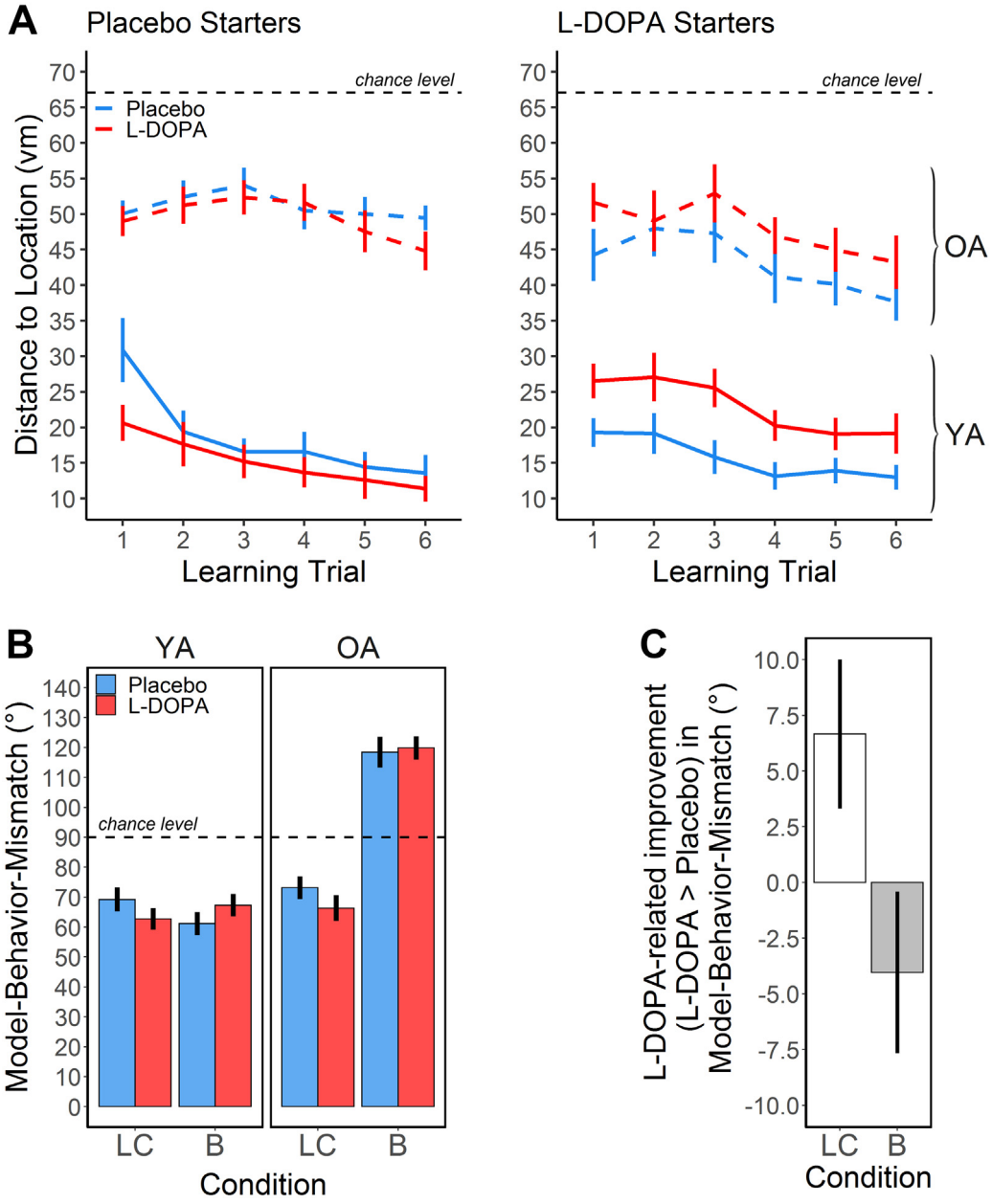

Fig. 2. Results of behavior and model-behavior mismatch (compared to chance-level performance, see Supplementary Material). (A) Mean distance between correct and remembered locations (i.e. object location memory performance) across six trials (with all five objects being presented in every trial) stratified by age group, intervention and intervention order. (B) Mean mismatch between the predictions of the boundary and location cue model with participants' behavior (i.e. angle deviations) separated by age group, intervention and condition. (C) The L-DOPA-related change in model-behavior mismatch revealed an increase in location cue processing which differs significantly from the decrease in boundary processing under L-DOPA across both age groups. Error bars indicate one standard error of the mean. YA = young adults, OA = older adults, vm = virtual meters, LC = location cue, *B* = boundary.

effect remained. In the next step, the models were further split for starter groups, however only for the young adults, given the lack of a significant main effect of or interaction with Intervention Order in older adults. In the group of young Placebo Starters, only the main effect of Trial ($F_{(5,110)} = 19.17$, $p < 0.001$, $\eta_G^2 = 0.11$) remained significant, while young L-DOPA Starters showed significant main effects of Intervention ($F_{(1,21)} = 18.51$, $p < 0.001$, $\eta_G^2 = 0.10$) and Trial ($F_{(5,105)} = 11.62$, $p < 0.001$, $\eta_G^2 = 0.07$). These differences in Placebo and L-DOPA Starters appear to tentatively indicate intervention order dependent effects, with a main effect of Intervention, reflecting worse spatial learning performance under L-DOPA compared to placebo in young adults, but only in those who received L-DOPA in the first session. Thus, in this young adult group, L-DOPA seems to impair spatial learning in the first session. This impairment seems to be offset by cross-session learning improvements, which eventually causes both starter groups to perform equally well on the second session of the task (cf. Fig. 2A). Results of object location memory analyses for the placebo/placebo group can be found in the Supplementary Material.

3.2. Age effects on travelled path length and navigation duration during spatial learning

Since age and the drug intervention might also influence the path length or duration of runs in the learning phase, we examined both variables in additional analyses. During the replace period of the learning phase the average path length of individual runs

did not differ between drug conditions, but was longer in YA compared to OA ($YA_{(Placebo)}$: mean = 101.04 ± 15.94 vm, $YA_{(L\text{-}DOPA)}$: mean = 101.19 ± 20.87 vm, $OA_{(Placebo)}$: mean = 81.92 ± 29.01 vm, $OA_{(L\text{-}DOPA)}$: mean = 82.30 ± 30.95 vm). A mixed-effects ANOVA for path length with the between-subject factors Age Group and Intervention Order and the within-subject factor Intervention found a main effect of Age Group ($F_{(1,78)} = 16.13$, $p < 0.001$, $\eta_G^2 = 0.13$) as well as an Intervention × Intervention Order interaction ($F_{(1,78)} = 15.52$, $p < 0.001$, $\eta_G^2 = 0.039$). The latter represents a session effect, revealing overall longer path lengths in session two compared to session one ($mean_{(S1)} = 87.66$ vm, $mean_{(S2)} = 97.41$ vm, $t_{(78)} = -3.94$, $p < 0.001$). To address the question whether average replace path length is related to the precision of recalling object locations, we carried out a non-parametric Kendall's tau correlations between the distance to object location and path length, separately for both age groups. The results we obtained showed that longer path lengths are related to smaller location memory errors in YA ($\tau = -0.202$, $p < 0.005$), while in OA this effect was non-significant ($\tau = -0.155$, $p < 0.051$). To establish whether these within-group correlations significantly differ between age groups we converted Kendall's τ into Pearson's r coefficients (Walker, 2003) and subjected said r coefficients to Fisher's z transformation using the R package 'cocor' (Diedenhofen and Musch, 2015). This analysis revealed that YA do not differ significantly from OA regarding the relationship between path length and precision of object location memory ($z = -0.332$, $p > 0.7$). The absence of an effect of the drug intervention on path length alone might not exclude the possibility that the intervention leads to increased exploration of the environment. Therefore, we also examined the excess path length, which is defined as the difference between the path length taken and the Euclidean distance between starting point and drop position in every run. We performed another mixed-effects ANOVA with the same within- and between-subject factors as above and excess path length as the dependent variable. The only significant effect from this analysis was an Intervention × Intervention Order interaction ($F_{(1,78)} = 11.04$, $p < 0.001$, $\eta_G^2 = 0.032$) indicating a higher propensity to explore the environment in session two relative to session one ($mean_{(S1)} = 34.35$ vm, $mean_{(S2)} = 42.41$ vm, $t_{(78)} = -3.32$, $p < 0.002$). Finally, we also carried out a mixed-effects ANOVA with average replace duration as the dependent variable and the same factors as before. This analysis yielded no significant main effects or interactions (all p's > 0.6). The fact that replace duration does not differ between age groups although YA exhibit longer path lengths than OA is likely due to OA having a slower walking pace and more frequent periods of immobility in which they contemplated the virtual environment instead of approaching the target location.

3.3. Effects of age andL-DOPA on boundary and location cue sensitivity

We characterized individual and age-related differences in the sensitivity to boundary and location cue information during spatial navigation by comparing observed memory performance during the transfer phase with the assumptions made by the boundary or location cue models (see details in Section 2.6 above). Differences between model predictions and observed behavior result in model-behavior mismatch values, where higher magnitudes of such mismatches reflect lower sensitivity to boundary or location cue information (Schuck et al., 2015). We analyzed the data using a mixed-effects ANOVA with the between-subject factors Age Group (YA or OA) and Intervention Order (Placebo Starters or L-DOPA Starters) and the within-subject factors Condition (Boundary or Location Cue) and Intervention (Placebo or L-DOPA). The results revealed a main effect of Age Group ($F_{(1,78)} = 67.05$, $p < 0.001$, $\eta_G^2 = 0.21$) and Condition ($F_{(1,78} = 68.74$, $p < 0.001$, $\eta_G^2 = 0.12$) as well as an Age Group × Condition interaction ($F_{(1,78)} = 79.36$, $p < 0.001$, $\eta_G^2 = 0.16$). As can be seen in Fig. 2B, and in line with previous work (Glöckner et al., 2021; Schuck et al., 2015), these effects show that while young adults have comparable levels of location cue and boundary processing, older adults demonstrate much lower boundary sensitivity, compared to their sensitivity to the location cue during spatial navigation.

Furthermore, a Condition × Intervention interaction ($F_{(1,78)} = 5.33$, $p < 0.024$, $\eta_G^2 = 0.007$) revealed that L-DOPA had a differential effect on location cue and boundary processing. To identify the direction of this effect, we calculated the L-DOPA-related gain (subtracting model-behavior mismatches in the L-DOPA from the placebo session) separately for location cue and boundary processing sensitivity and compared both conditions via a paired t-test. This comparison revealed an L-DOPA induced increase in location cue sensitivity relative to a decrease in boundary sensitivity ($t_{(81)} = 2.45$, $p < 0.0164$; see Fig. 2C). Lastly, an Intervention × Intervention Order interaction ($F_{(1,78)} = 15.72$, $p < 0.001$, $\eta_G^2 = 0.024$) again represented a cross-session learning effect with overall better model-behavior mismatch values i.e. improved sensitivity to both environment features in session two compared to session one ($mean_{(S1)} = 83.22$, $mean_{(S2)} = 73.47$, $t_{(78)} = 3.96$, $p = 0.002$). There were no further main effects or interactions.

3.4. Correlations between L-DOPA induced changes in the learning and transfer phase

The fact that there were no consistent main effects of L-DOPA intervention might stem from substantial within-age group differences in individual responsiveness to the intervention. Visual inspection of L-DOPA-induced effects on the outcome measures of the learning and transfer phase appears to corroborate this notion (see Fig. 3A). To explore whether L-DOPA-related changes in object location learning covary with L-DOPA-related changes in location cue or boundary sensitivity, we calculated non-parametric Kendall's tau correlation coefficients between standardized trial-difference values and location cue or boundary sensitivity, separately for young and older adults. In both measures, higher values represent an increase in learning magnitude and location cue or boundary sensitivity associated with the L-DOPA intervention. The results revealed a significant correlation between the L-DOPA-induced learning improvements and the L-DOPA-induced increase in boundary sensitivity in older adults ($\tau = 0.285$, $p_{(FDR)} = 0.025$), but neither a significant correlation of these variables in young adults ($\tau = -0.067$, $p_{(FDR)} = 0.869$) nor significant correlations between learning magnitude and location cue sensitivity in both age groups (YA: $\tau = 0.018$, $p_{(FDR)} = 0.869$; OA: $\tau = 0.063$, $p_{(FDR)} = 0.594$; see Fig. 3B). We further converted Kendall's τ coefficients into Pearson's r coefficients and subjected said r coefficients to Fisher's z transformation to directly compare observed coefficients in the young and older adult group. The result showed that the correlation between the L-DOPA-related increase in learning magnitude and the L-DOPA-related increase in boundary processing in older adults indeed differs significantly from the (non-significant) correlation between both variables in young adults ($z = -2.466$, $p = 0.014$).

As an additional control analysis, we also investigated whether spatial working memory performance might be implicated in the observed results. Spatial working memory performance (in the low working memory condition, in the high working memory condition and averaged across both conditions (cf. Glöckner et al., 2021; Nagel et al., 2008) showed no significant rank correlation with L-DOPA induced gains in object location memory, location cue or boundary sensitivity neither in the young nor in the older adults (all p-values > 0.16).

3.5. Functional MRI results

Our analyses of task-related BOLD responses were concentrated on the two stages of the learning phase trials: (1) the replace phase, covering the time between object-cue onset until replacement (drop) of the object and (2) the feedback phase, spanning the duration between feedback display (i.e. object is shown in correct position) until the object was picked up again at its correct location. For both stages of the

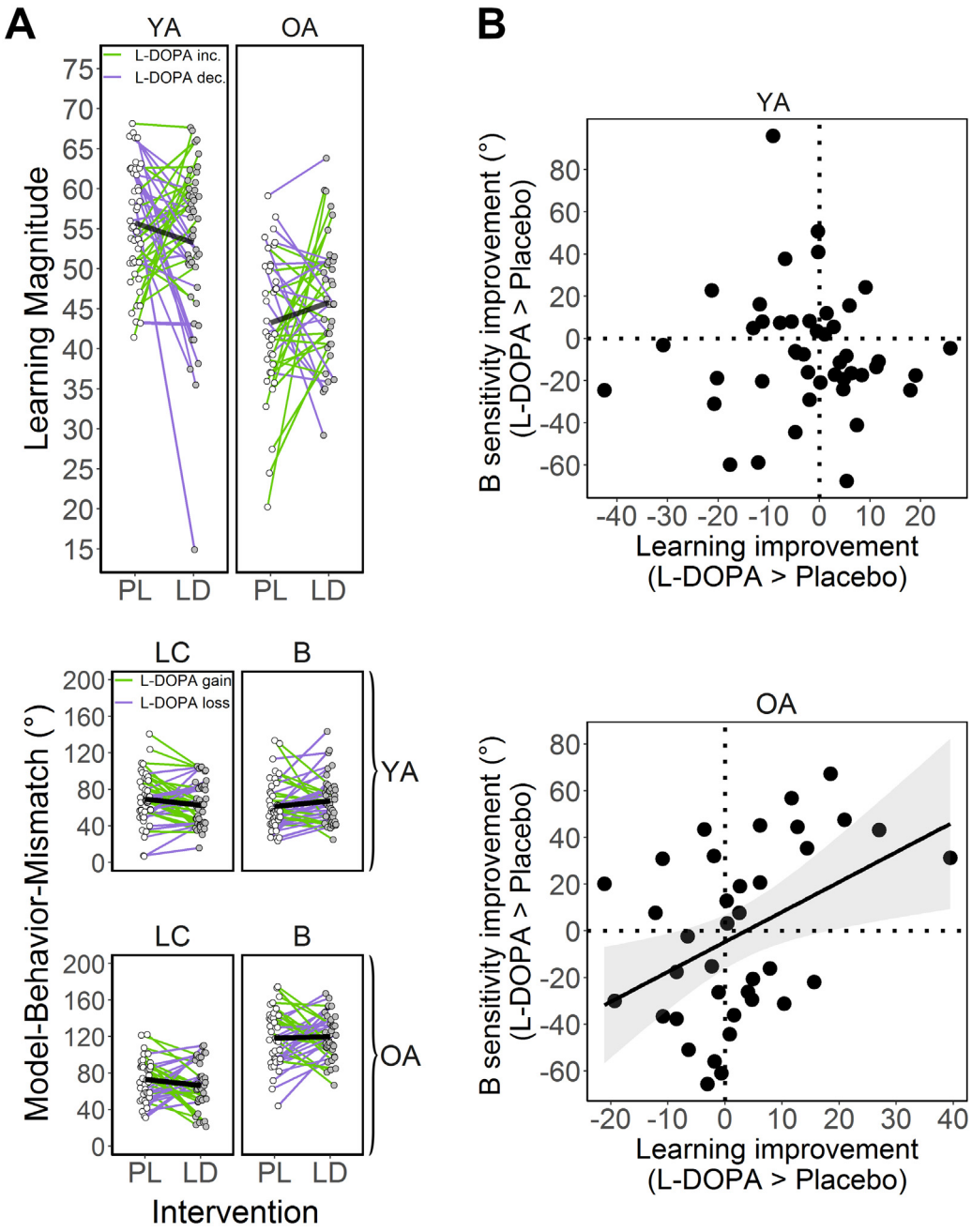

Fig. 3. Individual behavioral responses under L-DOPA intervention. (A) Differences in learning magnitude, defined as the normed difference between the first and the last trial of the learning phase (top) and differences in model-behavior-mismatch (bottom) under LL-DOPA and placebo respectively, displayed for young and older adults. Individual responses during L-DOPA and placebo intervention are connected by either a green line (if L-DOPA improved performance/processing), or a violet line (if L-DOPA impaired performance/processing). (B) Shown are correlations between L-DOPA-related improvements in learning magnitude and L-DOPA-related improvements in boundary processing in young (top) and older adults (bottom). The only significant correlation was between improvements in learning and boundary sensitivity in old participants as indicated by the black regression line. YA = young adults, OA = older adults, PL = placebo, LD = L-DOPA, B = boundary.

learning phase, we calculated separate mixed design models with Intervention as a within-subject factor, and Age and Intervention Order as between-subject factors and investigated all main effects and positive interactions. All results were FWE-corrected ($p = 0.05$) on the cluster level. Analyses of the replace phase revealed stronger activations in young compared to older adults (YA > OA) in right frontal regions, including the middle and inferior frontal gyrus, but no significant effects for the opposite contrast (OA > YA). Crucially, we also observed an Age Group × Intervention interaction of the following pattern in the right medial temporal lobe (including hippocampus and parahippocampus) and brainstem: an increase of activity in older adults under L-DOPA relative to placebo but a decrease of activity in young adults under L-DOPA relative to placebo. Analyses of the feedback phase also revealed stronger activations in young compared to older adults (and no effect for the opposite comparison) in bilateral frontal, parietal and occipital regions. Finally, an interaction between Intervention and Intervention Order during the feedback phase, which reflected an increase in brain activity in the second imaging session compared to the first one, was observed in the left frontal pole, middle frontal and precentral gyrus. Additional model-based analyses using $\text{Replace}_{(\text{boundary})}$

Table 2
Anatomical labels for fMRI peaks in group-level mixed design models of whole-brain analyses.

	MNI coordinates			*Z* (peak)
	X	Y	Z	
Replace Phase: YA > OA (bootstrap: k_Z > 105 voxel)				
Middle Frontal Gyrus	27	3	45	5.18
Precentral Gyrus	59	9	24	4.41
Middle Frontal Gyrus	57	12	27	4.35
Postcentral Gyrus	66	−18	36	3.67
Superior Frontal Gyrus	21	−12	51	3.31
Replace Phase: Age Group x Intervention (bootstrap: k_Z > 91 voxel)				
Amygdala	30	0	−27	4.01
Hippocampus	9	−12	−21	3.73
Parahippocampal Gyrus	24	−6	−33	3.38
Brainstem	3	−24	−33	3.26
Feedback Phase: YA > OA (bootstrap: k_Z > 100 voxel)				
Middle Frontal Gyrus	33	3	57	6.21
Precuneus	−3	−54	54	5.28
Angular Gyrus	42	−63	21	5.50
Superior Frontal Gyrus	−12	−3	63	4.42
Lateral Occipital Cortex	−33	−84	15	4.74
Occipital Fusiform Gyrus	24	−69	−9	5.71
Superior Temporal Gyrus	63	−21	0	4.10
Feedback Phase: Intervention x Intervention Order (bootstrap: k_Z > 86 voxel)				
Precentral Gyrus	−57	0	18	4.38
Inferior Frontal Gyrus	−39	6	21	4.28
Frontal Pole	−30	51	15	4.26
Middle Frontal Gyrus	−36	30	24	3.66
Postcentral Gyrus	−66	−12	24	3.35

Results are cluster corrected (p = 0.05, FWE). YA = young adults, OA = older adults, MNI = Montreal Neurological Institute, k_Z = cluster-size threshold for obtaining significant results in the respective statistical contrast.

and Feedback$_{(\text{location cue})}$ as parametric regressors using a hippocampal/parahippocampal and a caudate nucleus ROI as previously implemented by Schuck et al. (2015), respectively, did not yield any significant effects. Brain regions involved in the task are depicted in Fig. 4 and summarized in Table 2.

4. Discussion

Aging is accompanied by a gradual decline of cognitive function, including episodic memory (Leal and Yassa, 2015) and spatial navigation abilities (Lester et al., 2017), even in the absence of disease-related neurodegenerative processes. There is considerable agreement that these two functions are closely related (Bellmund et al., 2018; Burgess et al., 2002; Buzsaki and Moser, 2013; Solomon et al., 2019) and that they are amenable to dopamine neuromodulation (e.g. Chowdhury et al., 2012; Packard and Teather, 1998). In this study, we investigated the interactions between aging and L-DOPA intervention during a computerized spatial navigation task in a placebo-controlled double-blind crossover design. We found age group differences with regard to object location memory and boundary versus location cue sensitivity during spatial navigation at the behavioral level. At the brain level, we also observed a clear age-related under-recruitment of several brain regions. As for L-DOPA-induced effects at the brain activation and behavioral level, the patterns of results are more complex and are influenced by large interindividual differences in L-DOPA responses. More specifically, in the analyses of the fMRI data, an interaction between age and intervention revealed an upregulation of brain responses in older adults and a downregulation of brain responses in young adults under L-DOPA compared to placebo in a cluster extending from the medial temporal lobe (MTL), including hippocampus and parahippocampus, to the brainstem. During spatial learning, L-DOPA did not lead to the expected overall performance improvement in older adults. However, L-DOPA decelerated spatial learning in the young when they received the drug in the first session, without negatively affecting cross-session learning capacity. Furthermore, both age groups relied slightly more on location cue relative to boundary information when under L-DOPA. Lastly, we found that only in older adults were L-DOPA-induced improvements in boundary processing associated with L-DOPA-induced improvements in object location learning. In the following, these results are discussed in more detail.

Our behavioral results replicate previously observed age effects in studies that used slightly modified versions of the task employed here (Glöckner et al., 2021; Schuck et al., 2015, 2013; Thurm et al., 2016). Specifically, our findings corroborate previous reports of superior object location memory and a steeper within-session learning of locations in young compared to older adults. Similarly, our results also replicated a previously observed deficiency of boundary processing in older compared to young adults, while location cue processing was comparable in both age groups. In the current study, we extend these results by adding the factor of dopamine neuromodulation. Notably, although there was no overall effect of drug intervention on object location memory, splitting up the analysis by age group and intervention order tentatively showed that taking L-DOPA on the first session (while being task-naïve) impairs memory in young but not in older adults. However, cross-session learning effects appear to offset this impairment in the young, which eventually causes Placebo- and L-DOPA Starters to perform equally well at the end of the learning phase during the second session. A previous study by Vo et al. (2016) found the very same pattern of effects in young adults undergoing an L-DOPA intervention while performing a probabilistic reversal learning task. The authors observed detrimental effects of L-DOPA on young males' task performance, especially when L-DOPA was administered in the first session of their within-subject crossover design. They concluded that this treatment order effect could be explained by a combined effect of L-DOPA-induced impairment of performance in session one and a practice-induced augmentation of performance in session two. These findings and the findings from our own study are compatible with the hypothesis of an inverted-U-shaped relationship between dopamine levels and cognitive functioning (see Cools and D'Esposito, 2011; for a review). Accordingly, dopamine levels in young adults, which are believed to reside at, or close to, the plateau of the inverted-U curve (Li and Sikstrom, 2002), might have been elevated beyond the optimum, causing spatial learning performance to decline in our young adult group.

It is important to note that young adults walked longer distances during the object-replacement period than older adults, and this might be related to overall age group differences in object location memory. This may have allowed younger adults to encode spatial information at a greater depth. Indeed, in the young adult group and as a trend also in the older adult group, individuals who travelled longer distances also recalled object locations more precisely. Together these findings are in line with the depth of processing concept of memory in aging, suggesting that older adults tend to engage shallower processing during encoding (e.g. Craik and Rose, 2012). Interestingly, this fact was independent of the drug intervention or the drug intervention order in our given sample, which means that despite the increased path lengths in young adults in general, receiving L-DOPA in the first session still decreased their object location memory. The observed differences of the L-DOPA intervention between the two age groups might therefore underestimate the L-DOPA effect in spatial navigation tasks with a more limited event duration.

With respect to location cue and boundary processing, our analyses again did not show a general effect of drug intervention. Rather, we found an L-DOPA-induced increase in location cue processing relative to an L-DOPA-induced decrease in boundary processing across age groups. In a study by Wiener et al. (2013) the authors demonstrated age-specific biases in spatial navigation strategies, in the absence of a dopamine intervention, with young adults tending to apply a place strategy (corresponding to boundary processing) and older adults more relying on beacon and associative-cue strategies (corresponding to location cue processing), even in situations where the application of the preferred strategy is disadvantageous. This might suggest that in our study,

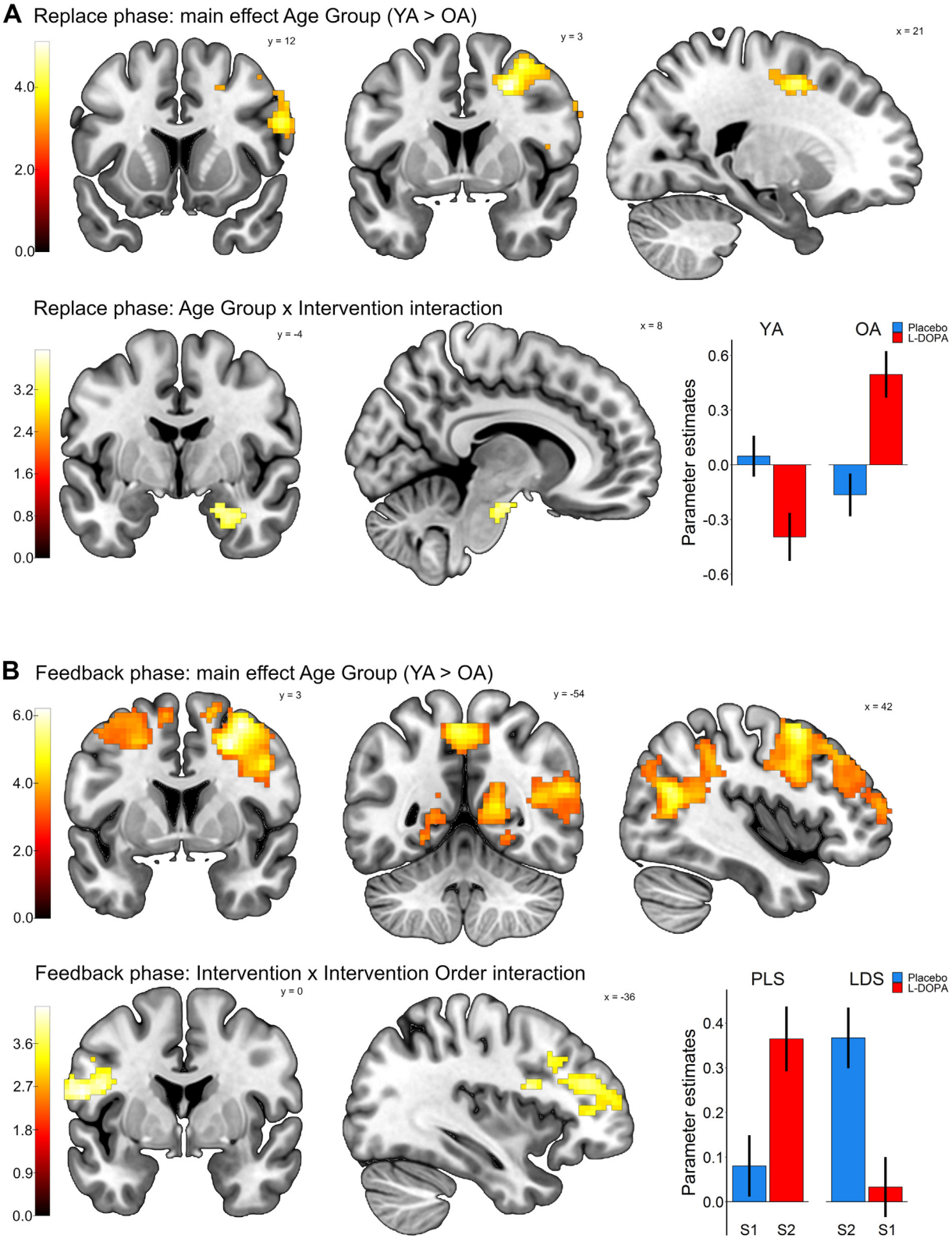

Fig. 4. Brain responses from cluster-corrected ($p = 0.05$, FWE) whole-brain analyses during (A) the replace phase and (B) the feedback phase of the learning phase. Bar plots display the mean parameter estimates (beta values) for the Age Group × Intervention interaction (A) and the Intervention × Intervention Order interaction (B). Error bars indicate one standard error of the mean. A list of brain regions with coordinates of their peak activations can be found in Table 2. YA = young adults, OA = older adults, PLS = Placebo Starters, LDS = L-DOPA Starters, S1 = session one, S2 = session two.

the L-DOPA boost slightly biased young adults towards adopting a more age-atypical or "older" spatial processing mode, whereas in older adults, L-DOPA slightly increased the spatial processing mode that is typically associated with that age group. Overall, these differential modulations of location cue and boundary sensitivity did not manifest themselves as changes in object location memory at the group average level.

Our analyses of neural activity showed that, in general across both drug interventions, young adults recruited more brain areas than older adults during retrieval and during re-encoding of the object locations. Specifically, age comparisons revealed greater activity in frontal regions during retrieval and greater activity in bilateral frontal, parietal (i.e. precuneus and angular gyrus) and occipital regions during re-encoding in young compared to older adults. According to the frontal aging hypotheses, aging disproportionally affects the frontal lobes (DeCarli et al., 2005; Pfefferbaum et al., 2005) which may underlie the underrecruitment of frontal areas in older relative to young adults in our study in general. The surplus activity in right middle frontal gyrus (MFG) during spatial memory retrieval in young adults is specifically interesting, as a previous study found that only in young adults was the volume of right MFG associated with better retrieval of item and context memory (Rajah et al., 2011). Regarding the memory re-encoding period, our results are consistent with studies reporting more activation in young compared to older adults in the occipital cortex (Antonova et al., 2009; Boccia et al., 2014), as well as in the precuneus and the angular gyrus (Boccia et al., 2014) during allocentric spatial navigation.

Most significantly, our analyses of brain responses during object memory retrieval revealed an upregulation of activity in older adults under L-DOPA relative to placebo and a downregulation of activity in young adults under L-DOPA relative to placebo, in a cluster that includes hippocampus, parahippocampal gyrus, amygdala and brainstem. This is interesting, since, as noted above, overall brain activity across sessions was more pronounced in young compared to older adults in our study, both during object memory retrieval and during re-encoding of the object (i.e. during feedback and object re-collection). The hippocampus and the parahippocampal gyrus are regarded as primary brain areas underlying spatial navigation and episodic memory (Baumann and Mattingley, 2021; Chersi and Burgess, 2015), and hippocampus functioning is known to crucially depend on tonic dopamine signaling (Shohamy and Adcock, 2010). Therefore, the L-DOPA-induced decrease in brain activity and behavioral performance observed in young adults are in line with the inverted-U-shaped hypothesis of a dopamine overshoot in that age group (Cools and D'Esposito, 2011). Somewhat surprisingly, the drug-related increase in brain responses in older adults did not directly translate into improvements in spatial learning and memory performance in that age group overall. However, we obtained evidence that L-DOPA did improve spatial learning in some older adults, namely in those who also showed a drug related enhancement of boundary processing, which relies on hippocampus and parahippocampal gyrus (Doeller et al., 2008; Schuck et al., 2015; Wiener et al., 2013). This relationship between L-DOPA induced increase in learning and boundary sensitivity was only present in older adults and did not exist between learning and location cue sensitivity. That only a subgroup of older adults would benefit from an L-DOPA intervention was also observed in a study by Chowdhury et al. (2013) which investigated reward processing using a similar age-comparative placebo-controlled design. In their study, older adults who displayed improved task performance and increased learning rates under L-DOPA also expressed complete neural reward prediction errors (RPE), whereas RPEs were incomplete in older adults under placebo and in older adults who did not benefit from L-DOPA. It is possible that the upregulation of brain activity in older adults under L-DOPA in our study was more strongly driven by those individuals whose behavioral performance was augmented by the intervention.

Finally, given the wide distribution of dopamine receptors in the brain (Beaulieu and Gainetdinov, 2011) our drug intervention might have acted upon all regions in the activated cluster. Alternatively, amygdala and brainstem might also have been involved as a direct consequence of the dopaminergic innervation of hippocampus and parahippocampal gyrus. In older adults, the hippocampus might be particularly well suited to utilize an additional dopamine boost, since the structure experiences one of the lowest aging-related decline in dopamine D2-like receptors and might therefore be more susceptible to interventions at lower, non-clinical doses (Seaman et al., 2019).

5. Limitations and conclusions

Although we could replicate behavioral effects found in earlier studies, we were unable to detect significant brain responses in the model-based fMRI analyses (cf. Schuck et al., 2015). We also did not find significant activity in the striatum, which was previously observed. A potential source of the discrepancy between our and the results reported in Schuck et al. (2015) could be that the latter study sample was male-only and with a wider age range of 56 – 74 years in the older adults group also covering middle age adulthood, while our own older adults sample was comprised of males and females between 65 – 75 years. Males frequently outperform females in spatial navigation tasks, with effect sizes ranging from small to medium (see Nazareth et al., 2019 for a review). The difficulties in comparing our results to those of male-only studies are further compounded by the fact that the sex composition in our sample was unequal in both age groups and the female-to-male ratio in older adults was also slightly lower than in young adults, which renders a reliable estimate of sex effects on our data infeasible. In addition, the current version of the task comprised two modifications: First, the manipulation of the spatial boundary only involved an increase in diameter, whereas in Schuck et al. (2015) boundary increase and shrinkage in diameter were applied independently. Second, the number of transfer trials was increased by the factor two in our task design. Regarding striatal effects specifically, age group differences in the striatum in the study by Schuck et al. (2015) were only detected using a more lenient threshold, whereas we only reported family-wise error-corrected imaging results in this work. Notably, behavioral age differences concerning location cue processing, which presumably involves the striatum, were absent in our own study and in the study of Schuck et al. (2015), while both studies equally demonstrated distinct differences in boundary processing (which involves the hippocampus / parahippocampus). It is therefore possible that any age group or drug intervention related differences in striatal responses in our study were subtle and did not result in detectable group differences that would survive correction for multiple comparisons. Furthermore, hippocampal-striatal interactions during spatial navigation are complex and context-dependent (Goodroe et al., 2018). The established distinction of hippocampal regions supporting the "navigation-to-place" behavior, whereas the dorsal striatum supports a response-learning strategy, was originally based on animal studies (Packard and McGaugh, 1996) and later human studies (Bohbot et al., 2012) that involved either cross-maze or other forms of multi-armed mazes for which response strategies at different decision points are particularly relevant and associated with explicit rewards. In contrast, the spatial navigation task we utilized did not require the participants to make any specific response decisions other than recalling object locations. The memory recall was also not explicitly rewarded. These features of our task may also have contributed to the results of not observing activity in the striatum.

In this study, we also gathered data from a group that received a placebo on both imaging sessions. In addition to age group differences, the placebo/placebo group results also suggest a between-session increase in boundary processing in the young adults in contrast to a between-session increase in location cue processing in the older adults. Especially in the young adult group, this might imply that L-DOPA may have counteracted the relative bias towards hippocampus-dependent spatial processing which is usually observed over time in young adults (cf. Wiener et al., 2013). However, the obtained sample size of that group was rather small which does not allow us to relate it to our drug intervention group in a meaningful way. In the interpretation of some

of our behavioral and neural findings, we resorted to the hypothesis of an inverted-U-shaped relationship between dopamine signaling and cognitive function. However, the applicability of this hypothesis seems to depend on various factors including cognitive domain, type and difficulty level of the experimental task, and baseline cognitive performance (see Cools, 2006; Cools and D'Esposito, 2011; Floresco, 2013 for reviews; Marino and Levy, 2019). In the context of a pharmacological dopamine challenge, factors such as type and dosage of the administered drug, targeted dopamine receptor type (D1-like, D2-like) and targeted dopamine activity state (tonic, phasic), baseline dopamine levels, as well as dopamine availability relative to dopamine receptor density (Papenberg et al., 2020) might further complicate the interpretation of observed dopamine effects on cognition. Therefore, all these factors need to be weighed in when interpreting findings obtained from dopamine intervention studies such as the one reported in this work.

In conclusion, our results showed that although L-DOPA had no overall effect on behavior, it hampered spatial memory in young adults who received the drug in their first, task-naïve session. In addition, on the group average level, L-DOPA modulated location cue processing in both age groups, making young adults appear older regarding their typical spatial navigation behavior and affirming older adults' bias towards less resource-demanding strategies. More importantly, we found that L-DOPA interacted with age on a neural level, boosting activity in older and decreasing activity in young adults within the MTL and brainstem. These findings speak for an inverted-U-shaped relationship between dopamine signaling and cognitive function. Moreover, older adults whose spatial learning improved under L-DOPA also displayed a drug-induced increase in boundary processing, which suggests that increasing dopamine availability facilitates allocentric place learning in some older adults.

Data and code availability

The code underlying our data analyses will be made openly available at https://www.osf.io/yp5qt/. The data supporting the findings of this study will be shared in preprocessed form that ensures full anonymity of subjects, in line with funding and ethical regulations.

Declaration of Competing Interest

The authors declare no conflict of interest.

Credit authorship contribution statement

Christian Baeuchl: Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Franka Glöckner:** Conceptualization, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Christoph Koch:** Data curation, Writing – review & editing. **Johannes Petzold:** Resources, Writing – review & editing. **Nicolas W. Schuck:** Methodology, Software, Writing – review & editing. **Michael N. Smolka:** Supervision, Writing – review & editing, Funding acquisition. **Shu-Chen Li:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

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Supplementary materials

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