Title

Being on target: visual information during writing affects effective connectivity in Parkinson's disease

Authors

Evelien Nackaerts, PhD;[a] Jochen Michely, MD, PhD;[b] Elke Heremans, PhD;[a] Stephan Swinnen, PhD;[c] Bouwien Smits-Engelsman, PhD;[d] Wim Vandenberghe, MD, PhD;[e] Christian Grefkes, MD, PhD;[b,f] Alice Nieuwboer, PhD[a]

Affiliations

[a] Department of Rehabilitation Sciences, KU Leuven
Tervuursevest 101, bus 1501, 3001 Heverlee, Belgium

[b] Department of Neurology, Cologne University Hospital
Kerpener Straße 62, 50924 Köln, Germany

[c] Department of Kinesiology, KU Leuven
Tervuursevest 101, bus 1501, 3001 Heverlee, Belgium

[d] Department of Health and Rehabilitation Sciences, University of Cape Town
Old Main Building Groote Schuur Hospital, Cape Town, South-Africa

[e] Department of Neurology, University Hospitals Leuven
Herestraat 49, 3000 Leuven, Belgium

[f] Institute of Neuroscience and Medicine - Cognitive Neurology (INM-3), Research Centre Jülich
52425 Jülich, Germany

Corresponding author

Evelien Nackaerts
KU Leuven
Tervuursevest 101, bus 1501, 3001 Heverlee, Belgium
Phone: +32 16 32 93 60
evelien.nackaerts@kuleuven.be

ABSTRACT

A common motor symptom of Parkinson's disease (PD) is micrographia, characterized by a decrease in writing amplitude. Despite the relevance of this impairment for activities of daily living, the underlying neural network abnormalities and the impact of cueing strategies on brain connectivity are unknown. Therefore, we investigated the effects of visual cues on visuomotor network interactions during handwriting in PD and healthy controls. Twenty-eight patients with early disease, ON dopaminergic medication, and 14 age-matched controls performed a pre-writing task with and without visual cues in the scanner. Patients displayed weaker right visuo-parietal coupling than controls, suggesting impaired visuomotor integration during writing. Surprisingly, cueing did not have the expected positive effects on writing performance. Patients and controls, however, did activate similar networks during cued and uncued writing. During cued writing, the stronger influence of both visual and motor areas on the left superior parietal lobe suggested that visual cueing induced greater visual steering. In the absence of cues, there was enhanced coupling between parietal and supplementary motor areas (SMA) in line with previous findings in healthy controls during uncued motor tasks. In conclusion, the present study showed that patients with PD, despite their compromised brain function, were able to shift neural networks similarly as controls. However, it seemed that visual cues provided a greater accuracy constraint on handwriting rather than offering unequivocal beneficial effects. Altogether, the results suggest that the effectiveness of using compensatory neural networks through applying external stimuli is task dependent and may compromise motor control during writing.

KEYWORDS

Parkinson's disease; Micrographia; Visual cueing; Dynamic causal modeling

ABBREVIATIONS

BMS = Bayesian Model Selection; BOLD = Blood Oxygen Level Dependent; CB = cerebellum; DCM = Dynamic Causal Modeling; PMC = premotor cortex; HADS = Hospital Anxiety and Depression Scale; H&Y = Hoehn & Yahr; M1 = primary motor cortex; HC = healthy control; MAM-16 = Manual Ability Measure; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; MT/V5 = motion sensitive Middle Temporal visual area; PD = Parkinson's disease; ROI = Region Of Interest; SMA = Supplementary Motor Area; SPL = Superior Parietal Lobe

INTRODUCTION

Micrographia is a common disabling symptom of Parkinson's disease (PD) and is defined as '*an impairment of a fine motor skill manifesting mainly as a progressive or stable reduction in amplitude during a writing task'* (Wagle Shukla et al., 2012). Dopaminergic medication and deep brain stimulation only partially alleviate writing amplitude (Lange et al., 2006; Tucha et al., 2006a; Bidet-Ildei et al., 2011). Therefore, non-pharmacological therapeutic interventions are needed to address this clinically relevant motor deficit. Discrete external stimuli, or "cues", have been shown to improve motor performance and motor learning in patients suffering from PD (Nieuwboer et al., 2007; Nackaerts et al., 2013; Spaulding et al., 2013), though some studies have also found negative effects (Chee et al., 2009; Heremans et al., 2015; Nackaerts et al., 2016b). The benefits of cues are often attributed to different brain networks that are active during internally- versus externally-guided movements, first hypothesized by Goldberg (1985). Several studies confirmed that in healthy subjects the supplementary motor area (SMA) and basal ganglia play an important role in internally-guided movements, whereas the parietal cortex, lateral premotor cortex (PMC) and cerebellum are key areas involved in externally-triggered movements (Jueptner and Weiller, 1998; Jenkins et al., 2000; Debaere et al., 2003). Irrespective of cues, a common finding in PD is that brain activity in the SMA and basal ganglia is decreased during motor performance, while increased activity has frequently been shown in parietal, premotor and cerebellar areas (Samuel et al., 1997; Sabatini et al., 2000; Herz et al., 2014; Wu et al., 2015b). This altered neural recruitment is commonly interpreted as a spontaneous compensatory strategy (Wu et al., 2010; Wu et al., 2015b).

Until now, the majority of behavioral cueing studies in PD focused on gait rather than on fine motor skills such as handwriting. As handwriting is both a highly automated and visually-controlled movement (Tucha et al., 2006b), it is possible that the distinction between 'internal' and 'external' generation of movement is blurred during this task. Wu et al. (2016) showed that directing attention to writing size led to additional recruitment of the anterior putamen and dorsolateral prefrontal cortex in PD. However, the effects of visual cueing on the underlying neural networks of writing in PD are unknown. Therefore, we investigated the network interactions of patients with PD and healthy controls during handwriting with and without external visual cues using Dynamic Causal Modeling (DCM), a technique which adopts probabilistic modeling of the coupling between brain regions based on the hemodynamic response for each brain region in the model (Friston et al., 2003). For this study, we expected stronger connections in the occipito-parietal and premotor-cerebellar networks during cued versus uncued writing and this more so in PD patients because of their known reliance on cued motor control (Jenkins et al., 2000; Debaere et

al., 2003; Wu et al., 2011). Alternatively, it could also be possible that, as the compensatory neural networks in PD are already hyperactive during uncued tasks, the distinction between networks becomes more indistinct, as was found in healthy elderly subjects (Heuninckx et al., 2010). Finally, behavioral studies have highlighted the possible influence of visual impairments on gait rehabilitation in PD (Ekker et al., 2016; Stuart et al., 2016). Hence, this is the reason why we specifically focused on the networks involved in visuomotor processing, thereby comparing performance of PD versus controls.

EXPERIMENTAL PROCEDURES

Subjects

Forty-two PD patients and 15 healthy controls (HC) were recruited as part of a larger behavioral study, described in a previous paper (Nackaerts et al., 2016a). After screening, nine patients of the larger cohort did not meet inclusion criteria for the MRI study. Four additional patients were excluded from the analysis due to excessive head movement (12%) and one because time-series for effective connectivity analysis could not be extracted (3%) (see below). This resulted in the inclusion of 28 patients in the final analysis. Data of one HC were not considered due to technical problems during scanning. The task-related functional imaging data are reported here for the first time.

All participants were right-handed, as determined by the Edinburgh handedness scale (Oldfield, 1971). Inclusion criteria for PD consisted of: (i) diagnosis according to the Brain Bank criteria (Hughes et al., 1992); (ii) Hoehn & Yahr (H&Y) stage I to III while on medication (Hoehn and Yahr, 1967); (iii) right disease-dominance in patients in H&Y I; and (iv) presence of micrographia defined by a score > 1 on item II.7 of the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008). Exclusion criteria for all participants were: (i) Mini-Mental State Examination (MMSE) < 24 (Folstein et al., 1975); (ii) visual impairments that could not be corrected by glasses; (iii) other upper limb problems impeding handwriting; (iv) contra-indications for MRI; and (v) head tremor, determined using the MDS-UPDRS-III.

The local Ethics Committee of the University Hospitals Leuven approved the study in accordance with the Declaration of Helsinki. Prior to participation and after explanation of the protocol, written informed consent was obtained. The trial was registered as ClinicalTrials.gov Protocol Record G.0906.11.

Behavioral assessment

All participants underwent a clinical test battery, including the MDS-UPDRS-III and H&Y staging scale (Hoehn and Yahr, 1967; Goetz et al., 2008). The Levodopa Equivalent Dose was calculated for each

patient (Tomlinson et al., 2010). Daily-life writing was assessed using the Systematic Screening for Handwriting Difficulties test (SOS-test) (Nackaerts et al., 2017) and questioned using item II.7 of the MDS-UPDRS-II on writing skills (Goetz et al., 2008). Fine motor skills were evaluated by means of the Manual Ability Measure (MAM-16) questionnaire (Chen et al., 2005). Cognitive abilities were assessed using the MMSE (Folstein et al., 1975) and emotional status was evaluated using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983).

Handwriting was assessed with and without visual cues (target zones) during behavioral tests in- and outside the scanner. The primary writing outcome comprised a simple repetitive pre-writing task of making three loops continuously, similar to the letter 'e', on a touch-sensitive writing tablet with the instruction to write from the bottom of the blue to the top of the yellow target zone (**Fig. 1B**) (Nackaerts et al., 2016b). Patients were not explicitly instructed to attempt to write within the target zones. After completion of the third loop, participants had to return to the start circle via the gray zone to avoid left-to-right arm movements. Each loop-sequence disappeared from the screen upon re-entering the start circle, which allowed continuous repetition of the same figure without hand repositioning movements until the end of the 27 s trial (Nackaerts et al., 2016b). This pre-writing task allowed assessment of pure writing performance and avoided the involvement of language and higher cognitive demands. The distance between the bottom of the blue and top of the yellow target zone was 0.6 cm. We chose this metric as it best represents the size of daily life writing (van Drempt et al., 2011). The cued writing task was performed in the presence of colored target lines. In the without-cue condition the colored target zones disappeared after 1.5 s.

In the scanner, the writing test was assessed using a custom-made MRI-compatible tablet (**Fig. 1A**). Participants performed the three-loop-sequence described above, while real-time visual feedback of what was written was provided via a double mirror built into the head coil. The three-loop sequence was specifically chosen as this is the maximal amount of letters that can be written without moving the hand, thereby minimizing the effects of small hand movements on head motion. Furthermore, the head of all participants was firmly fixated with semi-rigid foam materials within the head coil. A pacing tone was used to standardize performance, i.e. participants were expected to complete one loop sequence in 2 s. Each of the two conditions (cued - uncued) lasted 27 s, was preceded by a rest period of 6 s and an instruction of 3 s, and repeated four times within one run in random order. All participants performed three runs. Of five patients only two runs could be included due to excessive head movements. All participants performed a practice session in a dummy scanner to become acquainted with the protocol.

All patients were tested while on dopaminergic medication, i.e. approximately 1 h after the last medication intake.

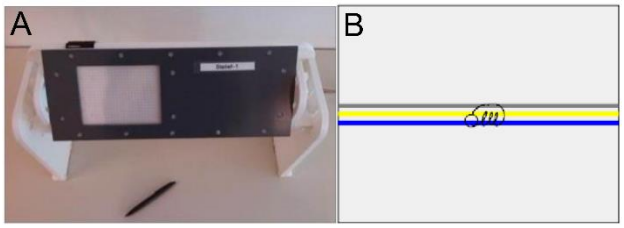

Figure 1: Measurement equipment and writing tasks inside scanner.

Processing and statistical analysis of handwriting performance

Data from the touch-sensitive tablet were filtered at 7 Hz with a 4^{th}-order Butterworth filter (Broeder et al., 2014) and processed using Matlab (R2011b; The Mathworks Ltd., US). The primary outcome variable was writing amplitude (cm). Additionally, variability in amplitude (COV_{Ampl}, expressed as a percentage) and speed (cm/s) were determined.

Statistical analysis was performed using SPSS (version 24, IBM, US), for writing performance in and outside the scanner separately. A mixed model ANOVA was computed with GROUP (patient - control) as a between-subject factor and CONDITION (cued - uncued) as a within-subject factor, including the HADS-D score and gender as covariates, as these differed between groups (see further). A Greenhouse-Geisser correction was applied to all analyses as the assumption of sphericity was violated. The significance level was set at $p < 0.05$.

Functional MRI acquisition and preprocessing

Imaging was carried out in a Philips Achieva 3T scanner (Best, The Netherlands). A standard head coil was used with foam padding to restrict head motion. High-resolution T1-weighted anatomical scans (T1 Turbo Field Echo sequence, duration = 383 ms; slice number = 182; slice thickness = 1.2 mm; time repetition = 9.624 s; time echo = 4.6 ms; flip angle = 8°; matrix = 256 x 256; field of view = 218.4 x 250 x 250 mm) and T2-weighted functional images were acquired for each participant using gradient echo-planar imaging pulse sequence (50 transversal slices, slice thickness = 2.5 mm, slice gap = 0.25 mm, time echo = 30 ms, time repetition = 3000 ms, flip angle = 90°, matrix = 80 × 80, voxel size = 2.5 mm^3).

Functional imaging data were pre-processed using SPM8 (Wellcome Department of Imaging Neuroscience, University College London, UK) implemented in Matlab (R2011a). All functional images were realigned to the reference (mean) image and co-registered to each subject's T1 anatomical image.

All images were normalized to Montreal Neurological Institute space using the segmented anatomical image and smoothed with a 6-mm full width at half maximum Gaussian kernel. Participants were excluded from further analysis in case translations exceeded 2 mm or rotations 2° (Horovitz et al., 2013; Wu et al., 2016). Averages and standard errors of the mean (SEM) can be found for both groups in **Table 1**. Differences in head motion parameters between groups were tested using the framewise displacement method (Power et al., 2012). There was no difference between PD patients and HCs ($p = 0.812$).

Table 1: Head motion parameters (mean ± SEM)

	HC	PD
	Translations	
X (mm)	0.299 ± 0.062	0.222 ± 0.024
Y (mm)	0.254 ± 0.073	0.311 ± 0.049
Z (mm)	0.500 ± 0.063	0.413 ± 0.045
	Rotations	
Pitch (°)	0.018 ± 0.004	0.013 ± 0.002
Roll (°)	0.009 ± 0.001	0.006 ± 0.001
Yaw (°)	0.008 ± 0.001	0.008 ± 0.001

Brain activity analysis

Data were analyzed using the general linear model approach in SPM8. The two experimental conditions (cued - uncued) were modeled and head motion parameters, were added as covariates of no interest to correct for confounding effects. Basic main effects for both conditions were calculated for each participant. Next, individual contrasts were entered in a second-level ANOVA using a full factorial design with factors GROUP (patient - control) and CONDITION (cued - uncued), including HADS-D and gender as covariates. Post hoc t-tests were performed to explore the main differences and interactions ($p < 0.05$, FWE-corrected).

Dynamic causal modeling

DCM is a Bayesian inference method to model the directed influence that one neuronal system exerts over another, i.e. effective connectivity (Friston et al., 2003). It relies on *a priori* defined hypothesis-driven neuronal models of interacting brain regions that are relevant to a specified task or the studied pathology. Hence, DCM does not explore all possible models, but starts with defining the relevant regions of interest (ROIs) and the connections, pertaining to specific hypotheses.

Region of interest selection

In the present study, the ROIs were selected based on their known involvement in handwriting/visuomotor control (Horovitz et al., 2013; Planton et al., 2013), internal versus external control of movement (Jueptner and Weiller, 1998; Jenkins et al., 2000; Debaere et al., 2003) and altered activation and connectivity patterns in PD (Samuel et al., 1997; Sabatini et al., 2000; Herz et al., 2014; Wu et al., 2015a). Additionally, only areas that were activated in each condition in both patients and controls were included (**Fig. 2**). This resulted in the inclusion of bilateral motion sensitive Middle Temporal visual area (MT/V5), bilateral SPL, left M1, left dorsal PMC, left SMA and right cerebellar lobule VI.

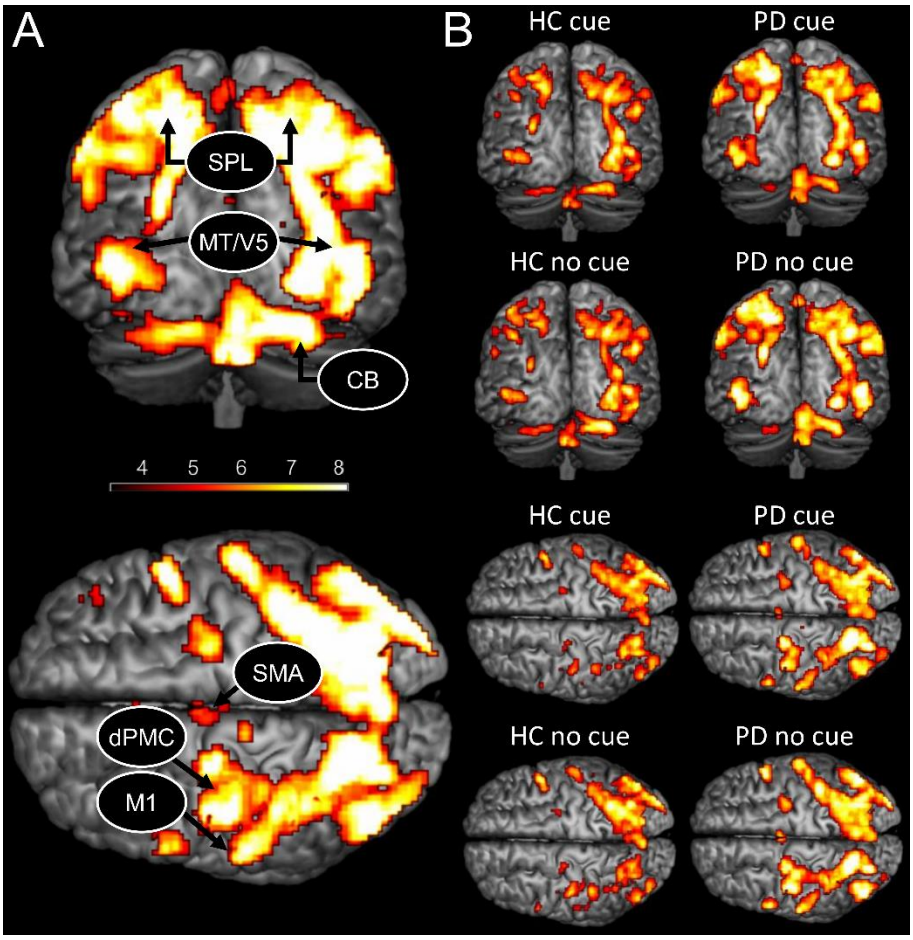

Figure 2: BOLD activation pattern during handwriting. (A) Activated network for both conditions combined in both PD patients and healthy controls; (B) Activated network in each condition and group separately. CB = cerebellum; HC = healthy controls; PD = Parkinson's disease; dPMC = dorsal premotor cortex; M1 = primary motor cortex; SMA = supplementary motor area; SPL = superior parietal lobe; MT/V5 = motion sensitive Middle Temporal visual area. The threshold was set at $p < 0.001$ (uncorrected) to achieve better visualization of all areas.

As DCMs are computed at the single-subject level, we extracted the first eigenvariate of the BOLD time-series adjusted for effects of interest from the eight ROIs at subject-specific coordinates. ROIs were defined as spheres (4 mm radius) centered upon individual activation maxima based on individually normalized SPMs (threshold $p < 0.001$; in case of non-significant voxels, the threshold was lowered to $p < 0.05$).

Connectivity models

The endogenous structure of the network (DCM-A) was based on previous studies on effective connectivity of the extended motor system (Grefkes et al., 2010; Michely et al., 2015; Wu et al., 2015a). As the right hand was used by all participants, we assumed that the main motor involvement would be present in the left hemisphere (Herz et al., 2014). Therefore, we included left M1, dPMC and SMA. In accordance with the literature on the motor network in PD, right CB was included as well (Michely et al., 2015; Wu et al., 2015a). Connections among these areas were assumed, based on the work of Michely et al. (2015) and Wu et al. (2015a). Second, handwriting requires visuomotor integration, a role taken on by the dorsal visual stream (Kravitz et al., 2011). As such, bilateral MT/V5 and SPL were included in the model, as these were also strongly activated. The connections between MT/V5 and SPL, between SPL and dPMC and between SPL and SMA were anticipated based on the work of Grefkes et al. (2010). Finally, interhemispheric connections for MT/V5 and SPL were included given the role of the right hemisphere in processing visual stimuli and guiding spatial attention in motor tasks (Woolley et al., 2010).

We also set up alternative models (DCM-B) of varying complexity representing biologically plausible hypotheses on how connectivity might be modulated depending on the experimental conditions, i.e. the presence or absence of visual cues (**Fig. 3**). These modulations would not necessarily have affected all intrinsic connections and led to the construction of 10 different models sharing the same endogenous structure. te Woerd et al. (2015) previously noted that the specialization of PMC and SMA in external and internal movement generation is not as straightforward as earlier literature suggested (Jueptner and Weiller, 1998; Jenkins et al., 2000; Debaere et al., 2003). As such, models 1-4 aimed to assess the differing roles of PMC, CB and SMA in cueing by systematically excluding these areas from the models. Additionally, Gowen and Miall (2007) showed that an externally-controlled movement, such as tracing, did not recruit any additional brain areas compared to a more internally-controlled movement, such as drawing, with the exception of visual areas in healthy adults. In combination with the specific role of the right hemisphere in processing visual stimuli and guiding spatial attention in motor tasks (Woolley et al., 2010), model 5 addressed the necessity of interhemispheric connections for visual cueing. Finally, in

models 6-10, the complexity of the models (i.e. the number of connections) was assessed by only including forward connections. For all models, we assumed that neural activity was driven by area MT/V5 across conditions, as handwriting is highly dependent on visual input (Debaere et al., 2003).

Bayesian model selection (BMS) was used to identify the model with the highest probability, using a random effects approach (Stephan et al., 2009). This statistical method determines the probability of a certain dataset depending on the proposed models. A good model will explain the data as well as possible, while guaranteeing minimal complexity (Stephan et al., 2010). The most likely model was identified by taking into account the exceedance probability for the model-set, capturing the greatest likelihood to have generated the observed BOLD signal. BMS was followed by inference on model parameters, extracting the coupling estimates of the winning model for each participant.

Statistical analysis of connectivity data

A mixed model ANOVA was performed on the coupling estimates with GROUP (patient - control) as a between-subject factor and CONDITION (cued - uncued) and CONNECTION as within-subject factors, including the HADS-D score and gender as covariates. Only connections that survived a Bonferroni-corrected 1-sample t-test for the entire group of participants (taking into account the number of connections) were included. Additionally, Greenhouse-Geisser corrections were applied and post-hoc p-values were Bonferroni-corrected (taking into account the number of connections included after the 1-sample t-test). Finally, a partial correlation analysis was performed between coupling estimates of altered connections and writing performance in the different conditions and groups. The significance level was set at $p < 0.05$.

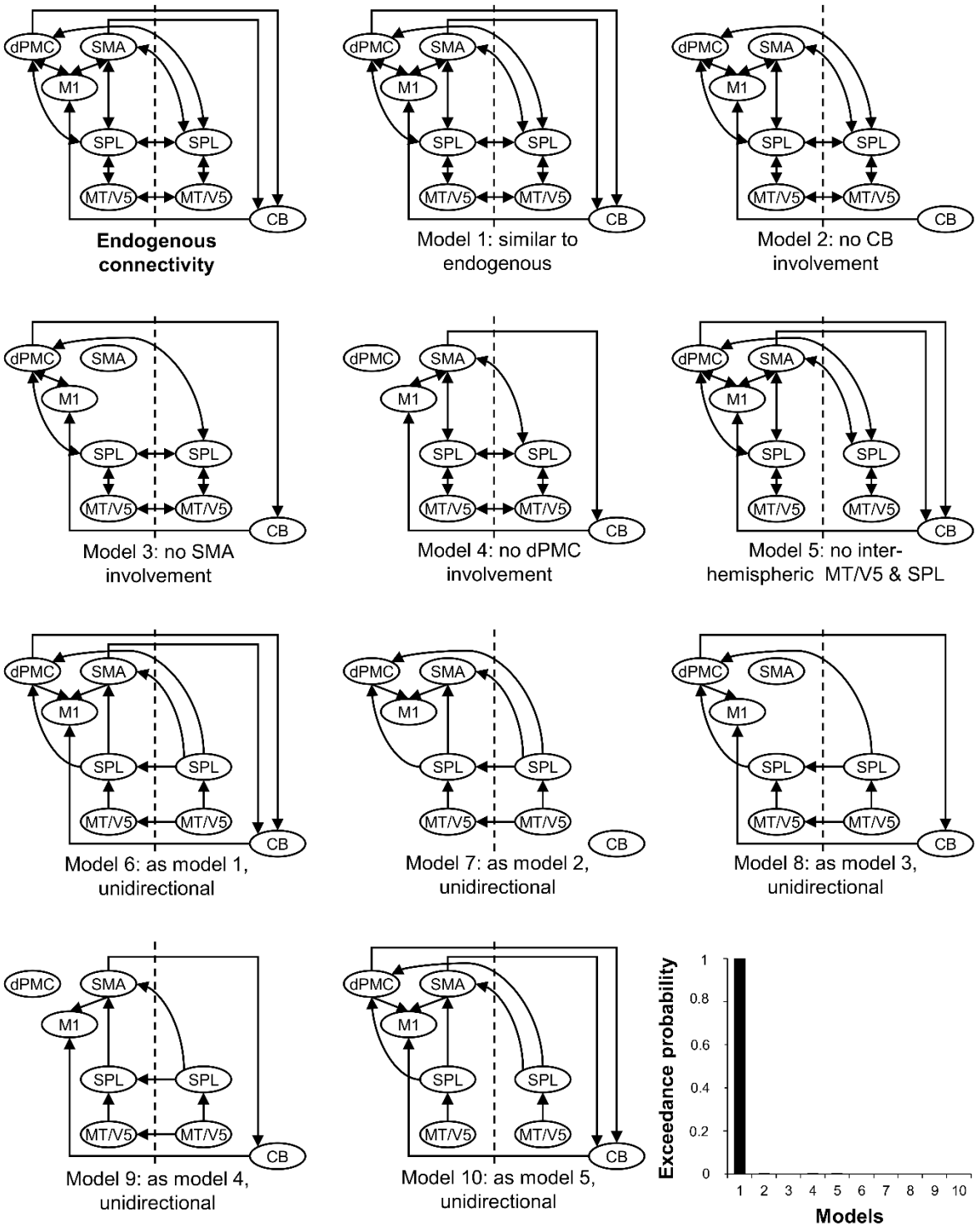

Figure 3: Ten models compared using Bayesian Model Selection. (A) Model 1-10 represent modulations of the connections (DCM-B). The input was set at bilateral V5. (B) Baysian Model Selection. CB = cerebellum; CT = healthy controls; PD = Parkinson's disease; dPMC = dorsal premotor cortex; M1 = primary motor cortex; SMA = supplementary motor area; SPL = superior parietal lobe; MT/V5 = motion sensitive Middle Temporal visual area.

RESULTS

The effects of PD on writing

Behavioral data

Demographics and clinical characteristics of patients and controls are described in **Table 2**. Groups were similar, but PD displayed more difficulties with handwriting in daily life (MDS-UPDRS-II.7: $p < 0.001$), reduced fine motor skills (MAM-16: $p \leq 0.001$), higher depression scores (HADS-D: $p \leq 0.01$) and less female subjects ($p \leq 0.05$).

Table 2: General characteristics and writing performance.

	HC (N = 14)	PD (N = 28)	p-value
	General characteristics		
Age (years)	62.9 ± 10.2	62.9 ± 7.8	0.910
Gender (♂/♀)	4 / 10	17 / 11	0.050
EHI (%)	100.0 (87.0, 100.0)	90.0 (90.0, 100.0)	0.802
MMSE (0-30)	29.0 (29.0, 30.0)	29.0 (29.0, 30.0)	0.607
MAM-16 (0-64)	64.0 (64.0, 64.0)	58.0 (52.75, 60.25)	<0.001
HADS-Anxiety (0-21)	3.5 (2.0, 5.0)	4.0 (2.5, 8.25)	0.147
HADS-Depression (0-21)	1.5 (0.0, 2.0)	3.5 (1.75, 6.25)	0.010
Disease duration (years)	-	4.9 ± 3.6	-
MDS-UPDRS-III (0-132)	-	24.0 ± 11.7	-
MDS-UPDRS-III UL (0-56)	-	12.4 ± 6.1	-
H&Y (1/2/3)	-	3 / 21 / 4	-
LED (mg/24h)	-	390.0 (195.0, 642.5)	-
	Writing skills		
MDS-UPDRS-II.7 (0/1/2/3/4)	14 / 0 /0 / 0 / 0	0 / 13 / 8 / 4 / 3	<0.001
SOS size (mm)	2.5 (2.5, 2.9)	2.0 (2.0, 2.5)	0.076
SOS score (0-10)	2 (1, 3)	4 (2, 4)	0.147
SOS speed (letters in 5 min)	510.0 (496.8, 548.5)	405.5 (304.5, 476.5)	<0.001
Writing on tablet			
Amplitude (cm)	0.537 ± 0.066	0.481 ± 0.075	0.056
COV_{Ampl} (%)	7.701 ± 3.480	9.589 ± 3.926	0.210
Speed (cm/s)	1.525 ± 0.410	1.125 ± 0.392	0.001

Mean ± standard deviation are presented in case of normal distribution and equality of variances, otherwise Median (first, third quartile) are displayed. **Abbreviations**: EHI = Edinburgh Handedness Inventory; HADS = Hospital Anxiety and Depression Scale; HC = healthy control; H&Y = Hoehn & Yahr stage; LED = Levodopa Equivalent Dose; MAM-16 = Manual Ability Measure; MDS-UPDRS-II.7 = MDS Unified Parkinson's Disease Rating Scale part II, question 7 (writing skills); MDS-UPDRS-III = MDS Unified Parkinson's Disease Rating Scale part III; MMSE = Mini Mental State Examination; PD = Parkinson's disease; SOS = Systematic Screening for Handwriting Difficulties test; UL = upper limb items.

We found a significant main effect of GROUP, indicating slower writing in PD both inside ($F_{(1, 38)} = 7.205$, $p \leq 0.05$; $\eta_p^2 = 0.159$) and outside the scanner ($F_{(1, 38)} = 12.115$; $p \leq 0.001$; $\eta_p^2 = 0.242$). Also, amplitude

tended to be smaller in PD compared to HC outside the scanner ($F_{(1, 38)}$ = 3.620; p ≤ 0.1; $\eta_p^2 = 0.087$) (**Table 2**). COV_{Ampl} did not differ in- or outside the scanner.

Neural activation pattern

During writing, a network comprising bilateral MT/V5, bilateral SPL, left dPMC, left SMA, left M1 and right cerebellar lobule VI was activated across conditions in all participants (**Fig. 2**). No differences between groups were found (p ≤ 0.05, FWE-corrected).

Bayesian model selection

Ten different models were compared in a random-effects BMS. Model 1 was revealed as the winning model for the PD-HC comparison with an exceedance probability > 99% (**Fig. 3**).

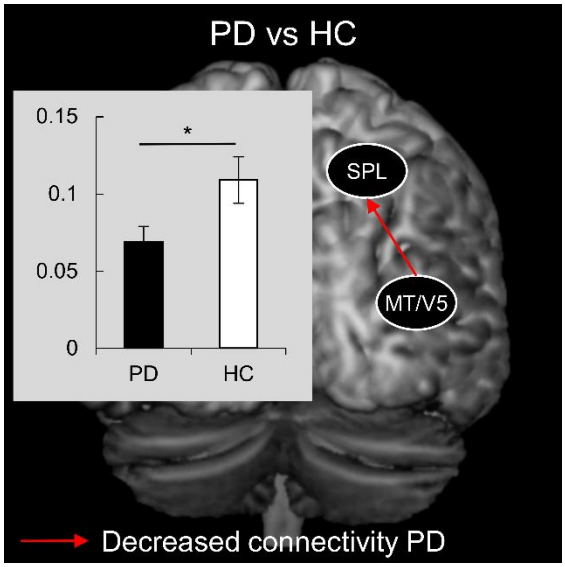

Figure 4: Difference in network connectivity between patients (PD) and controls (HC) during handwriting (DCM-B). Only excitatory connections are displayed, all corrected for HADS-D and gender. CB = cerebellum; HC = healthy controls; PD = Parkinson's disease; dPMC = dorsal premotor cortex; M1 = primary motor cortex; SMA = supplementary motor area; SPL = superior parietal lobe; MT/V5 = motion sensitive Middle Temporal visual area. (* p < 0.05, uncorrected) Error bars represent standard errors.

Connectivity analysis

The condition-independent coupling (DCM-A) was not significantly different between groups. In contrast, when comparing the condition-dependent connectivity (DCM-B), we found a GROUP x CONNECTION interaction ($F_{(20, 760)}$ = 2.509; p ≤ 0.05; $\eta_p^2 = 0.062$). Post-hoc tests revealed that patients featured significantly altered coupling strength for interhemispheric connectivity between homologous MT/V5 areas and between right MT/V5 and SPL (all p ≤ 0.05, uncorrected). For the former, there was a stronger inhibitory coupling from left to right and a weaker inhibitory coupling from right to left MT/V5 in

patients. For the latter, excitatory coupling was reduced in patients compared to controls (**Fig. 4**). Hence, patients displayed reduced visuo-parietal coupling.

No significant correlations were found between these parameters and behavior.

The effects of visual cueing

Behavioral data

Writing was significantly smaller ($F_{(1, 38)}$ = 4.642; p ≤ 0.05; $\eta_p^2 = 0.109$) and slower ($F_{(1, 38)}$ = 4.728; p ≤ 0.05; $\eta_p^2 = 0.111$) with cue compared to without inside the scanner, indicating that both groups performed worse during cued writing. COV_{Ampl} did not differ significantly. Outside the scanner, similar results were apparent.

Neural activation pattern

The significant effect of CONDITION (p ≤ 0.05, FWE-corrected) revealed an increased BOLD activity during cued writing in bilateral visual cortex and an increased activation of right cerebellum lobule VI in the uncued condition (**Table 3**). No interactions between group and condition were found.

Table 3: Difference in BOLD activation between conditions

	Coordinates				
Brain region	**X**	**Y**	**Z**	**z-value**	**K_E**
With > without cue					
Left lingual gyrus	-13	-88	-6	Inf	418
Right lingual gyrus	13	-6	-2	Inf	330
Left mid occipital	-31	-88	14	6.556	112
Left fusiform gyrus	-29	-60	-12	6.312	89
Without > with cue					
Right cerebellar lobule VI	13	-58	-20	6.031	53

P < 0.05 FWE-corrected, voxel threshold = 20

Connectivity analysis

We found a significant CUE x CONNECTION interaction ($F_{(20, 760)}$ = 3.149; p ≤ 0.01; $\eta_p^2 = 0.077$). Cueing effects were driven by an increased connectivity to the left SPL from left MT/V5, right SPL, left dPMC and left SMA (resp. p ≤ 0.1; p ≤ 0.01; p ≤ 0.001 and p ≤ 0.05, Bonferroni-corrected, **Fig. 5A**). In contrast, during uncued writing we found stronger connectivity to the left SMA from bilateral SPL (p ≤ 0.05 and p ≤ 0.05, Bonferroni-corrected), to right cerebellum from left dPMC and left SMA (resp. p ≤ 0.05 and p ≤ 0.01, Bonferroni-corrected) and to left M1 from left dPMC, left SMA and right cerebellum (resp.

$p \leq 0.001$; $p \leq 0.001$ and $p \leq 0.01$, Bonferroni-corrected, **Fig. 5B**). In summary, cues increased the connectivity targeting SPL and writing without cues led to enhanced parieto-(pre)motor-cerebellar coupling.

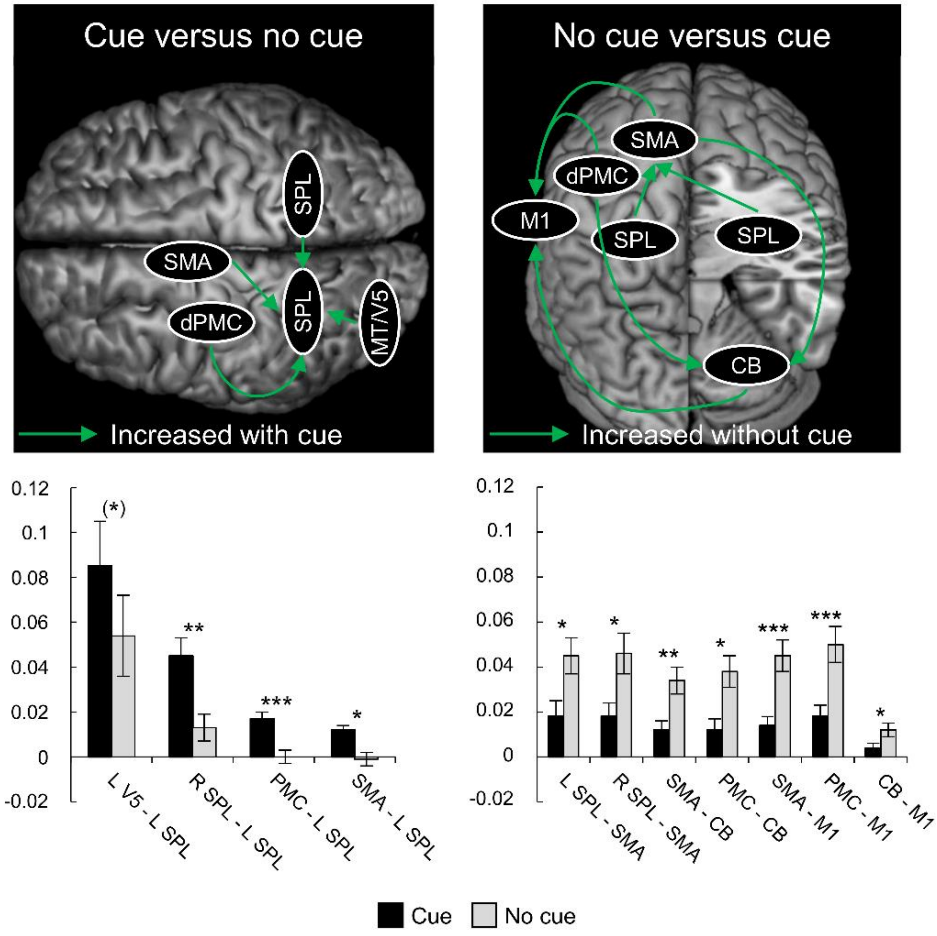

Figure 5: Difference in network connectivity between handwriting with and without cue (DCM-B). (A) Increased connectivity with cue compared to without cue; (B) Increased connectivity without cue compared to with cue. Only excitatory connections are displayed, all corrected for HADS-D and gender. CB = cerebellum; HC = healthy controls; PD = Parkinson's disease; dPMC = dorsal premotor cortex; M1 = primary motor cortex; SMA = supplementary motor area; SPL = superior parietal lobe; MT/V5 = motion sensitive Middle Temporal visual area. ((*) $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, Bonferroni-corrected) Error bars represent standard errors.

Correlation analysis revealed that a stronger effect of left SMA onto left SPL resulted in an increased variability of amplitude (COV_{Ampl}) during cued writing inside the scanner ($r = 0.409$; $p \leq 0.05$, Bonferroni-corrected) (**Fig. 6**).

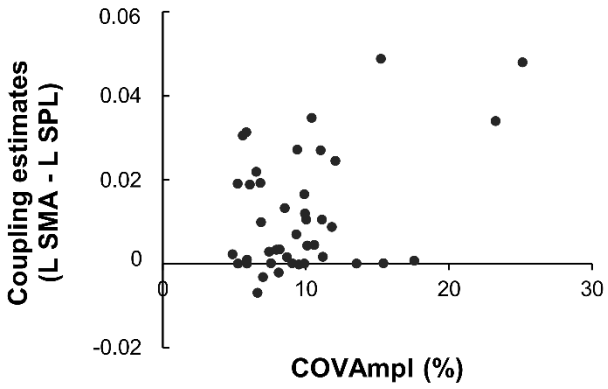

Figure 6: Correlation between connectivity from left SMA onto left SPL and COVAmpl during cued handwriting. L = left; SMA = supplementary motor area; SPL = superior parietal lobe.

DISCUSSION

In this study, we showed for the first time that both patients and healthy controls activated similar networks during cued and uncued writing. This circuitry shift was characterized by stronger connectivity with the left SPL during cued writing and enhanced connectivity in the parieto-(pre)motor-cerebellar network during uncued motor execution. In addition, patients with PD revealed a reduced visuo-parietal connectivity in the right hemisphere compared to healthy controls during handwriting.

The effect of PD on network dynamics during handwriting

Irrespective of cues, PD patients displayed a reduced excitatory influence of right MT/V5 on SPL and stronger inhibitory interhemispheric MT/V5 coupling during handwriting compared to controls, though this result was uncorrected for multiple testing. Importantly, these differences in effective connectivity were found while handwriting amplitude between patients and healthy controls did not differ during scanning. This is a notable result as patients showed clear markers of micrographia in daily life. Outside the scanner, they wrote with a smaller amplitude, had significantly more writing problems as captured by the MDS-UPDRS-II item and lower MAM-16 scores indicating fine motor skill loss. The disappearance of the group differences during scanning was probably due to the imposed experimental control deliberately aimed to achieve similar performance, thus enabling significant comparison at the neural level (Price and Friston, 2002).

The observed reduction in visuo-parietal coupling is in line with findings of reduced resting state activity and regional cerebral blood flow demonstrated in the occipital cortex in PD (Abe et al., 2003; Wu et al., 2015b). Moreover, right hemispheric visual areas were found to be crucial in processing visual stimuli

and guiding spatial attention in motor tasks (Woolley et al., 2010). Although our correlation analysis did not support this, it is plausible that impaired visuomotor integration underlies parkinsonian handwriting deficits at least to an extent. van der Hoorn et al. (2014) found a decreased BOLD-activation in bilateral V5 extending to the posterior parietal areas in PD during a task that investigated the relation between vision and gait, also suggesting impaired visuomotor processing. This is particularly interesting as our results refine the current view of visual cueing as a helpful compensatory method. The fact that our data showed no unequivocal benefits may be partially explained by the difficulties experienced by PD patients with processing these visual stimuli.

The immediate effect of visual cueing on network dynamics

Similar negative responses of patients and healthy controls to cueing at the behavioral level as described in this study, have been reported previously and were interpreted as due to making the task more difficult (Nackaerts et al., 2016b). Interestingly, both groups displayed similar neural activation and connectivity patterns during cued and uncued movements. This suggests that patients switched in a similar fashion between different modes of motor control and can retain the capacity to recruit different networks depending on the conditions of the motor task. This is somewhat surprising given the large overlap found between internal and external networks in healthy elderly, unlike the highly distinct circuitry apparent in young adults (Heuninckx et al., 2010). In contrast to what we hypothesized, we also did not observe stronger connectivity in the external network during cued conditions, suggesting an over-reliance on externally generated motor control in PD.

During cued writing, we found a stronger positive influence of visual and motor areas onto the left SPL. This increased parietal processing probably reflects a continuous visuomotor steering to adjust writing performance and is consistent with the known role of the SPL in planning, execution and monitoring of handwriting (Menon and Desmond, 2001; Yuan and Brown, 2015). Additionally, studies on reaching and grasping movements also suggested that the SPL, as part of the posterior parietal cortex, has its role in both feedforward and feedback processes (Buneo and Andersen, 2006; Archambault et al., 2015). We speculate that the increased parietal cortex involvement observed in both groups is in line with this dual role. First, the presence of target lines acting as a motor target may have increased the feedforward processing, reflected by the positive effect that MT/V5 exerted on SPL. Second, the positive effects of both PMC and SMA on the parietal cortex may have represented feedback processes, based on the comparison of the written trace with the visual target zones. As such, feedback control may come at some cost to the fluency of movements. Correlation analysis partially supported this assumption, as we

found that an increased effect of the SMA on the SPL was related to a greater variability in amplitude. In addition to PMC and SMA, the cerebellum is also often suggested to play an important role in error correction and control of an ongoing movement (Penhune and Steele, 2012), though this was not reflected by our data. The task-related 'mixed' function of cues, i.e. providing a visual drive for the desired amplitude as well as enhancing online visual guidance, may explain why cueing led to a decrease in writing speed without the expected increase of amplitude in both groups. These behavioral findings are supported by a recent review stressing the fact that additional visual information can increase difficulty for the writer, due to greater accuracy requirements, resulting in slower handwriting movements (Danna and Velay, 2015). Despite the fact that accuracy was not encouraged by the instructional set during the experiment, PD patients and controls may have perceived aiming for the targets as an accuracy requirement, with compromised performance as a result (Rand et al., 2000).

The enhanced coupling between parietal and supplementary motor areas in the absence of cues is consistent with the greater involvement of the SMA during internally-controlled handwriting movements (Jenkins et al., 2000; Debaere et al., 2003). The greater participation of the cerebellum and dPMC during uncued writing is somewhat more surprising, as these regions have also been denoted as important nodes of the external network (Debaere et al., 2003). However, the specialization of SMA and dPMC in 'internal' and 'external' movement generation, is not only cue- but also task-dependent, which may explain this unexpected finding (Gowen and Miall, 2007; te Woerd et al., 2015). The same may be true for the increased connections with the cerebellum (Horovitz et al., 2013).

Interpretational issues

Patients were purposefully tested while on dopaminergic medication to match test conditions with real-life performance. The relative normalization of brain connectivity with medication may explain that few differences were found when comparing PD with controls (Haslinger et al., 2001; Michely et al., 2015). The fact that only a trend towards micrographia was found for writing on the tablet outside the scanner in PD compared to HC could be attributed to the fact that patients who were excluded (e.g. because they were not able to perform the task) had significantly more cognitive problems (MMSE) and a longer disease duration than patients included in the scanner. Additionally, due to the exclusion of several patients, the remaining sample size was relatively small, which compromised the statistical power of the study. Hence, the lack of brain-behavior correlations, which hampers a firm interpretation of our findings, could be resolved by including a larger sample size in future studies. Moreover, as suggested by Tzvi et al. (2014) future research could also incorporate behavioral parameters into the models to

address this issue. Unfortunately, we could not include the basal ganglia in our DCM models, as BOLD activity did not reach significance. We presume this is a task-related result, associated with the continuous online trajectory control required during handwriting. Finally, it is essential to note that coupling parameters obtained from DCM-technique refer to functional interactions, but do not necessarily reflect direct axonal connection. The effects of relay regions can (usually) be neglected in models of effective connectivity (Eickhoff et al., 2009). Hence, the relay of visual information towards the premotor regions, via other brain areas that were not explicitly modeled in the DCM, should be implicitly reflected in the derived rate constants of our model for effective connectivity within the cortical motor system.

The present study provides a much more nuanced picture of the effects of cueing in PD than explored until now, as adding visual cues did not lead to the predicted positive effects. The results showed that patients with PD, despite their compromised brain function, were able to shift neural networks similarly as controls. However, it seemed that visual cues provided a greater accuracy constraint on handwriting rather than offering beneficial effects. Altogether, the results suggest that the effectiveness of using compensatory neural networks through applying external stimuli is task-dependent and may compromise motor control during writing.

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