

L-DOPA enhances hippocampal direction signals in younger and older adults

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Abstract

1
2 Previous studies indicate a role of dopamine in hippocampus-dependent spatial navi-
3 gation. Although neural representations of direction are an important aspect of spatial
4 cognition, it is not well understood whether dopamine directly affects these representations,
5 or only impacts other aspects of spatial brain function. Moreover, both dopamine and spa-
6 tial cognition decline sharply during age, raising the question which effect dopamine has
7 on directional signals in the brain of older adults. To investigate these questions, we used
8 a double-blind cross-over L-DOPA/Placebo intervention design in which 43 younger and 37
9 older adults navigated in a virtual spatial environment while undergoing functional magnetic
10 resonance imaging (fMRI). We studied the effect of L-DOPA, a DA precursor, on fMRI ac-
11 tivation patterns that encode spatial walking directions that have previously been shown to
12 lose specificity with age. This was done in predefined regions of interest, including the early
13 visual cortex, retrosplenial cortex, and hippocampus. Classification of brain activation pat-
14 terns associated with different walking directions was improved in the hippocampus and the
15 retrosplenial cortex following L-DOPA administration. This suggests that DA enhances the
16 specificity of neural representations of walking direction in these areas. In the hippocampus
17 these results were found in both age groups, while in the RSC they were only observed in
18 younger adults. Taken together, our study provides evidence for a mechanistic link between
19 DA and the specificity of neural responses during spatial navigation.

20 **Significance Statement:** The sense of direction is an important aspect of spatial navi-
21 gation, and neural representations of direction can be found throughout a large network of
22 space-related brain regions. But what influences how well these representations track some-
23 one's true direction? Using a double-blind cross-over L-DOPA/Placebo intervention design,
24 we find causal evidence that the neurotransmitter dopamine impacts the fidelity of direction
25 selective neural representations in the human hippocampus and retrosplenial cortex. Inter-
26 estingly, the effect of L-DOPA was either equally present or even smaller in older adults,
27 despite the well-known age related decline of dopamine. These results provide novel insights
28 into how dopamine shapes the neural representations that underlie spatial navigation.

29 **Keywords:** spatial navigation; aging; neural dedifferentiation; tuning functions; fMRI;
30 MVPA; dopamine

1 Introduction

A role of dopamine (DA) in spatial navigation is well established. Anatomically, spatial cognition depends on a network of brain regions centered around the hippocampus (HC) (Burgess, Maguire, & O'Keefe, 2002; Chersi & Burgess, 2015) that is a target of dopaminergic innervation from the ventral tegmental area and the locus coeruleus (McNamara & Dupret, 2017). Behaviorally, spatial navigation abilities are influenced by DA functioning in younger as well as older animals and humans (Granado et al., 2008; El-Ghundi et al., 1999; Thurm et al., 2016; Kentros, Agnihotri, Streater, Hawkins, & Kandel, 2004).

Much less is known about how DA might change the neural representations that support spatial navigation. Particularly interesting for human neuroscience are direction selective representations (Taube, 2007), which have been found, amongst others, in the HC, the retrosplenial cortex (RSC) and visual cortex (Shine, Valdés-Herrera, Hegarty, & Wolbers, 2016; Flossmann & Rochefort, 2021; Guitchounts, Masís, Wolff, & Cox, 2020; Cacucci, Lever, Wills, Burgess, & O'Keefe, 2004), and can be decoded from human fMRI signals (Koch, Li, Polk, & Schuck, 2020). We hypothesized that DA affects direction encoding in the human brain and tested this idea using a double-blind placebo controlled intervention design. Specifically, we predicted that oral administration of L-DOPA, a dopamine precursor, would influence how accurately walking direction can be decoded from multi-voxel fMRI patterns.

Next to its role in spatial navigation, DA has also received much attention in the context of aging, where reduced DA functions are prevalent and are thought to underlie age-related cognitive declines (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Li, Lindenberger, & Bäckman, 2010; Volkow et al., 1998; Chowdhury et al., 2013). Computational models have shown that declining neuromodulatory effects of DA lead to losses in the signal-to-noise ratio of neural responses (Cohen & Servan-Schreiber, 1992; Servan-Schreiber, Printz, & Cohen, 1990), which in the aging brain can lead to neural representations that are less specific or "dedifferentiated" (Li, Lindenberger, & Sikström, 2001; Li & Rieckmann, 2014). In line with these models, dedifferentiation has repeatedly been observed in older adults (OA) at the behavioral and neural levels (Park et al., 2004; Carp, Park, Polk, & Park, 2011; Carp, Park, Hebrank, Park, & Polk, 2011; Koch et al., 2020; Kobelt, Sommer, Keresztes, Werkle-Bergner, & Sander, 2021; Li et al., 2004). Neural dedifferentiation, in turn, has been

61 linked to decreased memory performance (Koen, Hauck, & Rugg, 2019; Sommer et al., 2019;
62 St-Laurent, Abdi, Bondad, & Buchsbaum, 2014), establishing an explanatory link between
63 DA, neural representations and cognitive aging.

64 These roles of DA in spatial navigation and aging might contribute to the pronounced
65 decline in spatial cognition with age (Moffat, 2009; Lester, Moffat, Wiener, Barnes, & Wol-
66 bers, 2017; Wolbers, Dudchenko, & Wood, 2014; Schuck, Doeller, Polk, Lindenberger, & Li,
67 2015), and to the neural dedifferentiation of direction-selective (Koch et al., 2020) and hip-
68 pocampal signals (Schuck et al., 2015) in the aging brain. Moreover, since the sharp decline
69 of DA with age should lead to lower baseline availability of DA in OA, the effects of DA
70 might be stronger in OA relative to younger adults (YA) – reflecting DA’s inverted-U-shape
71 relation to cognitive performance (Cools & D’Esposito, 2011; Li et al., 2013; Vijayraghavan,
72 Wang, Birnbaum, Williams, & Arnsten, 2007; Li et al., 2010). Indeed, one previous study
73 found age-related effects of the DA receptor agonist bromocriptine on dedifferentiation in
74 the HC (Abdulrahman, Fletcher, Bullmore, & Morcom, 2017). Moreover, HC-dependent
75 episodic memory, spatial navigation, and learning have been found to be affected by genetic
76 polymorphisms related to dopamine D2 receptor availability (COMT Val158Met, C957T CC;
77 Papenberg et al., 2014; Li et al., 2013) or hippocampal function (KIBRA SNP rs17070145;
78 Schuck et al., 2013, 2018) in OA, but not YA. Based on these findings, we therefore also tested
79 whether L-DOPA effects on walking direction decoding would be stronger in OA relative to
80 YA.

81 Finally, we expected that DA could also influence the shape of population-based tuning
82 functions of direction. Although direction-sensitive cells often have a preferred direction,
83 they also fire in response to non-preferred directions in proportion to their similarity to the
84 preferred direction (Taube, 2007). Hence, encoding of direction information seems to follow a
85 Gaussian tuning function, in particular on a population level (Averbeck, Latham, & Pouget,
86 2006). Research has also shown that age-related neural dedifferentiation results in increased
87 width of such tuning functions with age (Liang et al., 2010; Leventhal, Wang, Pu, Zhou, &
88 Ma, 2003; Schmolesky, Wang, Pu, & Leventhal, 2000), which we too have reported previously
89 using fMRI (Koch et al., 2020). We therefore also investigated whether L-DOPA has effects
90 on the precision of fMRI-derived tuning functions of direction information and whether such

91 effects may interact with age.

92 **2 Materials and Methods**

93 **2.1 Participants**

94 This study was part of a larger project in which the same participants performed multiple
95 tasks, including a sequential decision making task and a virtual reality spatial memory task
96 inside the scanner and other decision tasks outside of the scanner.

97 Here, we only report results from the MRI analysis of the VR task described below.
98 Specifically, following our previous publication ([Koch et al., 2020](#)), our analyses were specific
99 to neural representations of direction signals during the spatial memory task performed while
100 undergoing fMRI. Other data from the same participants was not within the purview of this
101 study and was therefore not investigated. Data of 102 participants which were recruited for
102 two MRI sessions and randomly assigned to one of the two drug intervention groups (i.e., L-
103 DOPA–Placebo or Placebo–L-DOPA) was available for investigating our research question.
104 Ninety-one of these participants (46 OA, 45 YA) successfully completed both sessions. Four
105 OA were excluded from further analyses because they did not respond in at least a third
106 of the trials in at least one of the two sessions. Furthermore, technical issues during data
107 collection led to incomplete or inaccurate data for three other OA, resulting in an overall
108 exclusion of 7 OA. The main sample therefore consisted of 84 participants, out of which 39
109 were OA (age 65–75, 7 female) and 45 YA (age 26–35, 16 female). Note that the relatively
110 low number of female OA reflects difficulties in recruitment after the onset of the COVID-19
111 pandemic.

112 Decoding analyses of the L-DOPA effects introduced additional requirements for the
113 distribution of walking direction (see Materials and Methods) that were not met for four
114 participants (2 OA, 2 YA). Thus, the final effective sample for these analyses also excluded
115 these participants and comprise of a total of 37 OA (age 65–75, 6 female) and 43 YA (age
116 26–35, 16 female).

117 2.2 Virtual Reality Task

118 During each session of fMRI data collection participants had to complete a similar variant of
119 a spatial memory task that was used in previous studies (Schuck et al., 2015; Thurm et al.,
120 2016). Analyses of the present work are mainly concerned with directional signals obtained
121 during free navigation, and hence focus on the corresponding task phases. Specifically, to
122 avoid effects of changed environmental cues on directional signals (e.g. Taube, Muller, &
123 Ranck, 1990) or initial learning, we considered only data from the feedback phase for this
124 study (see below). On average, the included data reflected a period of 17.36 minutes from
125 free navigation per session.

126 Briefly, participants were placed in a virtual, circular arena in which they could move
127 around freely using a custom-made MRI-compatible joystick. The arena consisted of a
128 circular grass plane surrounded by a wall. Participants could also see distal cues (mountains,
129 clouds) as well as a local cue (traffic cone) to aid orientation (see Fig 1). We asked participants
130 to remember the location of five objects within the 360° arena. First, an initial encoding
131 phase took place in which participants could see and walk to the locations of all objects
132 appearing one after the other. Learning of object location then continued in a feedback phase:
133 participants were placed close to the center of the arena with a random heading direction.
134 After the brief presentation of a grey screen and fixation cross, a picture of the first object
135 was shown. Participants were asked to navigate as closely as possible to the location of this
136 object and indicate their final position with a button press within a maximum of 60 seconds.
137 To provide feedback, the true object location was shown to participants following their
138 response, and they were then asked to navigate to and walk over the shown location. After
139 the feedback, participants were shown another object and the procedure repeated without
140 placing the player in the center of the arena until all five objects were completed. The order
141 in which the five objects were shown was pseudo-randomized. Once all five objects were
142 completed, participants were again placed close to the arena's center and had to navigate to
143 all five objects in the same manner for a total of six repetitions (i.e., $5 \times 6 = 30$ feedback
144 trials). In a final transfer phase of the task (data not analyzed in this study, see above),
145 either the arena size or the location of the traffic cone were altered, and participants' object
146 location memory was tested again as above. For the second session participants had to learn

147 the location of five different objects, but the trial structure and procedures were identical
148 otherwise. Completing one session took participants between 14 and 49 minutes.

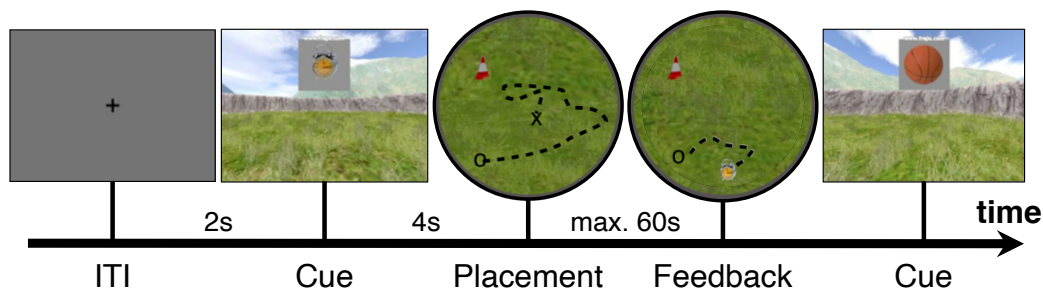


Figure 1: Task procedure during feedback phase. Each trial started with a fixation cross on a grey background for two seconds. Afterwards a cue was presented showing the object to which participants needed to navigate (object locations were learned during encoding phase). The participant then had 60 seconds to navigate from their starting location (cross) to the object location according to their spatial memory. Participants indicated that they had arrived at the remembered location (circle) by pressing a response button, after which the object appeared at its true location. Participants could observe the difference between their response and the correct location and were required to navigate towards and walk over the correct location, before the cue of the next trial was presented.

149 2.3 Drug administration

150 Following a double-blind drug administration design, participants were given either a total
151 of 225mg of L-DOPA (Madopar, Roche, Levodopa/Benserazid, 4:1 ratio) or a placebo (P-
152 Tabletten white 8mm Lichtenstein, Winthrop Arzneimittel) before each MRI session in the
153 form of two orally administered dosages. A first dosage (150mg L-DOPA/Placebo) was
154 given about 10 minutes before subjects entered the MRI scanner, roughly one hour before
155 the spatial navigation task began. To assure high dopamine availability during the task,
156 a second booster dosage (75mg L-DOPA/Placebo) was administered roughly ten minutes
157 before task onset (cf. [Kroemer et al., 2019](#)). Participants were pseudo-randomly assigned to
158 one of two groups with different session order, either the group that received L-DOPA in the
159 first session and placebo in the second session (Drug-Placebo group, 40 subjects) or the group
160 that started with the placebo in the first session (Placebo-Drug group, 44 participants).

161 2.4 Image acquisition

162 All data was collected on a 3 Tesla Siemens Magnetom Trio (Siemens, Erlangen, Germany)
163 MRI scanner. T1-weighted structural images were collected at the beginning of the first
164 session using a MP-RAGE pulse sequence ($0.8 \times 0.8 \times 0.8 \text{ mm}$ voxels, $TR = 2400 \text{ ms}$, $TE =$

165 2.19 ms, TI = 1000 ms, acquisition matrix = $320 \times 320 \times 240$, FOV = 272 mm, flip angle =
166 8° , bandwidth = $210 \frac{\text{Hz}}{\text{Px}}$). At the beginning of the second session T2-weighted structural scan
167 was collected ($0.8 \times 0.8 \times 0.8$ mm voxels, TR = 3200 ms, TE = 565 ms, acquisition matrix =
168 $350 \times 350 \times 2630$, FOV = 272 mm, bandwidth = $744 \frac{\text{Hz}}{\text{Px}}$).

169 Functional on-task data was collected using a T2*-weighted echo-planar imaging (EPI)
170 pulse sequence $3 \times 3 \times 2.5$ mm voxels, slice thickness = 2.5 mm, distance factor = 20%,
171 TR = 2360 ms, TE = 25 ms, image matrix = 64×64 , FOV = 192 mm, flip angle = 80° ,
172 48 axial slices, GRAPPA parallel imaging, acceleration factor: 2, interleaved acquisition). The
173 sequence lasted until the task was completed and took about 15 – 50 minutes. Additional
174 functional scans not analyzed in this manuscript included data from the transfer phase, data
175 from a decision making task, as well as data from a resting state scan collected at the start
176 of each session.

177 Quality of all collected functional sequences was assessed using MRI quality control
178 (MRIQC; [Esteban et al., 2017](#)). The quality measure of framewise displacement (FD,
179 threshold 3mm), a measure for movement during image acquisition ([Power et al., 2014](#)), was
180 extracted and used for statistical control.

181 2.5 ROIs

182 Each ROI was created from anatomical labels obtained from Mindboggle’s FreeSurfer-based
183 segmentation of each participant’s individual T1-weighted images ([Klein et al., 2017](#)). We
184 investigated three predefined ROIs in light of previous findings indicating direction selective
185 coding in these regions ([Taube, 2007](#); [Shine et al., 2016](#); [Flossmann & Rochefort, 2021](#);
186 [Guitchounts et al., 2020](#); [Cacucci et al., 2004](#); [Koch et al., 2020](#)). An early visual cortex
187 (EVC) ROI, consisting of the bilateral cortical masks of the cuneus, lateral occipital cortex,
188 and the pericalcarine cortex. A ROI of the retrosplenial cortex (RSC) constructed from
189 the bilateral, cortical masks of the cingulate isthmus. A mask of the hippocampus (HC)
190 was extracted from the respective bilateral masks of the parcellation. In addition to these
191 core masks, we added a ROI of the left motor cortex, constructed from the cortical mask of
192 the left precentral gyrus, to serve as a control. Although our resolution was suboptimal to
193 investigate small areas, we included a mask of the entorhinal cortex (EC) in order to explore

194 if direction signals could be found there as well.

195 **2.6 Image preprocessing**

196 **Copyright Waiver** Results included in this manuscript come from preprocessing per-
197 formed using *fMRIPrep* 20.0.6 (Esteban, Markiewicz, et al., 2018; Esteban, Blair, et al.,
198 2018; RRID:SCR_016216), which is based on *Nipype* 1.4.2 (Gorgolewski et al., 2011, 2018;
199 RRID:SCR_002502). The boilerplate text in this section (2.6) was automatically generated
200 by fMRIPrep with the express intention that users should copy and paste this text into their
201 manuscripts *unchanged*. It is released under the [CC0](#) license.

202 **Anatomical data preprocessing** The T1-weighted (T1w) image was corrected for
203 intensity non-uniformity (INU) with *N4BiasFieldCorrection* (Tustison et al., 2010), dis-
204 tributed with ANTs 2.2.0 (Avants, Epstein, Grossman, & Gee, 2008; RRID:SCR_004757),
205 and used as T1w-reference throughout the workflow. The T1w-reference was then skull-
206 stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from
207 ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal
208 fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted
209 T1w using `fast` (FSL 5.0.9; RRID:SCR_002823; Zhang, Brady, & Smith, 2001). Brain sur-
210 faces were reconstructed using `recon-all` (FreeSurfer 6.0.1; RRID:SCR_001847; Dale, Fis-
211 chl, & Sereno, 1999), and the brain mask estimated previously was refined with a custom
212 variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of
213 the cortical gray-matter of Mindboggle (RRID:SCR_002438; Klein et al., 2017). Volume-
214 based spatial normalization to two standard spaces (MNI152Lin, MNI152NLin2009cAsym)
215 was performed through nonlinear registration with `antsRegistration` (ANTs 2.2.0), using
216 brain-extracted versions of both T1w reference and the T1w template. The following tem-
217 plates were selected for spatial normalization: *Linear ICBM Average Brain (ICBM152)*
218 *Stereotaxic Registration Model* (Mazziotta, Toga, Evans, Fox, & Lancaster, 1995; Tem-
219 plateFlow ID: MNI152Lin), *ICBM 152 Nonlinear Asymmetrical template version 2009c*
220 (Fonov, Evans, McKinstry, Almlí, & Collins, 2009; RRID:SCR_008796; TemplateFlow ID:
221 MNI152NLin2009cAsym).

222 **Functional data preprocessing** For each of the 4 BOLD runs collected per subject
223 (two task related runs reported here and 2 resting state runs not reported here), the following
224 preprocessing was performed. First, a reference volume and its skull-stripped version were
225 generated using a custom methodology of *fMRIPrep*. Susceptibility distortion correction
226 (SDC) was omitted. The BOLD reference was then co-registered to the T1w reference using
227 **bbregister** (FreeSurfer) which implements boundary-based registration ([Greve & Fischl,](#)
228 [2009](#)). Co-registration was configured with six degrees of freedom. Head-motion parameters
229 with respect to the BOLD reference (transformation matrices, and six corresponding rotation
230 and translation parameters) are estimated before any spatiotemporal filtering using **mcflirt**
231 (FSL 5.0.9; [Jenkinson, Bannister, Brady, & Smith, 2002](#)). BOLD runs were slice-time cor-
232 rected using **3dTshift** from AFNI 20160207 ([Cox & Hyde, 1997](#); RRID:SCR_005927). The
233 BOLD time-series were resampled onto the following surfaces (FreeSurfer reconstruction
234 nomenclature): *fsnative*, *fsaverage*. The BOLD time-series (including slice-timing correction
235 when applied) were resampled onto their original, native space by applying the transforms
236 to correct for head-motion. These resampled BOLD time-series will be referred to as *pre-*
237 *processed BOLD in original space*, or just *preprocessed BOLD*. The BOLD time-series were
238 resampled into standard space, generating a *preprocessed BOLD run in MNI152Lin space*.
239 The first step in this process was that a reference volume and its skull-stripped version
240 were generated using a custom methodology of *fMRIPrep*. Several confounding time-series
241 were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS
242 and three region-wise global signals. FD and DVARS are calculated for each functional run,
243 both using their implementations in *Nipype* (following the definitions by [Power et al., 2014](#)).
244 The three global signals are extracted within the CSF, the WM, and the whole-brain masks.
245 Additionally, a set of physiological regressors were extracted to allow for component-based
246 noise correction (*CompCor*; [Behzadi, Restom, Liau, & Liu, 2007](#)). Principal components are
247 estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine
248 filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical
249 (aCompCor). tCompCor components are then calculated from the top 5% variable voxels
250 within a mask covering the subcortical regions. This subcortical mask is obtained by heavily
251 eroding the brain mask, which ensures it does not include cortical GM regions. For aComp-

252 Cor, components are calculated within the intersection of the aforementioned mask and the
253 union of CSF and WM masks calculated in T1w space, after their projection to the native
254 space of each functional run (using the inverse BOLD-to-T1w transformation). Components
255 are also calculated separately within the WM and CSF masks. For each CompCor decompo-
256 sition, the k components with the largest singular values are retained, such that the retained
257 components' time series are sufficient to explain 50 percent of variance across the nuisance
258 mask (CSF, WM, combined, or temporal). The remaining components are dropped from
259 consideration. The head-motion estimates calculated in the correction step were also placed
260 within the corresponding confounds file. The confound time series derived from head motion
261 estimates and global signals were expanded with the inclusion of temporal derivatives and
262 quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5
263 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can
264 be performed with *a single interpolation step* by composing all the pertinent transformations
265 (i.e. head-motion transform matrices, susceptibility distortion correction when available, and
266 co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were
267 performed using `antsApplyTransforms` (ANTs), configured with Lanczos interpolation to
268 minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) re-
269 samplings were performed using `mri_vol2surf` (FreeSurfer).

270 Many internal operations of *fMRIPrep* use *Nilearn* 0.6.2 (RRID:SCR_001362; Abraham
271 et al., 2014), mostly within the functional processing workflow. For more details of the
272 pipeline, see [the section corresponding to workflows in fMRIPrep's documentation](#).

273 2.7 fMRI analyses

274 **Classification of walking direction** All classification of walking direction was per-
275 formed in Python (Python Software Foundation; Python Language Reference, version 3.7.8;
276 available at <http://www.python.org>) and relied on `scikit-learn` (Pedregosa et al., 2011)
277 and `nilearn` (Abraham et al., 2014). Statistical analysis was performed using R (version
278 4.0.3, R Core Team, 2021) and the packages `lme4` (Bates, Mächler, Bolker, & Walker, 2015)
279 and `emmeans` (Lenth, 2021). All statistical figures were created using the `ggplot2` package
280 (Wickham, 2016).

281 Functional data was prepared for classification by smoothing images with a 3mm FWHM
282 kernel. Next, `nilearn`'s `signal.clean` function was used to detrend, high-pass filter ($\frac{1}{128}$ Hz),
283 de-noise (using 10 components of aCompCor) and z-standardize the time courses.

284 Participants' walking direction was extracted from navigated paths within the virtual
285 environment. The complete 360°-space of direction was binned into six equally spaced bins of
286 60°. Classifier training examples were then constructed by taking fMRI multi-voxel patterns
287 in response to consistent walking within one binned direction for at least one second. Hence
288 the number of classifier examples for each participant and direction were dependent on the
289 travelled paths and the number of direction changes. If the same example spanned multiple
290 TRs (i.e., was longer than 2.36s) all TRs spanned were averaged to assure a single voxel-
291 pattern per example. Voxel responses were taken two TRs (4.72s) after the event to adjust
292 for hemodynamic lag. A multinomial logistic regression classifier (L2 regularization, $C = 1$,
293 tolerance = 10^{-4} , 1000 maximum iterations; as implemented in `scikit-learn`) was applied
294 to the resulting activation patterns in order to test whether walking direction could be
295 classified. Two cross-validation approaches were used for classification: cross-session and
296 within-session. Cross-session decoding was used to assess overall decoding, irrespective of
297 drug intervention. Within-session decoding was used to separately assess decoding in the
298 L-DOPA and placebo sessions. Results for both approaches are reported separately.

299 For cross-session cross-validation, in order to reduce auto-correlation of noise, the data
300 of each session was first split into two sets, one consisting of odd and one of even walking
301 direction events. Cross validation approaches as described below were then performed sep-
302 arately for each split. This approach ensured that walking direction events within each of
303 the sets had a higher temporal separation (average: 8.31 seconds, median of 5.70 seconds)
304 as compared to the original data. In consequence, auto-correlation of noise between consec-
305 utive examples was reduced, resulting in classifiers that were less biased by autocorrelated
306 event structure (for details, see [Koch et al., 2020](#)). Each set was further split into four folds
307 for cross-validation purposes. Specifically, each of the two sessions was split once such that
308 both resulting folds contained the same amount of examples. Separate leave-one-fold-out
309 classification analyses were then performed within each of the two sets (odd/even). The test
310 set, as opposed to the training set, included odd as well as even examples to maximize the

311 number of predictions. Cross-validated decoding results from both sets were combined only
312 afterwards.

313 Because session was associated with intervention type (placebo or L-DOPA), we also
314 adopted a within-session approach for cross-validation. Specifically, cross-session cross-
315 validation was problematic in two ways: First, it could not be used to assess intervention
316 effects that may differ between sessions. Second, training on data from a DA session and
317 testing on a Placebo session (and vice versa) would risk that DA induced changes in direction
318 specific activation patterns could result in reduced classification. To address these issues,
319 data from one session was separated into three folds, and cross-validated decoding was per-
320 formed across these folds from the same session. An equal number of events per direction in
321 each fold was ensured as above. The separation into odd and even events was dropped due
322 to reduced data amount when considering only one session. Nevertheless, four participants
323 (2 OA, 2 YA) had to be excluded for missing examples of at least one class in any of the two
324 sessions, leaving a final sample of 80 participants (37 OA, 43 YA).

325 In both cross-validation approaches, we ensured a balanced number of training examples
326 for each class by upsampling underrepresented classes if necessary. Trained classifiers were
327 then used to predict the walking direction from examples in a testing set given by the remain-
328 ing fold. A balanced accuracy score was calculated for each test set and results were pooled
329 across all cross-validation runs. The resulting score was compared to a permutation distri-
330 bution resulting from repeating the same classification 1000 times with randomly permuted
331 class labels in the training set. Additionally, a linear mixed model (LMM) of classification
332 accuracy with fixed effects of age group and ROI, and a random effect of participant was used
333 to assess possible group- or ROI-based differences, as well as their interaction. The model
334 for session-specific decoding results included main- and interaction effects of intervention
335 (L-DOPA vs. Placebo), age group (OA vs. YA), ROI, and session order (L-DOPA – Placebo
336 vs. Placebo – L-DOPA; to allow assessing order effects of the drug intervention). To assess
337 whether drug effects scaled with the administered drug dosage relative to body weight the
338 model also included a relative dosage/kg \times intervention interaction. Additionally, in both
339 models main effects of FD and an FD \times intervention interaction were included in the model
340 as a nuisance variable to capture possible effects of drug-related head motion. Random ef-

341 facts included a random intercept of participant and a random slope of intervention to assure
342 a within-subject comparison of decoding accuracy in both sessions.

343 **Influence of spatial angular difference on fMRI pattern similarity** To test
344 if neural representations of walking direction show the same circular similarity structure as
345 directions in geometrical space, we analysed the structure of classifiers predictions as in [Koch](#)
346 [et al. \(2020\)](#). If the similarity of two fMRI patterns of two different directions is associated
347 with their angular distance in space, this should be reflected in the probability distributions
348 over all possible directions. Specifically, we extracted the probability estimates of each of the
349 six classes for each example of the testing set as calculated by the logistic regression classifier.
350 These estimates were aligned with regard to relative angular difference from the target class
351 (-120° , -60° , 0° , 60° , 120° , 180°) and then averaged over all examples, resulting in a single
352 curve for each participant which we refer to as the *confusion function*. Two simple models
353 of the confusion function with one parameter each were compared: A Gaussian curve in the
354 form of

$$g(x) = \frac{1}{Z} e^{-\frac{1}{2}\tau x^2}, \quad (1)$$

355 where x denotes the angular difference and τ the precision (the inverse of the variance, $\frac{1}{\sigma^2}$).
356 Furthermore, Z normalizes the curve. This model captures an inverse relationship between
357 the angular difference of two walking directions and the confusability of their associated
358 neural patterns. An alternative model expressing an absence of such relationship is described
359 by a uniform distribution of classification errors over the remaining five off-center bins. This
360 model could still accommodate high classification for the target class, but would assume that
361 the probabilities of other classes are flat, i.e unrelated to the distance from the target class.
362 Such a model is given by

$$u(x) = \begin{cases} a, & \text{if } x = 0 \\ \frac{100-a}{5}, & \text{otherwise} \end{cases} \quad (2)$$

363 where a denotes the classification accuracy. Models were fitted separately within each par-
364 ticipant and ROI. Because both models had only one free parameter (τ and a , respectively),
365 we compared the square root of the mean squared errors (RMSE) between off-center model

366 predictions for both models directly. A better model fit of the Gaussian model indicates
367 directional tuning, i.e. an inverse relationship between the angular difference of directions
368 and the similarity of their neural representations.

369 In addition to comparing model fits, the Gaussian model allowed us to assess age-
370 differences in directional tuning specificity, which were captured by the precision parameter
371 τ . A LMM identical to the one modelling classification accuracy described in the previous
372 section was used to analyze differences in precision.

373 2.8 Behavioral analysis

374 Task performance during the feedback phase was measured by the distance error: the Eu-
375 clidean distance between the true location of an object and the location the participant
376 placed the respective object (measured in virtual meters; vm; 1vm = 62.5 Unreal units).
377 Performance for each trial was given by the average distance error across all five presented
378 objects within a trial (missing responses due to exceeding the time limit were excluded).
379 Kolmogorov–Smirnov tests indicated that performance scores of YA were not normally dis-
380 tributed ($D = .169$, $p = .010$, $D = .064$, $p = .881$, for YA and OA, respectively; tested
381 for performance on the last trial). To assure normality, the average distance errors in each
382 trial were log-transformed ($D = .054$, $p = .941$, $D = .106$, $p = .323$ after transform for
383 YA and OA, respectively). To assess the process of learning during the feedback phase of
384 the task, we compared the difference between the first and last trial. Note that in light of
385 non-linear learning curves we did not use a linear model across all trials on purpose. The dif-
386 ference between the two log-transformed measures was modeled using an LMM including the
387 fixed effects of intervention (L-DOPA vs. Placebo), age group, and session order (L-DOPA–
388 Placebo vs. Placebo–L-DOPA) as well as a random intercept of participant. Additionally,
389 we compared performance after learning (last trial) with an identical LMM. Furthermore,
390 group-level performance was compared to chance given by the average distance error as-
391 suming random responses for every object. To this end, we uniformly sampled 10^5 possible
392 locations within the circular arena. The task was then simulated 1000 times while each
393 response of each participant was randomly drawn from the pool of possible locations. This
394 yielded a distribution of 1000 group-means assuming random performance over a given trial

395 and allowed a comparison of trial-specific group-means

396 Finally, we aimed to quantify the relationship between the specificity of direction signals
397 and task performance to see if more specific direction signals allow better performance on
398 the given task. To this end, we used previous LMMs of classification accuracy but added the
399 regressor of performance in the last trial of the experiment. To assure normally distributed
400 values the log-transformed performance variable was used. Furthermore, performance values
401 were demeaned to eliminate a possible confound between age group and task performance.
402 The FD-related nuisance regressors as well as the interaction between dosage per body weight
403 and intervention were dropped from the model. To see if L-DOPA enhanced signal specificity
404 in proportion to its enhancement of task performance the above model was adapted to predict
405 the difference between sessions in classification accuracy (L-DOPA - Placebo). The increase
406 in task performance was given by the session difference (L-DOPA - Placebo) of the log-
407 transformed performance in the last trial of the task.

408 **3 Results**

409 **3.1 Behavioral results**

410 Log-transformed average distance errors on each trial for both age groups and interventions
411 (L-DOPA vs. placebo) are displayed in Fig. 2. We first investigated log transformed distance
412 errors on the last trial after learning, using a linear mixed model with fixed effects of interest
413 for intervention and age group and a random effect of participant.

414 The LMM showed a significant main effect of age group ($\chi^2(1) = 167.010, p > .001$, the
415 χ^2 reflect likelihood ratio tests, see Methods). Post-hoc tests showed that OA had higher
416 distance errors compared to YA at the end of learning ($t(80) = 12.811, p < .001$). The
417 model did not display any significant main effect of intervention ($\chi^2(1) = 1.479, p = .224$)
418 or intervention by age interaction.

419 Next, we investigated performance increases, i.e. log distance errors on the first minus
420 the last trial. Again, a LMM revealed a significant main effect of age group ($\chi^2(1) = 61.054$,
421 $p > .001$), but no main effect of intervention or intervention \times age interaction.

422 Investigating the nuisance variable of session order revealed no main effects in either

423 end-of-learning performance ($\chi^2(1) = 0.1784, p = .673$) or in performance changes ($\chi^2(1) =$
424 $0.948, p = .330$). No session order \times intervention effect was found for performance changes.
425 Unexpectedly, we found a significant interaction of intervention \times session order in end-of-
426 learning performance ($\chi^2(1) = 13.744, p < .001$), reflecting a trend for a positive effect of
427 DA if L-DOPA was given in the second session ($t(80) = -1.693, p = .094$), while this was
428 reversed if L-DOPA was given in the first session ($t(80) = 3.368, p = .001$).

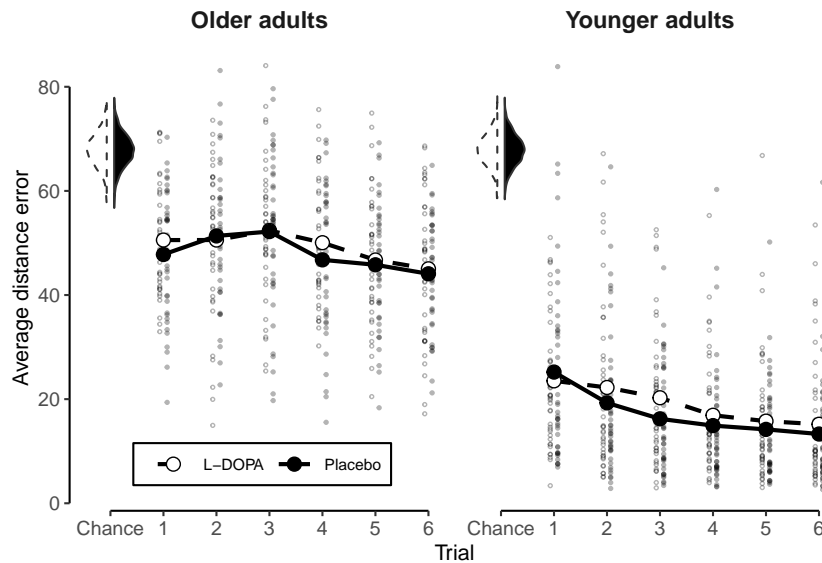


Figure 2: Behavioral results. Average error in object placement for all six trials for OA and YA. Error was measured as the Euclidean distance in vm between the true location of an object and the participants' placement. Reduction in error shows better task performance. All values of the placebo session depicted in black, all values of the L-DOPA session depicted in white. Small dots indicate individual values of participants. Average over participants in each trial shown by the large dots. Shown on the upper left are session-specific distributions of 10^3 average performance values in a trial assuming random placement of objects. Note that, in turn, only the trial averages (large dots) can be compared to this chance-distribution.

429 3.2 Decodability of walking direction

430 We first assessed decoding using a cross-validation approach across intervention sessions
431 (see Methods). In line with previous work (Koch et al., 2020), walking direction could be
432 decoded in the EVC ($p < .001$) and RSC ($p = .040$), but not in the left motor cortex
433 ($p = .255$), entorhinal cortex ($p > .999$) and HC ($p > .999$), compared to a permutation test
434 (Bonferroni corrected for five comparisons, one sided). A LMM of classification accuracy
435 with fixed effects of interest for age group and ROI, and a random effect of participant
436 revealed a significant main effect of age group ($\chi^2(1) = 16.209, p < .001$), a main effect
437 of ROI ($\chi^2(4) = 194.810, p < .001$), and a ROI \times age group interaction ($\chi^2(4) = 37.851,$

438 $p > .001$). Post-hoc mean comparisons showed significantly higher classification accuracy in
439 YA in the EVC ($t(320) = -7.280, p < .001$), but no such age-related effects in the RSC or
440 HC ($t(320) \geq -1.489, p \geq .138$), see Fig. 3A. Although classification accuracy was higher in
441 YA in the EVC, a permutation test revealed significant above-chance decoding also in OA
442 ($p < .001$). No main effect of the nuisance variable FD was found ($\chi^2(1) = .482, p > .487$).

443 Investigating the predicted probabilities by the logistic regression directly, rather than the
444 percent of correctly predicted events, revealed a peak at the true direction and decreasing
445 probabilities for the off-target directions in RSC and EVC, as expected (see Fig. 3B).
446 Notably, in this more sensitive analysis also the HC exhibited an above-chance probability
447 of the target direction ($t(83) = 5.346, p < .001, \text{corr.}$).

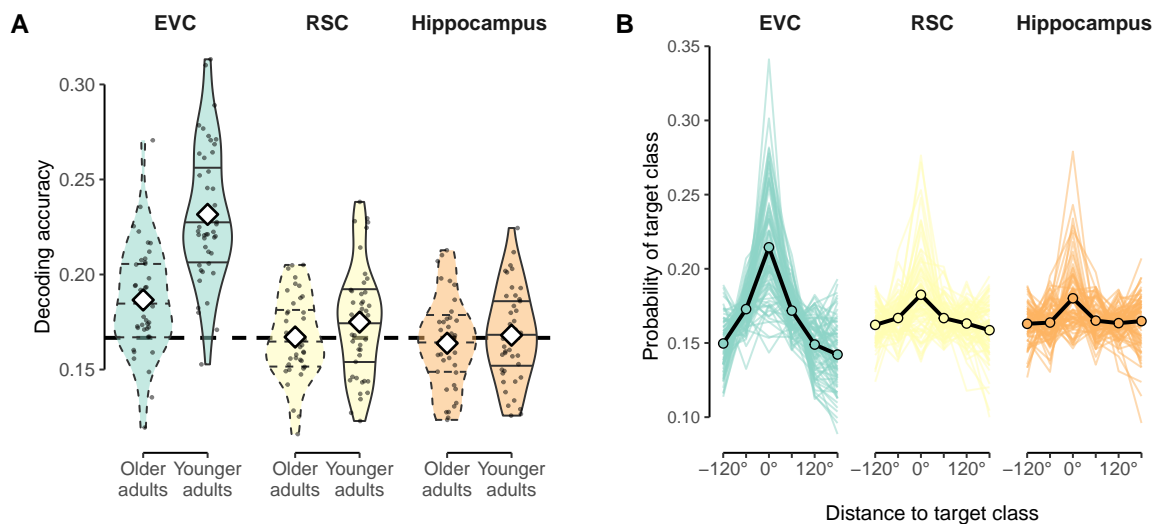


Figure 3: Cross-intervention walking direction decoding. **A:** Cross-validated decoding accuracy of walking direction within both age groups for the cross-session approach, in which the classifier was partially trained on the placebo session and tested on the DA session, or vice versa. Results are shown separately for EVC (green), RSC (yellow), and hippocampus (orange) and each age group (dashed/solid lines). Violin plots indicate distributions, dots represent individual participants and white diamonds mean accuracy. Horizontal, dashed line indicates chance level. **B:** Confusion function for each classifier. Depicted are class probabilities of the logistic classifier as a function of angular distance from the target class. Colored lines indicate individual participants, black lines the group average. Colors as in A.

448 3.3 Influence of L-DOPA intervention on decodability

449 Decoding analyses reported above combined data across sessions/interventions and thus cannot
450 be used to examine the effects of intervention type. We therefore used a within-session
451 decoding analysis to investigate the influence of L-DOPA administration on the decodability
452 of walking direction (see Methods). A LMM of classification accuracy indeed showed a

453 significant main effect of L-DOPA intervention ($\chi^2(1) = 6.796, p = .009$), which indicated
454 higher decoding in L-DOPA compared to placebo sessions. As before, we also found main ef-
455 fects of ROI ($\chi^2(4) = 271.674, p < .001$), but no L-DOPA \times ROI interaction ($\chi^2(4) = 3.847,$
456 $p = .427$). Despite the lack of an interaction, post-hoc tests revealed that significantly higher
457 decoding accuracy in the drug compared to the placebo condition was most apparent in the
458 HC ($t(603) = 2.153, p = .032$) and trending in the RSC ($t(603) = 1.916, p = .055$), while no
459 comparable effects were found in the EVC ($t(603) = 1.447, p = .148$). Results are displayed
460 in Fig. 4A.

461 In addition, we also found a main effect of age group ($\chi^2(1) = 6.273, p = .012$) and a
462 age group \times ROI interaction ($\chi^2(4) = 60.970, p < .001$). We will elucidate these age effects
463 further below, using separate LMMs per ROI. None of the included nuisance regressors of
464 FD ($\chi^2(1) = 3.064, p = .080$) or an interaction between FD and intervention ($\chi^2(1) = .048,$
465 $p = .826$) showed a significant effect on decodability of walking direction. The same was true
466 for any effects of session order ($\chi^2(1) = .083, p = .774$). There was no significant interaction
467 between the intervention and the administered dosage per body weight ($\chi^2(2) = .286, p =$
468 $.867$).

469 To further specify the region-specific effects of DA, LMMs were run separately for each
470 ROI. These ROI-specific LMMs reproduced the main effects of intervention within the HC
471 ($\chi^2(1) = 5.263, p = .022$) and the RSC ($\chi^2(1) = 4.868, p = .027$). In addition, we found
472 an intervention \times age group interaction within the RSC ($\chi^2(1) = 3.877, p = .049$), but no
473 such interaction in HC ($\chi^2(1) = 1.518, p = .218$). Post-hoc comparisons showed that the
474 effect in RSC was driven by higher decodability of walking direction in the DA compared to
475 placebo session in young adults ($t(75.6) = 2.879, p = .005$), but not in OA ($t(75.4) = -.161,$
476 $p = .872$). Within the EVC, only a main effect of age group ($\chi^2(1) = 16.350, p < .001$), but
477 no effect of DA intervention ($\chi^2(1) = 2.038, p = .153$) was found.

478 Fig. 4B shows the increase in decodability of walking direction in the L-DOPA condition
479 for the HC and RSC, respectively for each age group. Note that the random slope of inter-
480 vention had to be dropped from these models to avoid having the same number of random
481 effects as there are data points.

482 Investigating nuisance variables, we found no impact of dosage per body weight on the

483 intervention effect in any ROI ($\chi^2(2) < 3.578$, $p \geq .167$, for the interaction). Investigating
 484 the movement related variable FD, we found no significant main effects of FD ($\chi^2(1) \leq 1.448$,
 485 $p \geq .229$) or an interaction between FD and intervention ($\chi^2(1) \leq .644$, $p \geq .422$) in HC
 486 or RSC. A significant main effect of FD was found in the EVC, however ($\chi^2(1) = 4.935$,
 487 $p = .026$). This reflected worse classification accuracy with higher movement during image
 488 acquisition (linear regression relating classification accuracy to FD: $b = -.118$, $t(158) =$
 489 -6.302 , $p < .001$).

490 A final control analysis within the left motor cortex did neither identify a main effect of
 491 intervention ($\chi^2(1) = .027$, $p = .869$) nor any other main effects. Post-hoc tests confirmed
 492 that direction decodability under L-DOPA was not significantly different from decodability
 493 under placebo, regardless of session order ($t(74.9) = -1.519$, $p = .133$, and $t(74.1) = 1.202$,
 494 $p = .233$, L-DOPA–Placebo and Placebo–L-DOPA, respectively).

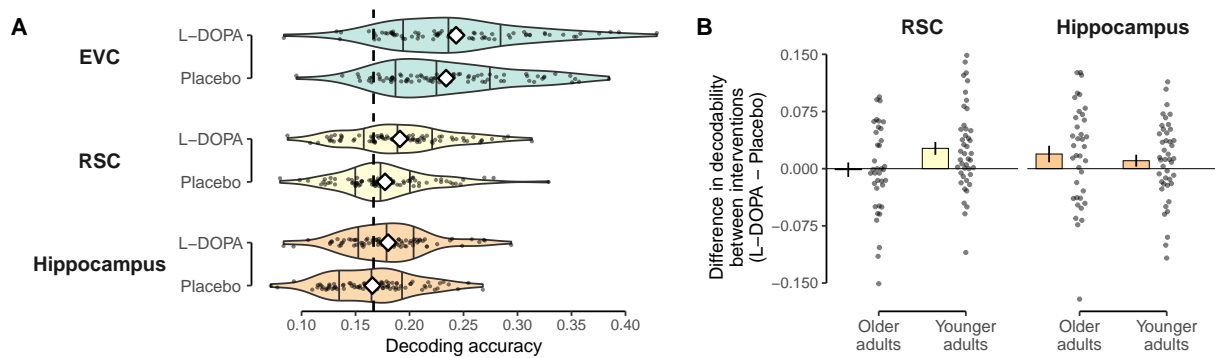


Figure 4: Effect of L-DOPA on decoding of neural walking direction signals. **A:** Intervention-specific decodability of walking direction within each ROI. Black dots show values of participants and violin plots depict intervention-specific distribution. Means are represented by white diamonds. Chance-level is shown by dashed line and based on the total number of classes (6 classes, 16.6% chance). **B:** Influence of drug intervention on decodability (L-DOPA – Placebo) shown for the RSC and hippocampus and split by age groups. Values higher than zero indicate higher decoding accuracy in the L-DOPA condition. Bars reflect group means and error bars reflect SEM. Black dots show individual values of each participant.

495 3.4 Influence of L-DOPA intervention on tuning specificity

496 We next investigated tuning width. Omnibus analyses across ROIs revealed no L-DOPA
 497 effect, a main effect of ROI ($\chi^2(2) = 281.509$, $p < .001$), and results otherwise consistent
 498 with those reported below. We therefore immediately report results of ROI-specific LMMs.
 499 A model of EVC tuning width found no main effect of intervention or intervention \times age
 500 effect was found in EVC. We did find a significant main effect of age group ($\chi^2(1) = 20.631$,

501 $p < .001$), reflecting lower precision of the fitted Gaussian curves in OA compared to YA
502 ($t(79.7) = -4.533, p < .001$). The same analyses in RSC an HC showed no significant main
503 effects of intervention, age, or intervention \times age interactions.

504 No nuisance effect of FD or FD \times intervention interaction were found in any ROI-specific
505 model ($\chi^2(1) \leq .857, p \geq .355$ and $\chi^2(1) \leq .578, p \geq .447$, respectively) just as there were
506 no main effects of session order ($\chi^2(1) \leq .257, p \geq .612$) Additionally, intervention was
507 not involved in any interaction with dosage per body weight ($\chi^2(2) \leq 4.412, p \geq .110$).
508 Unexpectedly, however, we found a significant intervention \times session order interaction in
509 the EVC ($\chi^2(1) = 10.713, p < .001$; see Fig. 5A), suggesting that tuning precision was
510 higher when L-DOPA was administered in the second session ($t(74.0) = 2.911, p < .005$)
511 compared to when it was administered in the first session ($t(75.2) = -1.607, p = .112$). No
512 intervention \times session order interaction was found in any other ROI. An exploratory follow
513 up of three-way interactions found a intervention \times age group \times session order effect in the
514 RSC ($\chi^2(1) = 6.626, p = .010$), which pointed towards L-DOPA effects only when given in
515 the second session, and only in YA ($t(74.6) = 2.818, p = .006$).

516 The means of the fitted Gaussian curves in the L-DOPA condition are shown in Fig.
517 5B. Please note that the interpretability of these results is limited since a model comparison
518 between a Gaussian and uniform model of the confusion function remained inconclusive
519 towards either model in both, the drug and placebo condition ($t(79) \leq 1.749$ or $t(79) \geq$
520 -1.921 , all $p \geq .350$, corr.).

521 **3.5 Relations between task performance, L-DOPA and direction** 522 **decoding**

523 Finally, we asked whether task performance (spatial distance error) was related to neural
524 direction encoding as well as to the effects of L-DOPA on these neural signals. We therefore
525 investigated the link between session-specific decoding accuracy and task performance on
526 the last trial, in addition to age group, intervention and session order. Because performance
527 on the last trial was highly confounded with age group (see 2) performance values were
528 demeaned within each age group to investigate effects unrelated to age-specific performance
529 differences.

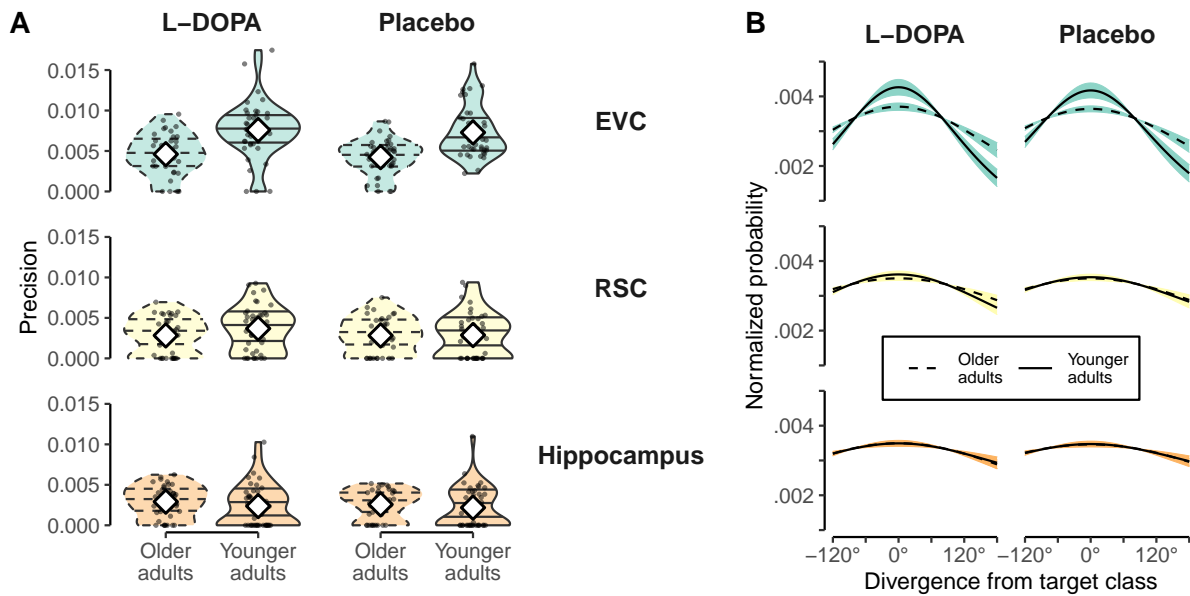


Figure 5: Effect of L-DOPA on tuning specificity. **A:** Precision of Gaussian curves fitted to individual confusion functions in both age groups. Shown separately for the L-DOPA and Placebo intervention in the EVC, RSC, and Hippocampus. Black dots show values of individual participants. Intervention-specific distributions are shown by violin plots. White diamonds depict means. Plots of OA shown in dashed lines for easier distinction. **B:** Mean Gaussian tuning curves shown separately for age groups and intervention (L-DOPA vs. Placebo). ROI separation identical to that of panel A. OA are depicted with dashed lines. Shaded area represents SEM and is colored according to ROI. For each participant a Gaussian curve was fitted to the individual confusion function (given by the classifier). The shown mean Gaussian curves were obtained by averaging participants' individual Gaussian curves.

530 No effects related to task performance were found in the RSC or the HC ($p \geq .053$). A

531 model within the EVC revealed a significant main effect of distance error on the last trial on

532 direction decoding ($\chi^2(1) = 7.594, p = .006$; see Fig. 6A), pointing towards better decoding

533 accuracy with better task performance ($b = .040$). Besides the main effect, task performance

534 in the EVC also interacted with age group ($\chi^2(1) = 3.921, p = .048$), reflecting that the

535 above mentioned relationship was present in YA ($F(1, 111.03) = 11.912, p < .001, b = .033$)

536 and absent in OA ($F(1, 121.83) = .066, p = .798, b = .006$). While there was no main

537 effect of session order ($\chi^2(1) = .009, p = .922$), the model furthermore indicated a separate

538 interaction between task performance and session order ($\chi^2(1) = 4.332, p = .037$). A post-

539 hoc test revealed a trend towards differing slopes depending if L-DOPA was given in the

540 first or second session ($t(132) = 1.904, p = .059$) but separate tests within each session order

541 did not display any significant relationships between performance and classification accuracy

542 ($F(1, 143.83) = .607, p = .437, F(1, 118.80) = 3.164, p = .078$, for L-DOPA – Placebo and

543 Placebo – L-DOPA, respectively). As expected the model of EVC decoding accuracy also

544 displayed a main effect of age group ($\chi^2(1) = 40.244, p < .001$; see results for influence of

545 DA on decoding accuracy).

546 We next investigated change-change relations, asking whether L-DOPA-related changes
547 in decoding were related to L-DOPA-related changes in task performance (see Fig. 6B).

548 Linear regressions revealed that in YA L-DOPA-related changes in direction decoding in EVC
549 were indeed positively related to changes in task performance ($F(1, 72) = 6.730, p = .011,$

550 $b = -.053,$ negative slopes since performance increase means less errors). In OA this was

551 not the case ($F(1, 72) = .049, p = .826, b = .006$). Linear models within the RSC and HC

552 did not show any significant effects in change-change relations.

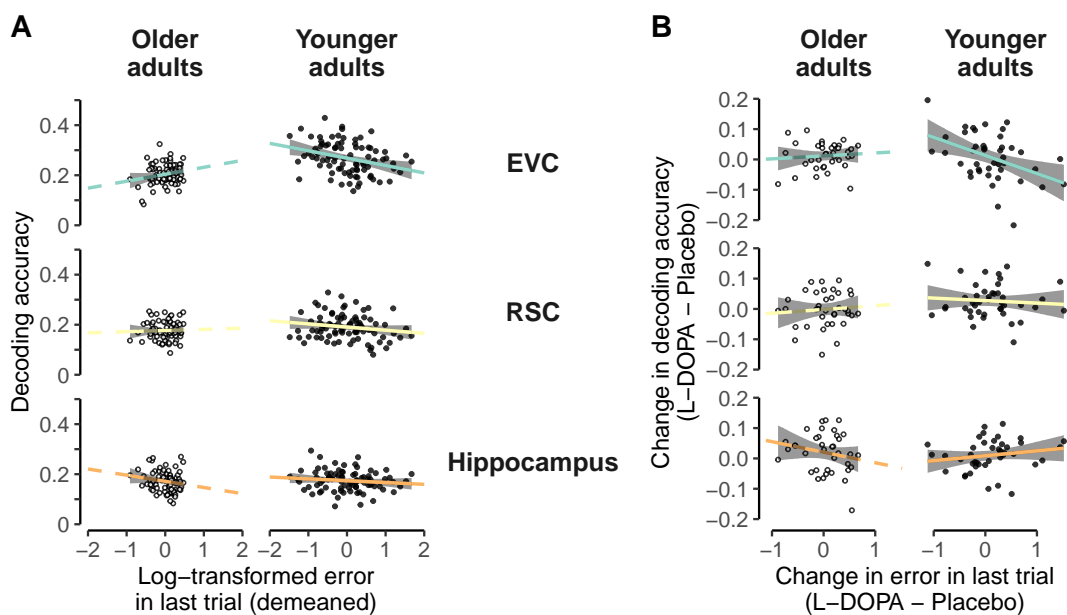


Figure 6: Relationship between decoding accuracy and behavioral performance. **A:** Relationship between decoding accuracy and log-transformed and demeaned distance errors. Shown for the EVC, RSC, and hippocampus separately for both age groups. Dots represent individual participants where OA are shown in white. Lines represent linear models of represented subset and are colored according to the ROI and shown in dashed for OA. **B:** Drug-related change-change relationship between decoding accuracy and behavioral performance. Axes show influence of L-DOPA administration by showing the difference in values between the L-DOPA session and placebo session. Depiction accordingly to A. Please note that in both, A and B, the slope lines were extended beyond the data points purely to aid visibility.

553 4 Discussion

554 In this work we tested the impact of L-DOPA on neural representations of walking direction

555 in younger and older adults, using a double-blind, cross-over intervention design. In addition

556 to a classic decoding approach, we assessed direction specificity of neural signals, a proxy

557 for tuning functions, using the relative structure of classifier probability estimates. Our

558 results revealed that decodability of walking direction signals in the hippocampus and the
559 retrosplenial cortex was enhanced following the administration of L-DOPA. L-DOPA had
560 comparable effects on HC walking direction signals in both age groups, but in the RSC these
561 DA effects were present only in YA. No L-DOPA effects were found in visual cortex (EVC).
562 Yet, behavioral investigations showed that in younger adults, EVC direction decoding was
563 related to task performance (spatial distance error), and that L-DOPA related changes in
564 EVC decoding were related to changes in task performance. An investigation of tuning
565 specificity revealed no main effects of L-DOPA or L-DOPA \times age group interactions.

566 Furthermore, decoding across interventions, we found evidence for stable direction sig-
567 nals in EVC and RSC, and so some extent also in HPC. Investigating age group differences,
568 we found higher classification accuracy and precision of tuning functions in the EVC of YA
569 compared to OA, a sign of neural dedifferentiation. No age effects on decoding in the HPC
570 or RSC were found. These results confirm our previous finding that neural representations
571 of walking direction can be found in EVC and RSC, and that strong age-related differenti-
572 ation is present particularly in EVC (Koch et al., 2020). We also showed that better EVC
573 classification accuracy was related to better performance on task, suggesting an important
574 functional role of this area in our task.

575 Importantly, our results also offer a number of novel insights. First, we show a causal
576 influence of L-DOPA on how walking directions are encoded in the brain, in particular in the
577 HC and the RSC. Both areas have been linked to directional and other spatial information
578 (Spiers & Barry, 2015; Shine et al., 2016; Burles, Slone, & Iaria, 2017), and have even been
579 shown to be part of the same dorsal pathway involved in visuospatial processing (Kravitz,
580 Saleem, Baker, & Mishkin, 2011). Additionally, both areas display dopaminergic innervation
581 (Berger, Verney, Alvarez, Vigny, & Helle, 1985; McNamara & Dupret, 2017), and previous
582 reports have linked DA and spatial cognition more generally (Granado et al., 2008; El-Ghundi
583 et al., 1999; Thurm et al., 2016). Second, the positive effects of DA on decoding are in line
584 with computational models and empirical findings which suggest that DA affects neuronal
585 gain (Li & Rieckmann, 2014; Cohen & Servan-Schreiber, 1992; Thurley, Senn, & Lüscher,
586 2008). Accordingly, DA's influence on neural gain could lead to a stronger separation between
587 signal and noise, which made different stimuli more specific and easier to distinguish for the

588 classifier. It should be noted, however, that we did not find any direct effects of L-DOPA on
589 neural direction tuning specificity, which measures how similar neural patterns are to similar
590 directions. Given the effects of DA on neural gain, we had hypothesized that this measure
591 could be more sensitive to the effects of our intervention, but this was not the case. One
592 possible explanation is that our design lacked the power to fully capture the neural tuning
593 functions within just one session. Tentative analyses of EVC and RSC tuning specificity
594 did show DA-related enhancement only in participants who received L-DOPA in the second
595 session. We will discuss these session-specific effects further below.

596 Third, our study was set up to ask whether the L-DOPA intervention might reduce age-
597 related neural dedifferentiation. Virtual walking direction offered a promising window to
598 answer these questions since it has previously been shown to be subject to age-related neural
599 dedifferentiation ([Koch et al., 2020](#)) and the broader domain of spatial cognition has been
600 shown to be highly age-sensitive ([Wolbers et al., 2014](#); [Lester et al., 2017](#)). Age is also known
601 to cause substantial loss of DA functioning (e.g. [Bäckman et al., 2006](#)), and we speculated
602 that a lower baseline DA availability might magnify the effects of L-DOPA. Surprisingly, we
603 did not find that the effects of L-DOPA were particularly pronounced in OA. Rather, the HC
604 showed age-equivalent effects, and decoding in RSC was in fact enhanced only in YA. Other
605 than individual differences in baseline DA level, task demand may also affect the inverted-U
606 function of DA modulation ([Cools & D'Esposito, 2011](#)). The spatial navigation task used in
607 our study is quite demanding, such that YA though have higher baseline DA level could still
608 benefit from the L-DOPA intervention, whereas in OA the task demand may still outweigh
609 the benefit of L-DOPA intervention. While unexpected, these results could offer interesting
610 insights into the complexity of how external DA medication might interact with neural
611 differentiation and compensatory plasticity mechanisms that counteract age-related losses.
612 One notable aspect in this regard is that we found no evidence of age-related dedifferentiation
613 in HC or RSC, which speculatively could be a sign of compensatory mechanisms. It seems
614 possible that DA interventions might only recover neural specificity in brain areas that are
615 affected by age-related dedifferentiation. Contrary to this idea, we found no age-related
616 L-DOPA effects in visual cortex, where dedifferentiation was observed – but this might be
617 due to the relatively low D2 receptor density in this area ([Lidow, Goldman-Rakic, Rakic,](#)

618 & Innis, 1989). Another possibility is that we did not observe age-specific effects of L-
619 DOPA on neural direction encoding in RSC and HC for the same reasons we did not find
620 age-related dedifferentiation in these regions. According to this idea, compensatory factors
621 that have mitigated dedifferentiation also affected the effectiveness of external dopamine
622 administration, for instance because of changed connectivity. Both ideas remain speculative
623 and further studies are needed to fully understand how the effects of L-DOPA interventions
624 on neural direction encoding interact with age and dedifferentiation.

625 Beyond these main implications, a number of interesting observations arose that warrant
626 further investigation. Although we did not find any main effects of session order, we found
627 some indications that session order could influence the effect of L-DOPA on neural signals
628 that underlie spatial navigation. Age-differences in learning were stronger when L-DOPA
629 was administered in the second compared to the first session. In addition, we found tuning
630 specificity in EVC and RSC to be enhanced by L-DOPA only in participants who received the
631 drug in the second session. Stronger effects when DA is administered in a second session have
632 previously been reported in the context of spatial navigation (Thurm et al., 2016). The reason
633 why session order effects could exist in this context are numerous. Garrett et al. (2015), for
634 instance, highlight two possible explanations in the context of DA effects on neural signal
635 variability. One is that previous training may increase the amount of baseline DA-release,
636 based on findings in rodents (Owesson-White, Cheer, Beyene, Carelli, & Wightman, 2008).
637 A DA intervention could therefore lead to differing DA-availability depending on whether
638 the participants had already been trained with the same or a similar task. A second possible
639 explanation raised by Garrett et al. (2015) is that the environment is either learned in a
640 state of higher or normal DA-availability. The state of the second sessions will consequently
641 always be mismatched to the first session, leading to effects of drug administration given the
642 respective session. Related to the first idea, we speculate that in our case general learning
643 about the environment in a first placebo session could have established beneficial baseline
644 for the effects of L-DOPA in the second session. Unfortunately, the present design is unfit
645 to address such explanations and further evidence is warranted.

646 One open question is why the effect of L-DOPA on decoding in HC and RSC was not
647 reflected in task performance, where no L-DOPA effect was found. In addition to generally

648 small effects on neural representations, another explanation might be that task performance
649 did does only depend on direction signals, but also relies on distance estimation and using
650 distal and local cues, processes which themselves are affected by age (Schuck et al., 2015).
651 The task might therefore have been too complex to provide a suitable behavioral measure.
652 Interestingly, however, we we did find some relationships between behavior and the specificity
653 of directional information in visual cortex, indicating that neural markers might have different
654 relations to performance in our task. This is shown by some of our results also offer insights
655 about age-related changes in the context of spatial navigation more generally. The results
656 in the EVC showed that OA exhibit lower precision of directional tuning functions. This
657 is a replication of findings reported in an earlier study using a similar analysis approach
658 (Koch et al., 2020). During natural navigation and the perception of direction vision plays a
659 major role as it allows stable directional signals (Goodridge, 1998) and corrects and prevents
660 the accumulation of errors during path integration (Jeffery, 2007). A less precise visual
661 signal in OA could therefore influence spatial signals downstream and contribute towards the
662 pronounced difficulties OA have in spatial tasks. Interestingly, we also found a relationship
663 between EVC direction decoding in YA and performance on task, suggesting better spatial
664 memory performance if walking direction could be decoded with higher accuracy. While this
665 concurs with previous reports of a link between (non-spatial) memory and signal specificity
666 (Koen et al., 2019; Sommer et al., 2019; St-Laurent et al., 2014), previous studies have mostly
667 reported such links in older adults. Future work is required to further understand how age-
668 related loss in specificity of visual signals might be involved in spatial cognition. That said,
669 a simple propagation of less specific visual signals to the retrosplenial complex network seems
670 unlikely, since there was no evidence for age-related dedifferentiation in the RSC or HC.

671 In summary, we provide first causal insights into the role of dopamine in the encod-
672 ing of spatial direction signals in the human hippocampus. In addition, our findings show
673 that dopamine also enhances direction encoding in retrosplenial cortex, albeit exclusively in
674 younger adults. In combination with the replication of our own previous results (Koch et al.,
675 2020), these findings offer insights into the neural processes underlying spatial navigation in
676 the human brain, and how they are affected by age more generally.

677 **Code availability**

678 TBD

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685 **Conflict of interest**

686 The authors declare no conflicts of interest.

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