Sensorimotor network segregation predicts long-term learning of writing skills in Parkinson's Disease - Supplementary Material

Nicholas D'Cruz *, Joni De Vleeschhauwer *, Martina Putzolu, Evelien Nackaerts, Moran Gilat, Alice Nieuwboer

*these authors contributed equally

Accepted for publication in Brain Sciences on the 9th of April 2024

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Supplementary Table S1. Rotated Component Matrix after Principal Component Analysis for writing performance (Rotation method: Varimax).

	Component 1 = Writing Accuracy	Component 2 = Writing Speed
Amplitude (%)	-0.979	-0.010
Speed (cm/s)	-0.125	0.915
COV_{Ampl} (%)	0.526	0.639
Deviation	0.988	0.039
% Variance explained	57.40	29.45

Component scores were subsequently inverted so that higher scores corresponded to larger amplitude, lower variability, and smaller deviation, or in other words, better accuracy.

Supplementary Table S2. Clinical demographics of all 28 patients with PD as well as the comparison between PD+FOG and PD-FOG at baseline.

	All patients (n = 28)	**PD+FOG (n = 13)**	**PD-FOG (n = 15)**	**p-value[a]**
Age (years)	63.93 ± 8.58	65.85 ± 8.17	62.27 ± 8.85	0.279
Sex (M/F)[+]	17/11	10/3	7/8	0.097
EHI (%)	100 (80; 100)	100 (70; 100)	100 (88.75; 100)	0.555
H&Y (1-5)[+]	2 (2; 2)	2 (2; 2)	2 (2; 2)	0.887
Disease Duration (years)	6.89 ± 3.93	8.54 ± 4.22	5.47 ± 3.14	0.036*
LEDD (mg/24h)	641.5 ± 288.47	610 (590; 765)	698.5 (355; 784.5)	0.555
MDS-UPDRS-III (0-132)	31.14 ± 15.07	36.69 ± 15.55	26.33 ± 13.32	0.069
MDS-UPDRS-III-UL (0-56)	15.29 ± 7.87	19 (12; 22)	12 (7; 15.5)	0.156
MAM-16 (0-64)	58 (55; 59)	58 (57; 59)	56 (53.5; 58.5)	0.294
MMSE (0-30)	29 (28; 29)	28 (28; 29)	29 (29; 29.5)	0.052
MoCA (0-30)	26.54 ± 1.73	26.69 ± 1.75	26.4 ± 1.76	0.664
HADS-Anxiety (0-21)	6.32 ± 4.16	6.23 ± 4.19	6.4 ± 4.29	0.917
HADS-Depression (0-21)	5.29 ± 3.21	6.15 ± 2.85	4.53 ± 3.40	0.187

Normally distributed variables are displayed as mean ± standard deviation. Non-normally distributed variables are presented as median (1st quartile; 3rd quartile). [+] Variables analyzed with Chi-squared tests. [a] Comparison between PD+FOG and PD-FOG * Significant at $p < 0.05$
Abbreviations: EHI = Edinburgh Handedness Inventory; HADS = Hospital Anxiety and Depression Scale; MAM-16 = Manual Ability Measure; MDS-UPDRS-III = Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; PD = Parkinson's disease; PD+FOG = freezers; PD-FOG = non-freezers; UL = upper limb

Supplementary Methods S1 – MRI preprocessing

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 1.5.9 (Esteban, Markiewicz, et al. (2018); Esteban, Blair, et al. (2018); RRID:SCR_016216), which is based on *Nipype* 1.4.2 (Gorgolewski et al. (2011); Gorgolewski et al. (2018); RRID:SCR_002502).

Anatomical data preprocessing

The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with `N4BiasFieldCorrection` (Tustison et al. 2010), distributed with ANTs 2.2.0 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` (FSL 5.0.9, RRID:SCR_002823, Zhang, Brady, and Smith 2001). Brain surfaces were reconstructed using `recon-all` (FreeSurfer 6.0.1, RRID:SCR_001847, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al. 2017). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.2.0), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* [Evans et al. (2012), RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym].

Functional data preprocessing

For each of the 1 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A B0-nonuniformity map (or *fieldmap*) was estimated based on a phase-difference map calculated with a dual-echo GRE (gradient-recall echo) sequence, processed with a custom workflow of *SDCFlows* inspired by the `epidewarp.fsl` script and further improvements in HCP Pipelines (Glasser et al. 2013). The *fieldmap* was then co-registered to the target EPI (echo-planar imaging) reference run and converted to a displacements field map (amenable to registration tools such as ANTs) with FSL's `fugue` and other *SDCflows* tools. Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` (FSL 5.0.9, Jenkinson et al. 2002). BOLD runs were slice-time corrected using `3dTshift` from AFNI 20160207 (Cox and Hyde 1997, RRID:SCR_005927). The BOLD time-series, were resampled to surfaces on the following spaces: *fsaverage5*. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD time-series were resampled into several standard spaces, correspondingly generating the following *spatially-normalized, preprocessed BOLD runs*: MNI152NLin2009cAsym, MNI152NLin6Asym. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA, Pruim et al. 2015) was performed on the *preprocessed BOLD on MNI space* time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding “non-aggresively” denoised runs were produced after such smoothing. Additionally, the “aggressive” noise-regressors were collected and placed in the corresponding confounds file. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values are retained, such that the retained components’ time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e., head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using `antsApplyTransforms` (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos 1964). Non-gridded (surface) resamplings were performed using `mri_vol2surf` (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.6.1 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation.

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