Selective influence of dopamine on electrocortical signatures of error monitoring: a combined EEG and immersive virtual reality study in Parkinson's disease

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Abbreviated title

Dopamine and error in Parkinson's Disease

Abstract

The saliency of detecting errors in one's own and other's actions is likely linked to the discrepancy between intended or expected and produced or observed output. Salient events seem related to dopamine, the balance of which is profoundly altered in Parkinson's disease (PD). EEG studies in healthy participants indicate that the occurrence of errors in observed actions triggers a variety of electrocortical indices (like mid-frontal theta activity and the Error Positivity, oPe), that seem to map different aspects of error detection and performance monitoring. Whether these indices are differently modulated by dopamine in the same individual has never been investigated. To explore this issue, we recorded EEG markers of error detection by asking healthy controls (HCs) and PD patients to observe ecological reach-to-grasp a glass actions performed by a virtual arm seen in first person perspective. PD patients were tested under their dopaminergic medication ('on-condition'), and after dopaminergic withdrawal ('off-condition'). HCs showed a clear oPe and an increase of theta power during the observation of erroneous vs. correct actions. In PD patients, oPe responses were always preserved. Crucially, however, an error-related increase of theta power was found in 'on' but not in 'off' state PD patients. Thus, different EEG error signatures may index the activity of independent systems and error related theta power is selectively modulated by dopamine depletion. Our findings may pave the way to the discovery of dopamine-related biomarkers of higher-order motor cognition dysfunctions that may have crucial theoretical and applied implications.

Significance Statement

Dopaminergic neurons respond to salient events during performance monitoring. Yet, the impact of dopamine depletion on the human reactivity to observed errors is still unclear. We recorded EEG in patients with Parkinson's Disease (PD) under dopaminergic treatment ('on-condition') and medication withdrawal ('off-condition') while they observed correct and erroneous goal-related actions performed by a virtual limb. Analysis of Error Positivity (oPe) and theta power increase, two markers of physiological error-monitoring, indicates that while the former was intact, the latter was preserved in the 'on' and altered in the 'off' condition. Thus, different EEG markers of error monitoring likely rely on independent circuits. Moreover,

mid-frontal theta activity alterations may represent a marker of dopamine-related neurophysiological impairments of higher-order cognition.

Introduction

The progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta that characterizes Parkinson's Disease (PD) brings about alterations in a complex circuit involving subcortical and cortical (mainly frontal and cingulate) regions (Parkinson, 1817; Ullsperger & Von Cramon, 2006; Wylie et al., 2010; Zavala et al., 2018) that lead not only to motor symptoms, but also to deficits of higher order cognitive functions (Chaudhuri et al., 2010; Ponsi et al., 2021), including performance monitoring (Seer et al., 2016). Studies about the influence of dopamine on cognitive functions hint at its role in regulating predictive processes (Clark, 2013; Friston & Kiebel, 2009). Indeed, dopamine is released in response to salient and unexpected events, such as unpredicted errors (Gardner, et al., 2018; Holroyd & Coles, 2002; Schultz, 1998, 2016).

Making an error triggers specific EEG signatures (Error-Related negativity, mid-frontal theta increase, and Positivity Error; Cavanagh et al., 2012; Joch et al., 2017; Ridderinkhof et al., 2004). Although, smaller in amplitude and higher in latency (Koban & Pourtois, 2014) similar signatures are also triggered by mere action error observation (de Bruijn et al., 2007; Van Schie et al., 2004). Specifically, observation of others' errors is accompanied by increased mid-frontal theta, frontal error-related negativity (oERN) and parietal Positivity Error (oPe) that may be seen not only when one observes an error committed by another person (van Schie et al., 2004), or by a partner during motor interactions (Era et al. 2019; Moreau et al., 2020) but also when committed by an embodied virtual arm seen in first-person perspective (1PP; Pavone et al., 2016; Spinelli et al. 2018). Mounting evidence suggests that the error-related mid-frontal theta/error-related negativity (ERN) may depend on dopamine balance (Cavanagh

& Frank, 2014; Jocham & Ullsperger, 2009; Parker et al., 2015; Pezzetta et al., 2021), while other monitoring processes (i.e., Pe) may not.

Testing PD patients while under their dopaminergic medication ('on-condition') and after dopaminergic withdrawal ('off-condition') may be crucial for exploring the selective influence of dopamine on different EEG correlates of error monitoring. However, no conclusive results have been obtained thus far from this approach. Some EEG studies in PD reported diminished amplitude of the ERN/theta during action execution and mixed results for the Pe (see Pezzetta et al., 2021 for review). It is worth noting that only two studies used the time-frequency approach (Beste et al., 2017; Singh et al., 2018) and only one found no difference due to dopaminergic medication (Singh et al., 2018). Thus, it is still unclear whether dopamine balance is necessary for human mid-frontal theta activity during error monitoring. Crucially, no study has thus far explored whether and how different aspects of error monitoring processes (e.g., theta activity and Pe response) are modulated by dopamine.

To investigate this issue, we recorded EEG in the same PD patients while in 'on' and 'off' condition, as well as in healthy controls. Participants were immersed in a virtual scenario and passively observed from a 1PP a virtual arm that executed correct or incorrect actions. This approach proved adept to induce the illusion of ownership over the virtual body, allowing to investigate error processing in highly realistic circumstances (Pavone et al., 2016; Pezzetta et al., 2018; Spinelli et al., 2018). Moreover, exploring action processing in the absence of overt movements allowed us to control for any confounds due the interindividual differences in task difficulty or response speed that might occur between patients.

We hypothesized that distinct and independent error processes co-exist (Di Gregorio et al., 2018), and that patients in 'off' condition would exhibit specific alteration of the electro-cortical markers of error processing purportedly modulated by dopamine (i.e. midfrontal theta) without affecting markers that appear to be less related to this neurotransmitter (i.e. oPe). Based

on the evidence that fronto-central theta is related to executive functions and working memory (Eckart et al., 2014), we also explored the relation between theta and tests assessing executive functions.

Methods and Materials

Participants

Seventeen patients with Parkinson Disease (PD) took part in the study. The MorePower (version 6.0.4, Campbell & Thompson, 2012) software used for computing the sample size indicated that 14 participants would be required in a design with a power of 0.85, alpha of 0.05 and a partial eta^2 of 0.4 (as found in a previous study using the same paradigm to assess the electroencephalographic markers of error monitoring; Pezzetta et al., 2018). All the participants had normal or corrected-to-normal visual acuity. The inclusion criteria were: i) diagnosis of idiopathic PD (United Kingdom Parkinson's Disease Society brain bank criteria, UPDRS; Huges et al., 1992); ii) absence of mental deterioration (Mini Mental State Examination, MMSE > 26); iii) absence of other neurological and psychiatric diseases; iv) treatment with daily doses of dopamine or dopamine agonists (L-Dopa equivalent doses). One patient was excluded due to probable misassumption of medication and lack of motor scale data; one patient dropped the study. Thus, a final group of 15 PD was included (5 females, 10 males; mean ± SD: Age: 70 ± 9; Years of Education: 12 ± 4). Sixteen healthy participants served as controls (HCs). One participant was excluded due to impaired vision and one to mental deterioration, thus, a group of 14 HCs - matched for age and education - was included in the study (5 females, 9 males. Mean ± SD: Age: 70 ± 6; Years of Education: 13 ± 3). HCs were included according to the following criteria: i) absence of neurological and/or psychiatric diseases in anamnesis; ii) absence of subjective cognitive disorders; iii) absence of medications with psychotropic action iv) MMSE > 26 (details in Table 1a).

1 a

	PD (N=15)	HCs (N=14)	
	Mean ± SD	Mean ± SD	p (< 0.05)
Sex	10 M, 5 F	9 M, 5 F	n.s. (0.89)
Age	69.93 ± 8.75	69.57 ± 6.06	n.s. (0.90)
Education	11.60 ± 4	13. 07 ± 2.58	n.s (0.25)
MMSE	29.13 ± 0.64	29.07 ± 1	n.s. (0.84)
MMPSE	29.79 ± 2.29	-	

1b

	PD on (N=15)	PD off (N=15)	
	Mean ± SD	Mean ± SD	p (< 0.05)
UPDRS – III	17.67 ± 6.80	37.21 ± 10.04	s. (0.0001)
H&Y	2.08 ± 0.18	2.32 ± 0.32	s. (0.02)

Table 1. a. Summary of demographics and clinical scores for PD group and control group (HC). Age: age in years; Education: education in years; MMSE: Mini Mental State Examination; UPDRS-III: Unified Parkinson's Disease Rating Scale section III; H &Y: Hoehn and Yahr scale; p: probability of difference between PD and healthy control participants (HC). **b.** Summary of motor scale scores of PD patients tested during dopaminergic medication ('on') and dopaminergic withdrawal ('off'). (n.s.: non-significant, s.: significant).

All participants were naïve as to the purposes of the study and signed the informed consent. The experimental protocol was approved by the local Ethics Committee at the IRCCS Santa Lucia Foundation of Rome (Reference number: CE/PROG.533) and was conducted in accordance with the ethical standards of the 2013 Declaration of Helsinki.

Apparatus and Stimuli

Participants sat in a Cave Automatic Virtual Environment (CAVE) with projectors directed to four walls of a room-sized cube (3 m X 3 m X 2.5 m; Cruz-Neira, et al., 1993). The virtual scenario consisted of a basic room with a table (scale 1:1). At the center of the table, a dark yellow parallelepipedon was located with a blue glass on top of it. The virtual glass was placed in the participant's peripersonal space at a distance of ~ 50 cm. Participants observed from a first-person perspective (1PP) a virtual right arm, projected outside their right shoulder, and congruent in dimension and shape with their real body (see Fig 1. A). The virtual arm and

the scenarios were created by means of Autodesk Maya 2015 and 3DS Max 2015, respectively. The kinematics of the avatar were realized in 3DS Max and implemented in the virtual scenario as an animated 3D mesh. The Virtual reality-EEG experiment was performed in an immersive three-dimensional immersive virtual environment rendered in CAVE by means of XVR 2.1 (Tecchia et al., 2014). Participants observed the virtual environment displayed through the Optoma 3D active glasses while their head position was tracked in real-time by means of an Optitrack System composed by eight infrared cameras placed inside the CAVE.

Experimental Procedure

Patients were tested in different sessions in separate days. First, an extensive neuropsychological assessment was administered while patients were under their dopaminergic treatment, to ascertain their cognitive profile, as part of clinical practice at the Foundation. For the experimental Virtual reality-EEG task, the patients visited the laboratory in two separate sessions, 15 days apart. In one session they were examined within 60 minutes from the first medication intake (‘on’ condition), while in the other after 18 hours washout from the individual prescriptions of dopaminergic medication used to treat PD (‘off’ condition; Langston et al., 1992). The order of on-off condition was counterbalanced across participants.

Before the beginning of the Virtual reality-EEG experiment, participants underwent a calibration phase where the size and the position of the virtual right arm was adapted to their real one. Then, they performed a brief practice session (8 trials, 4 correct and 4 erroneous) in which they familiarized with the virtual arm’s movements and the task. Each participant was requested to passively observe the virtual arm’s movements (by avoiding any real movements with their real upper limbs) and was informed that the goal of the movements was to reach and grasp the glass on the table. They were also informed that the action might or might not be successful. The Virtual reality-EEG task consisted in 110 trials per participant (70 correct and

40 incorrect virtual arm's movements) with a total duration of ~20 min. At the onset of each trial, a sound signaled the beginning of the action. During the trial, participants passively observed from a first-person perspective the movement of the virtual right arm. The total duration of the movement was 1000 ms; the kinematics of the movement, identical for the 70% of the action duration in both correct and incorrect conditions, could diverge in movement's trajectory in the last 30% of the time, leading to either a successful or unsuccessful grasp (Pavone et al., 2016; Pezzetta et al., 2018; Spinelli et al., 2018; Spinelli et al., 2022). The deviation from the to-be grasped object was identical in all the erroneous trials (Figure 1, panel B). The sequence of correct and incorrect trials was pseudorandomized. After the end of the action, the avatar's arm remained still for 1000 ± 50 ms before a black screen appeared. During the inter-trial interval (ITI), one of three events occurred: 1) in 10 out of 110 trials (4 incorrect, 6 correct), participants had to answer a catch question "Did the arm grasp the glass?" (yes/no) in order to verify the engagement in the Virtual reality-EEG task; 2) in 65 out of 110 trials, an empty black screen was presented; and 3) in 35 out of 110 trials (13 incorrect, 22 correct), participants had to rate their illusory sense of embodiment over the virtual arm. The illusion was verbally rated on a visual analog scale (VAS) between 0 and 100 answering the question "To what extent did you feel the virtual arm was yours?" (0 = no ownership to 100 = maximal ownership; (Casula et al., 2021; Fusaro et al., 2019; Fusco et al., 2020; Pyasik, 2020; Tieri et al., 2015a,b, 2017). In the first and third type of event, the black screen lasted until a vocal response was given, whereas in the second event, the experimenter pressed a key to start the next trial, producing a variable ITI (mean duration: ~ 4.000 ms, paradigm).

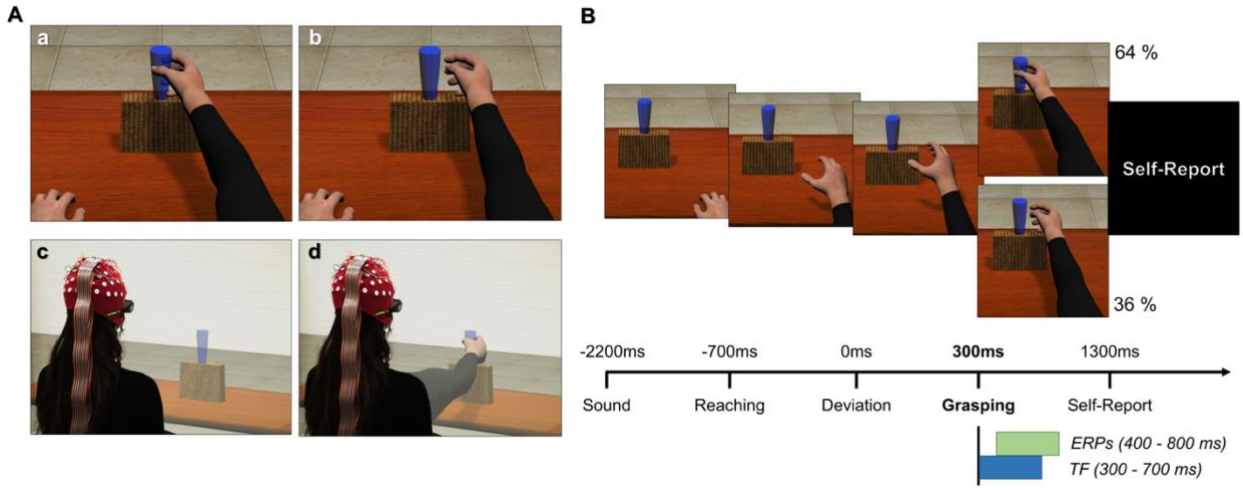

Figure 1 A: example of the experimental paradigm and setup. The image (c,d) shows the participant immersed in virtual scenario by the CAVE (cave automatic virtual environment) system, while observing the real-size virtual arm in first-person perspective, during a correct (a) or erroneous (b) grasping action. B: timeline of a single trial. The avatar's action lasted ~1,000 ms: the reaching phase was equal for both types of movements. The onset of the avatar's arm-path deviation is set at 0 ms; the end of the avatar's action occurs at 300 ms. The time windows for ERPs and TF analyses have been chosen a priori, based on existing literature.

After each EEG session, an expert neurologist administered PD patients the UPDRS-Part III (Fahn & Elton, 1987; a 27 items scale where each item is evaluated on a 5-point Likert scale, ranging from 0 to 4) and the Hoehn and Yahr scale (H&Y, Hoehn & Yahr, 1967; this scale identifies 8 illness stages, indicated with the following numbers: 0-1-1.5-2-2.5-3-4-5). These scales (UPDRS III and H&Y) estimate the patients' motor performance and allows to evaluate the efficacy of the dopaminergic medication in improving motor symptoms (higher scores mean higher disease severity). The two scales were administered in both 'on' and 'off' medication condition.

EEG recording and processing

EEG signals were recorded using a Neuroscan SynAmps RT amplifier system and 62 scalp electrodes embedded in a fabric cap (Electro-Cap International), arranged according to the international 10–10 system[1]. Horizontal electro-oculogram was recorded bipolarly from electrodes placed on the outer canthi of each eye. Online, EEG signal was recorded continuously in alternating current mode with a bandpass filter (0.05–200 Hz) and sampling rates of 1.000 Hz. Impedances were kept under 5 kΩ. All electrodes were physically referenced to an electrode placed on the right earlobe and re-referenced offline to the common average across all electrodes. Offline, raw data were band-pass filtered with a 0.1-100 Hz filter (finite impulse response filter, transition 40–42 Hz, stopband attenuation 60 dB). Independent component analysis (ICA; Jung et al., 2000) was performed on the continuous EEG signal and components that were clearly related to blinks and ocular artifacts were removed (on average, 5.8 ICA components). For ERP analyses, an additional bandpass filter (0.3–30 Hz) was applied on the continuous raw signal. EEG signal was then down-sampled to 500 Hz and epoched in wide windows of 3-s length, from -1.5 to +1.5 s to avoid edge artifacts induced by the wavelet convolution in the time-frequency analysis. Epochs were time-locked (0ms) at the avatar's arm-path deviation, with DC offset correction to the previous 300 ms preceding the deviation (Moreau et al., 2020; Pezzetta et al., 2018). Each epoch was then visually inspected to remove residual artefacts (e.g. eye blinks) by checking for epochs exceeding ±100 µV amplitude, (Drisdelle, Aubin, & Jolicoeur, 2017). After this procedure, a low number of trials was rejected from the original datasets (HCs: 4.5%, PD Dopa-ON: 1%, PD Dopa-OFF: 4%). Therefore, each group had a sufficient and comparable number of trials (mean ± SD; HCs: 105 ± 4.62; PD Dopa-ON: 108.5 ± 3.44; PD Dopa-OFF: 105.5 ± 5.00; Pontifex et al., 2010).

[1] Fp1, Fpz, Fp2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FC5, FC3, FC1, FCz, FC2, FC4, FC6, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PO1, PO2, PO7, PO3, AF7, POz, AF8, PO4, PO8, O1, Oz, O2, FT7, and FT8.

Unless otherwise specified, data were normally distributed (Shapiro-Wilk test); thus, parametric analyses were adopted. Analyses were performed using the Brainstorm toolbox (free open source for MEG/EEG analysis, https://neuroimage.usc.edu/brainstorm/; Tadel et al., 2011) and customized Matlab routines. Statistical analyses were performed using R software (R Core Team 2014). Effect sizes were calculated using Cohen d formula. ERPs and time-frequency statistical analyses were made using the *erpR* package (Arcara & Petrova 2014). Practice trials were excluded from the analyses.

EEG analyses

Analysis in the Time Domain

All ERPs analyses were based on mean amplitude, as recommended by (Luck, 2005). To analyze ERPs at a whole brain level, we performed a time-point cluster-based permutation analyses with 1000 repetitions (with significant differences for clusters set for $p < 0.05$) and MonteCarlo correction in the 0-1000 ms time window on all electrodes, with cluster comparison within and between groups. In addition, traditional analysis on the oERN and oPe were performed. oERN was not analyzed as it was not found during visual inspection of the time series (see discussion). The oPe is a P300-like component maximally peaking at electrode Pz (Overbeek et al. 2005). Planned comparisons within groups on the variable "condition" were performed on a-priori established time-windows of interest (400-800 ms) on the electrode of interest (Pz) to be consistent with previous studies (Pavone et al., 2016; Pezzetta et al., 2018; Spinelli et al., 2018). Then, by following golden-standard recommendations (Luck, 2014; Kappenman & Luck, 2016), the ERP differential (obtained by subtracting the erroneous from the correct condition) was compared with three t-tests namely one within the PD "Group" (PD on vs PD off), and two across the HCs vs PD groups (HCs vs PD 'on, and HCs vs PD 'off').

Analysis in the Time-Frequency domain

For the time-frequency analysis, we used a complex Morlet transformation to compute time-frequency decomposition. A mother wavelet with central frequency of 1 Hz and 3 s of time resolution (full width half maximum, FWHM) was designed as in Brainstorm software (Tadel et al., 2011). The other wavelets were computed from this mother wavelet and ranged from 1 to 80 Hz, with 0.5-Hz logarithmic frequency steps. To normalize each signal and frequency bin separately with respect to a baseline, we computed the relative power change (in %) over the time-frequency decomposition as

$$F = \frac{\mathrm{S(t,f)} - \mathrm{Sbase\ (t,f)}}{\mathrm{Sbase(t,f)}} * 100$$

where S(t, f) is the signal spectrum at a certain given interval of time (t) and frequency (f), and S_{base} (t, f) represents the signal power of the reference signal used as baseline (event related spectral perturbation, ERSP). To avoid edge effects, the power activity from -700 to -500 ms - the window in which the avatar's movement was identical in erroneous and correct conditions- was used as baseline interval. Positive and negative values index a decrease or an increase in synchrony of the recorded neuronal population (Pfurtscheller, Neuper, Brunner, & Lopes Da Silva, 2005) with respect to a given reference interval, where equal neural activity is expected between conditions. In our case, a relative power increase/decrease represents a modulation of power compared with the mean power activity at baseline (Figure 4). To investigate the effect on the whole brain, we performed a time-point cluster-based permutation analyses with 1000 repetitions for each run ($p < 0.05$) and Montecarlo correction on a wide window from 0 ms to 1000 ms to see the distribution on the scalp. Cluster comparisons within and between groups were performed. Also, in line with previous studies (Moreau et al., 2020; Pavone et al., 2016; Pezzetta et al., 2018; Spinelli et al., 2018), the main analyses for theta

activity were computed on the FCz electrode, focusing on theta band (4-8.1 Hz) in the preselected time interval (300-700 ms) corresponding to a total of 400 ms from the end of avatar's action. For the analyses at the electrode level (FCz), for each group, planned comparisons with a single factor "Condition" with two levels (correct/erroneous) was performed. Then, the theta band differential (obtained by subtracting the erroneous from the correct condition) was compared with three separate analyses (Luck, 2014; Kappenman & Luck, 2016: one t-test in PD with the within factor "Group" with two levels (PD on/PD off), and two across group t-tests (HCs/PD on; HCs/PD off). This has been done to follow the methodology of the cluster-based permutation, based on t-test comparisons. Beside theta (4-8.1 Hz), analyses at a cluster level were performed also on the frequencies of potential interest for error monitoring processes in Parkinson's disease namely: delta (2-4 Hz), alpha (8.1 –12.3 Hz), and beta (12.3–30.6 Hz) bands (Koelewijn et al., 2008; Luu et al., 2004; Moran et al., 2011).

Clinical and neuropsychological testing

Clinical data ascertaining motor ability in relation to dopaminergic medication were analyzed. For UPDRS and H&Y scales, two ANOVAs with dopaminergic "Medication" as factor with two levels (on/off) were performed. Correlations between clinical scales (UPDRS, H&Y) and EEG signals were performed to investigate clinical deficits in relation to EEG states during different dopaminergic conditions.

PD patients received an extensive neuropsychological assessment during the 'on' condition, as part of a specialized hospital clinical practice. We reasoned that, changes of fronto-central theta might be related to executive and working memory functions (Eckart et al., 2014; Fusco et al., 2018). Thus, we selected a-priori clinical tests that supposedly tap the same functions, namely: Trial Making Test (TMT subtest A, Giovagnoli et al, 1996), Trial Making

Test (TMT subtest B, Giovagnoli et al, 1996), and the Modified Card Sorting Test (MCST, Nocentini et al, 2002, with the MCSTcat for categories, MCST_p for perseverative errors and MCST_np for non perservative errors). It was also calculated the composite score of the TMT (i.e. the score obtained for the TMT B minus the score obtained at the TMT A: TMT-BA), which is traditionally computed to derive measures that highlight executive functions abilities (Sánchez-Cubillo et al., 2009). To assess the general cognitive functioning also the Mini Mental State Examination (MMSE; Measso et al., 1993) and Mini Mental Parkinson State Examination (MMPSE; Costa et al., 2013) were administered. Exploratory correlations between differential theta activity and tests assessing executive functions were conducted for the PD when in 'on' and 'off'. We also performed correlations between cluster-based permutation across time (0-1000 ms) in theta activity and the executive functions tests, with Montecarlo correction for multiple comparison, to observe the scalp distribution across electrodes. In Table 2 are shown demographic and clinicals information of PD patients and main neuropsychological tests that have been considered of interest for the current study.

Subject	Age	Education	Illness duration (months)	L_Dopa equivalent	BDI	MMSE	MMPSE	TMT_A	TMT_B	TMTB-A	WCSTcat	WCST_p	WCST_np	MMSE_pc	MMPSE_pc	TMT_A_pc	TMT_B_pc	TMTB-A_pc	WCSTcat_pc	WCST_p_pc	WCST_np_pc
P01	83	8	264	870	0	29	31	61	131	70	6	1	0	28.7	32.57	29.05	26.29	0	6	0	0
P02	58	13	108	650	11	29	31	30	72	42	6	2	1	26.2	30.07	13.95	16.44	2.47	6	1.83	0.5
P03	77	13	84	750	5	29	28	51	99	48	6	1	0	27.3	28.38	30.23	37.48	7.21	6	0	0
P04	58	8	276	810	12	28	31	110	265	155	6	0	3	26	30.94	94.1	209.91	115.79	6	0	2.51
P05	72	13	156	600	4	29	29	36	133	97	6	0	0	26.7	29.05	19	83.11	64.09	6	0	0
P06	70	13	84	550	5	30	31	51	117	66	6	0	1	30	31.05	34.49	68.65	34.13	6	0	0.48
P07	78	5	204	400	13	29	25	86	326	240	4	5	9	28.7	26.77	52.78	212.17	159.36	4.32	3.05	7.56
P08	82	8	24	312,5	0	29	25	55	127	72	4	3	13	28.7	26.57	23.77	24.5	0.69	4.38	0.49	11.79
P09	72	13	30	425	3	30	30	46	81	35	3	3	12	30	30.05	9.62	0	0	3.21	1.83	10.76
P10	60	13	84	725	7	30	31	20	77	57	4	5	15	30	30.4	10.27	49.6	39.31	4.06	4.75	14.79
P11	68	5	24	750	21	29	32	61	246	185	5	3	8	27.9	32	34.14	151.84	117.68	5.17	2.16	6.86
P12	57	18	36	400	6	28	31	19	74	55	4	6	10	25.2	29.38	18.38	83.4	65	4.04	5.89	10.22
P13	79	13	288	650	7	30	NA	55	137	82	6	1	7	30	NA	33.27	72.51	39.2	6	0	6.23
P14	68	18	144	950	18	29	32	30	83	53	3	4	8	26.2	32	22.1	69.89	47.76	3.17	3.15	7.88
P15	64	13	156	650	5	29	30	43	104	61	6	0	1	26.2	29.4	31.53	102.14	70.58	6	0	0.67
														cutoff:							
														23.8	22.85	94	283	187	4.25	7.65	10.75

Table 2. Demographic, clinical and a subset of neuropsychological tests which tap executive functions. PD Patients were tested during 'on' condition. The column labeled "L-Dopa equivalent" reports the daily dose of dopamine or a dopamine agonist taken by each patient. On the left side of the table demographic and clinical data are shown; in the central section of the table, raw scores for each patient are reported, while on the right-side of the table, the corrected values are shown ("pc" stands for post correction). Cutoff scores for each neuropsychological test are also reported at the end of the table. MMSE: mini-mental state examination; MMPSE: Mini-mental Parkinson State Examination; BDI: Beck depression inventory; TMT_A: trial-making test A; TMT_B: trial-making test B; TMT_B-A: trial making test BA; WCST_CAT: Wisconsin Card Sorting Test_categories; WCST_P: Wisconsin Card Sorting Test_perseverative errors; WCST_NP: Wisconsin Card Sorting Test_non perseverative errors.

Subjective reports

Embodiment ratings and the catch answers were calculated for correct and erroneous actions in the three groups. The embodiment question ("How much did you feel that the arm was yours" on a scale 0-100) was present only in a subset of trials (12% of incorrect, 20% of correct trials). For each participant, mean embodiment ratings for each type of trial were calculated. The scores were entered into three separate ANOVA with factors "Condition" (correct/erroneous) and "Group" (two anova with 'between variable': HCs-PD 'on'; HCs-PD 'off'; one anova with 'within variable': PD'on'-PD'off'). For the catch trials, the percentage of accuracy for each group was calculated.

Statistical analyses of clinical-neuropsychological data and subjective reports were performed using R software (R Core Team 2014). Greenhouse-Geisser correction for non-sphericity and Bonferroni correction for multiple comparisons were applied, when appropriate.

Data availability

The data are available in the Open Science Framework (OSF) repository https://osf.io/z9rbu/.

RESULTS

Clinical deficits in relation to the dopamine states as inferred from UPDRS and H&Y scales

Confirming the beneficial effect of dopamine assumption for extrapyramidal symptoms, the UPDRS scores of patients with PD decreased significantly from the 'off' (M = 37.21, SD = 10.04) to the 'on' (M = 17.67, SD = 6.80) treatment condition ($F_{(1,13)} = 29.14$, p= 0.0001, n^2_p= 0.69). Changes of H&Y scale values in the different dopamine levels point at a similar effect with significant higher values in 'off' (M = 2.32, SD = 0.32) than in 'on' (M = 2.08, SD = 0.18) condition ($F_{(1,13)} = 7.71$, p= 0.02, n^2_p= 0.37. See Table 1b). One patient was excluded from the analysis because off condition evaluation was missing. No significant correlation was found between UPDRS, H&Y and EEG signals (theta, oPe).

EEG

Time-Domain Analysis

Cluster-based statistics. We found significant differences in the three groups, but with dissimilar spatial distribution. In the HCs a significant difference (p = 0.008, range 360-876 ms) was found between correct and erroneous actions; similarly, the cluster-based permutation revealed a difference between the two conditions both in PD 'on' (p = 0.002, range 380-1000 ms) and in PD 'off' (p = 0.008, range 300-634 ms). From visual inspection of the results, PD 'off' showed an involvement of the fronto-central rather than parietal electrodes and they showed an increased activity during errors which however was limited in time, compared to both PD 'on' and HCs in which it lasted longer (Figure 2). Cluster-comparisons between groups did not show significant differences.

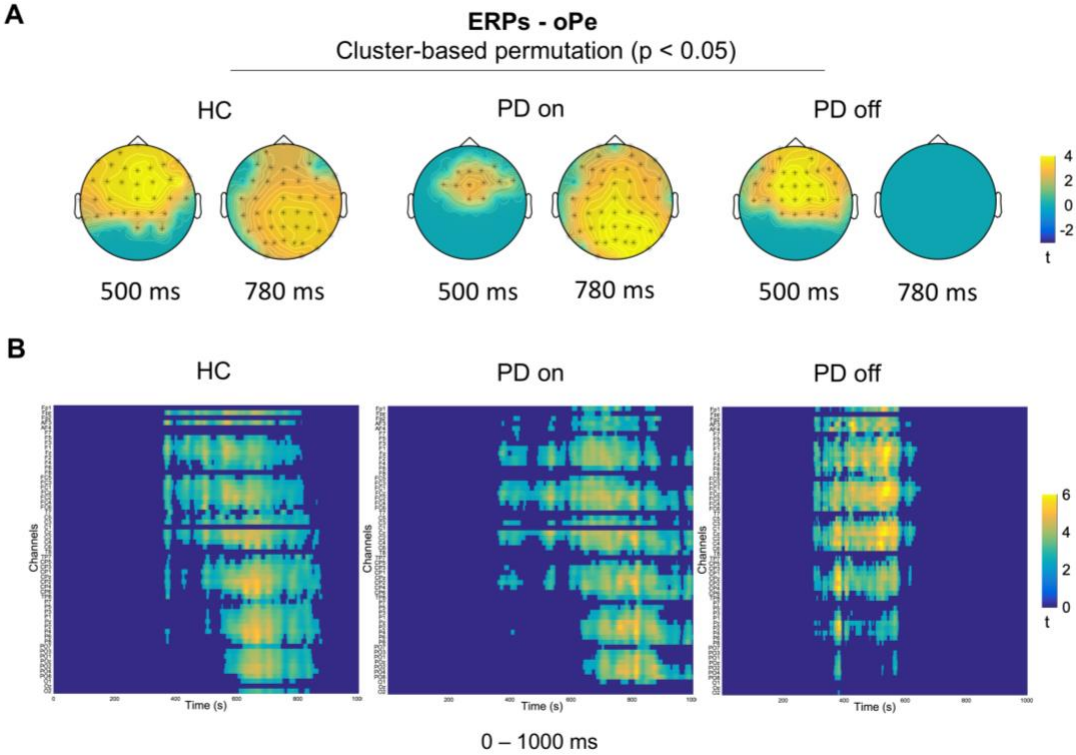

Figure 2. Cluster-based permutation in the time domain for each group. **A.** Scalp representation of the cluster-based permutations (dependent sample t-test with cluster-correction p<0.05) of erroneous versus correct action, extracted at two representative time points inside the window of interest. **B.** Channel (y-axis) x time (x-axis) representation of the cluster-based permutation for erroneous versus correct actions in the three groups.

Analyses on the electrode FCz. Analysis for the oERN were not performed as a clear peak was not found on visual inspection. For a possible interpretation of this negative finding, see the discussion section. **Analyses on the electrode Pz.** Traditional analyses on electrode Pz for the oPe (400-800 ms) showed that all groups had a significant difference between correct and erroneous actions (Figure 3); indeed HCs showed a significant difference, with greater amplitude for erroneous rather than correct actions [HCs: $t(13)= -3.27$, $p = 0.006$, $d=0.65$, $M_{ERR}= 7.59$ µV, $M_{CORR}= 5.10$ µV]; a significant difference was also found in the PD groups, both in 'on' [$t(14)= -3.08$, $p = 0.008$, $d= 0.61$; $M_{ERR}= 3.90$ µV, $M_{CORR}= 2.06$ µV] and 'off' [$t(14)= -2.22$, $p = 0.04$, $d=0.40$, $M_{ERR}= 4.96$ µV; $M_{CORR}= 3.09$ µV] condition, with greater oPe

for erroneous than correct actions. Analyses of differential voltage (obtained by erroneous minus correct trials) between groups showed no difference, all groups had greater activity during erroneous trials, in the time window of interest; in other words, all groups showed an oPe in response to observed errors.

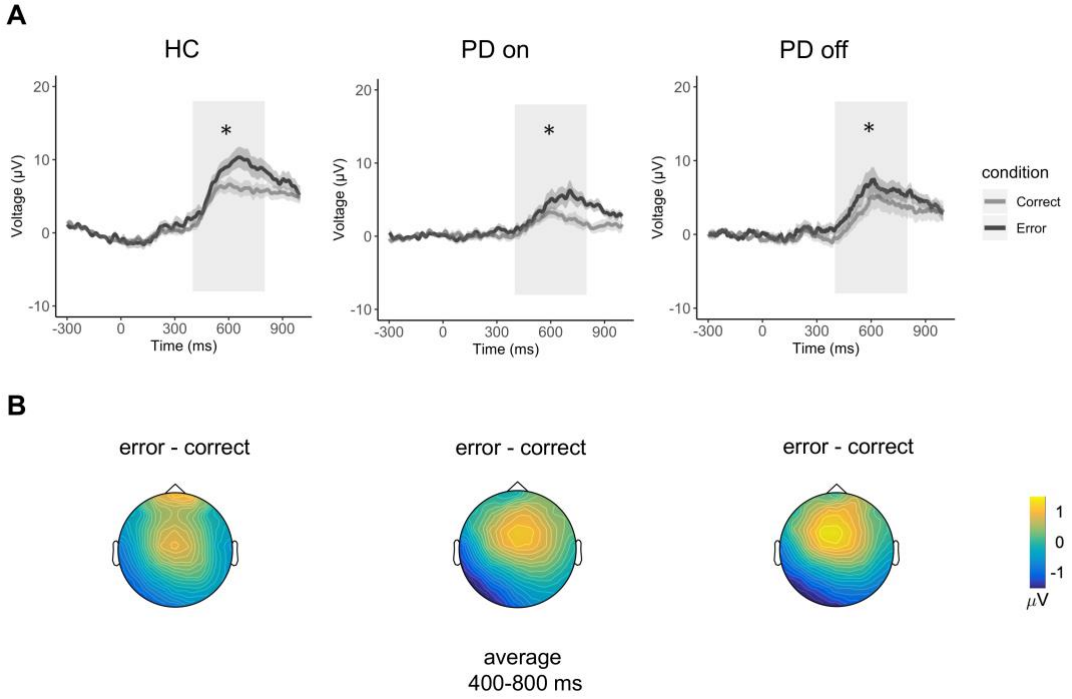

Figure 3. Electrophysiological results in the time domain for each group (ERPs). **A.** Grand average waveforms of oPe at electrode Pz. The end of avatar's movement is set at 0ms. Lighter colors denote the standard error around the mean. The light-gray rectangle represents the interval window of analyses. **B.** Graphical representation of voltage distribution. The values are the result of the erroneous-minus correct actions.

Time-Frequency Domain Analysis

Theta (4-8.1Hz)

Cluster-based statistics. We found a difference between erroneous and correct condition in the HCs (p= 0.004, range 208-888 ms) and in PD 'on' (p= 0.01, range 0-648 ms), with greater theta activity for erroneous actions; the difference was most pronounced over the central areas (see scalp distribution of the clusters, figure 6). In PD 'off' there was no

significant error vs correct grasping difference. When the HCs and PD ‘off’ were compared, we found a significant difference (p = .01, range 392-792 ms), most pronounced in the frontal and posterior areas. No other significant difference between groups was found (Figure 4).

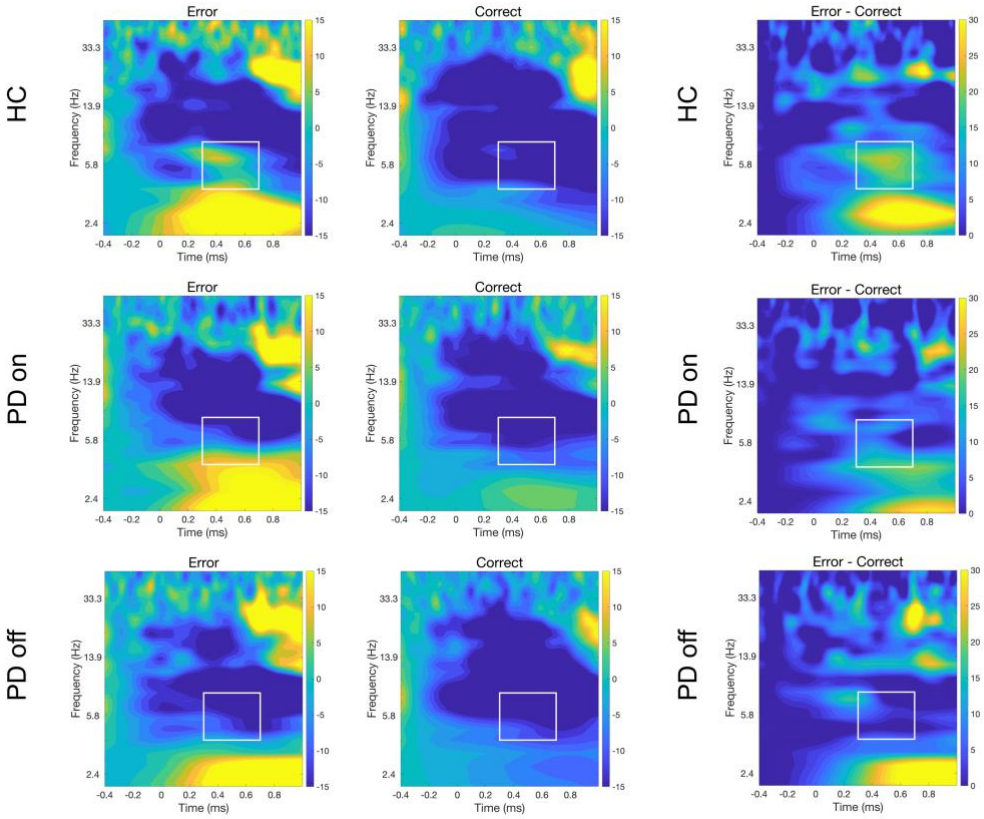

Figure 4. Time-frequency representation of Relative Power change (in %) with respect to the baseline for erroneous and correct conditions. The end of avatar’s arm-path deviation is set at 0ms. Erroneous and correct plots at electrode FCz in the three groups, frequencies from 1 to 50 Hz are displayed. In the third column, the differential plots are provided (erroneous – correct actions). The white rectangles highlight the a priori chosen window of interest between 300-700 ms and 4-8.1 Hz, that indicate the values used for statistical analyses.

Analyses on the electrode FCz. The HCs showed an effect of Condition [t(13)=-2.74, p=0.02, d=1.14, M_{ERR}= 0.10, M_{CORR}=-15.65], that was also present in PD ‘on’ [t(14)=-2.53, p=0.02, d=0.42, M_{ERR}= -6.94, M_{CORR}= -17.22], with greater theta activity for erroneous compared to correct actions. Contrary to the other two groups, ‘off’ patients did not show any

difference [t(14)=0.68, p=0.51, d=0.14, M_{ERR}= -17.08, M_{CORR}= -19.74] (Figures 5, 6). Group comparisons on differential theta (erroneous – correct actions) showed a trend when the HCs and PD 'off' were compared [t(27)=1.90, p=0.067, d=0.71, M_{HC}=15.75, M_{OFF}=2.66]. We found no difference between the HCs and PD 'on': [t(27)=0.79, p=0.44, d=0.29, M_{HC}=15.75, M_{ON}=10.27] and PD 'on' vs. PD 'off': [t(14)=1.31, p=0.21, d=0.50, M_{ON}=10.27, M_{OFF}=2.66].

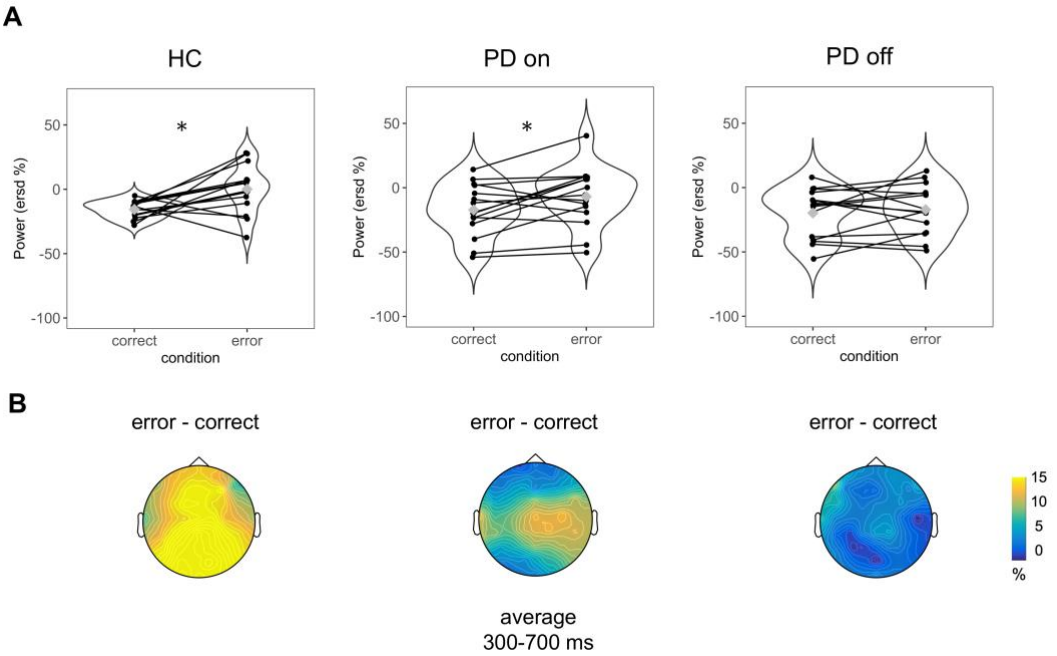

Figure 5. Graphical representation of Theta power (4-8.1 Hz) in the three groups. **A.** Violin plots represent theta activity in Correct and Erroneous actions. Y-axes represent theta power expressed in Relative Power change (in %). Gray diamonds in the violin plots represent the mean value; black lines connect individual subject observations (i.e., black points) in the two conditions. **B.** Graphical representation of voltage distribution. The values indicate the erroneous-minus correct action difference.

Other EEG frequencies potentially involved in error monitoring

Delta (2-4Hz)

Cluster-based statistics. We found significant difference for the three groups, respectively (HCs: p=0.008, range 0-1000 ms; PD 'on': p=0.002, range 0-1000 ms; PD 'off': p=0.004, range 0-1000 ms). The clusters showed greater delta activity for erroneous compared

to correct actions (see Figure 6), in all three groups. In the HCs the difference was more prominent in the frontal and parietal areas, whereas in PD it was more prominent in the fronto-central areas. No statistical differences between groups were found.

Alpha (8.1-12.3 Hz)

Cluster-based statistics. No significant activity was associated to erroneous rather than correct actions in any of the three groups.

*Beta (*12.3–30.6 Hz*)*

Cluster-based statistics. Cluster-based permutation indicates a trend in the HCs when erroneous and correct actions were compared (p= .07, range 280-440 ms) with central-contralateral distribution opposite to the observed arm (Figure 6). PD 'on' showed no significant difference of Condition. PD 'off' showed a significant difference (p = .004, range 150-1000 ms), mainly located on the central electrodes. The independent-samples comparison between groups revealed a significant difference between the HCs and PD 'off' (p=0.04, range 678-968 ms), accounted for by the fact that PD 'off' exhibited increased beta power in the central areas compared to the HCs (Figure 6, see Discussion).

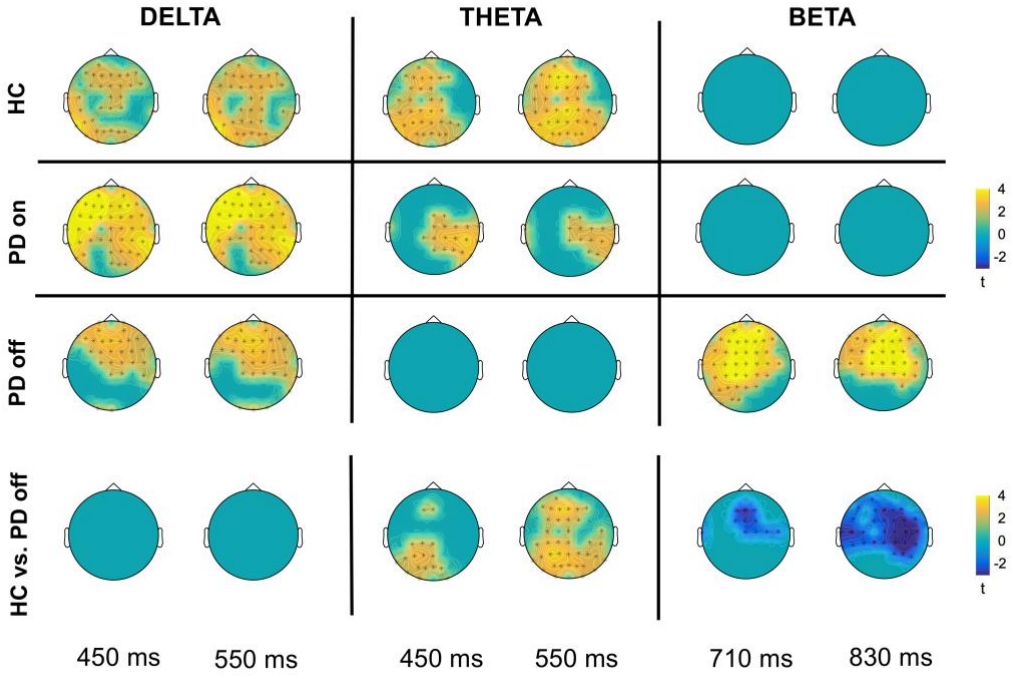

Figure 6. Cluster-based permutation in the time-frequency domain for each group. Scalp representation of the cluster-based permutation (dependent sample t-test with cluster-correction $p<0.05$) of erroneous versus correct action, extracted in two representative time points inside the window of interest. In the bottom line, cluster-based comparison between HCs and PD 'off' of differential activity (erroneous minus correct) in the frequency bands of interest. Analyses have been conducted on the wide window 0-1000 ms, two representative time points are shown.

Exploratory correlations between theta activity and executive function abilities

In the PD 'on' group, we found a positive correlation between theta activity (differential score) and both TMT-B and the TMT-BA (Figure 7). In specific greater theta correlated with longer RTs to perform the TMT task. While the TMT A requires mostly visuoperceptual abilities, the TMT B reflects primarily working memory and task-switching abilities. Tellingly, the TMT-BA provides an indication of executive control abilities (Sánchez-Cubillo et al., 2009). The fact that theta activity in PD 'on' did not correlate with the TMT A (only

visuoperceptual abilities) but did correlate with the TMT-B and TMT-BA might indicate a link between fronto-central slow-frequencies and increased cognitive effort.

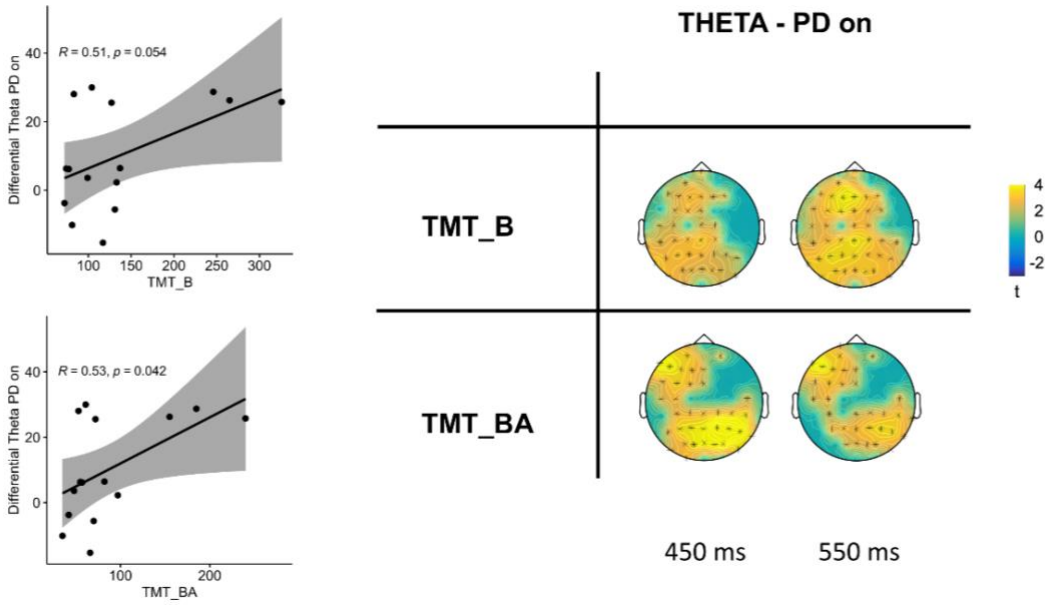

Figure 7. On the left side of the graph, exploratory correlations between theta activity and TMT-B (picture top-left) and TMT-BA (picture bottom-left). On the right, cluster-based permutation ($p<0.05$) between theta (4-8.1 Hz) in PD 'on' group and TMT-A and TMT-BA. Only effects that survived Montecarlo cluster-based multiple correction are showed.

Subjective reports during the Virtual reality-EEG task

Lower sense of ownership was reported for error than correct trials in all the three groups (HCs: M_{ERR}= 61.62, M_{CORR}= 62.55; PD 'on': M_{ERR}= 59.60, M_{CORR}= 65.37; PD 'off': M_{ERR}= 58.75, M_{CORR}= 63.77). However, analyses within and between groups showed no significant difference of 'group' or 'condition' (all ps > 0.05). Concerning the catch questions, overall participants in the three groups responded correctly to the questions, confirming the engagement in the task and the understanding of the observed action (correct answers: HCs: 94%, PD 'on': 97%; PD 'off': 93%).

Discussion

To explore the influence of dopamine on the electrocortical dynamics of error monitoring we recorded EEG in patients affected by PD while they observed correct and erroneous actions performed by a virtual arm seen from a first-person perspective. Using a within-subject approach, the same patients were tested under dopaminergic medication (PD 'on') and after dopaminergic withdrawal (PD 'off'). A control group of healthy participants was also included (HCs).

The first point of novelty is that an increase of theta power contingent upon observation of erroneous actions was found in HCs and PD 'on' but not in PD 'off' indicating that dopamine depletion modifies neurophysiological markers of performance monitoring. The second one is that unlike theta activity, higher oPe for erroneous vs. correct actions was found both in HCs and PD patients (both 'on' and 'off' condition) indicating that error monitoring comprises distinct and independent neurophysiological processes that may or may not be impacted by dopamine balance.

Dopamine does not modulate the oPe

Results revealed that observation of erroneous actions produced a clearly detectable oPe in all groups (electrode Pz). Importantly, however, cluster-based analyses showed that while HCs and PD 'on' displayed a distribution of activity spreading from frontal to posterior electrodes, PD 'off' had an effect that wassmostly pronounced over fronto-central rather than parietal electrodes, and with a different latency range. This may be in keeping with studies showing that oPe is a cortical response characterized by subcomponents spreading over frontocentral and centroparietal electrodes (Overbeek et al., 2005) and could be associated with age-related and neurophysiological compensatory mechanisms (Iijima et al., 2000; Reuter et al., 2013). Notably, finding a similar oPe in PD 'off', PD 'on' and HCs, is consistent with the

notion that generation of this component does not seem to depend on the dopaminergic system (Falkenstein et al., 2001). One may find surprising that we did not find any error-related negativity (oERN), a marker of error detection that was present in previous studies with young adults (Pavone et al., 2016; Pezzetta et al., 2018; Spinelli et al., 2018), but absent with older populations (Spinelli et al., 2022). We speculate that such absence may be related to weak modulation of oERN in aging (Nieuwenhuis et al., 2001; Thurm et al., 2020), or to its low amplitude compared to action execution ERN (van Schie et al., 2004). Another non-alternative explanation is that time-frequency analyses might be better able to capture phase- and non-phase-locked activity during continuous actions (e.g. theta) whilst ERPs are more tuned to discrete events (e.g. ERN; Wang et al., 2020). Indeed, prior data suggest that ERN is dominated by phase-locking of intermittent theta-band (Trujillo & Allen, 2007), but that the observation of an error also elicits non-phase locked activity; thus, not all mid-frontal activity is associated to oERN generation (Moreau et al., 2020; Pezzetta et al., 2018).

Dopamine does influence error-related, mid-frontal theta activity

PD in 'off' phase exhibited abnormal theta band activity with no power increase in response to errors. Crucially, when the same PD were tested just after their regular assumption of dopaminergic medication (PD 'on'), theta activity in response to errors was restored leading to the same HCs pattern (Cavanagh & Frank, 2014). One may note that, similarly to previous studies (Singh et al., 2018; Willemssen et al., 2008), we did not find a direct theta activity difference contingent upon error monitoring in PD 'on' and 'off'. Importantly, however, a significant theta power difference in response to action errors between HCs and PD 'off' was found. Compared to previous studies on PD (Seer et al., 2017), our patients in 'off' condition had a long withdrawal phase (~ 18 h) from their dopaminergic medication, which might have allowed to better highlight the contribution of dopamine in performance monitoring, when

compared with their ordinary pharmacological treatment. Tellingly, no differential error-related theta activity was found in HCs and PD 'on', further hinting at the central role of dopamine in performance monitoring-related mid-frontal theta and in regulating the precision of information during predictive processes, triggered by salient and unexpected events (Friston & Kiebel, 2009), as recently found also in social context (Moreau et al. 2022; Solié et al., 2022).

Delta, alpha and beta frequencies in response to errors

Studies indicate that alpha (van Driel et al., 2012), delta (Luu et al., 2004), and beta (Koelewijn et al., 2008) frequencies may be potentially associated to error monitoring processes. In the present research, no error related modulation was found for the alpha band. Instead, delta activity turned out to be higher for erroneous than correct actions in all groups. This is in keeping with the notion that in a filtered signal, delta activity is associated with the Pe response in the time-domain (Luu et al., 2004). Interestingly, this marker of error monitoring is not influenced by dopamine depletion.

Analysis of beta band showed error-related increased in PD off, within group and also when contrasted with HCs. Beta rhythm has been associated to sensorimotor control (Jurkiewicz et al., 2006; Pfurtscheller et al., 2005; Torrecillos et al., 2015), learning tasks (Viñales et al., 2021) and long-distance communication between visual and sensorimotor areas (Engel & Fries, 2010). Local field recordings from the subthalamic nucleus identified excessive beta activity in PD associated to with pathophysiological motor symptoms (Oswal et al., 2013), that was restored by the dopaminergic treatment (Doyle et al., 2005). Studies indicate that beta rebound was stronger after incorrect rather than correct actions, suggesting a potential role of beta in the evaluation of action significance and active response inhibition (Koelewijn et al., 2008; Ridderinkhof et al., 2004). In our study, PD 'off' showed stronger error-related beta

response. No such effect was found in the PD ‘on’ (in whom dopaminergic medication seem to suppress beta activity; Doyle et al., 2005). In sum, while HCs show greater involvement of theta rather than beta response to errors, PD ‘off’ seem to show an opposite pattern. Whether PD may compensate the involvement of mid-frontal theta with higher frequencies during dopaminergic withdrawal, has to be investigated in future studies. It may be of special interest to explore whether increased beta activity might be detrimental (Moran et al., 2011) or whether it might represent a compensatory mechanism rather than a pathophysiological marker (Pollok et al., 2013).

Subjective reports and clinical data

Concerning embodiment ratings, even if qualitatively participants reported greater sense of ownership during correct rather than erroneous actions, analyses did not show a significant difference of condition. This result is at odds with respect to our previous reports on young adults. However, here we tested older adults. Further, we asked to report embodiment in a 30% (rather than 100%; Pavone et al., 2016) of the trials to avoid long sessions for patients’ fatigue and we only asked questions concerning the feeling of ownership and not the feeling of agency, which has been linked to action monitoring (Villa et al., 2018, 2021).

Concerning the positive correlation between theta activity and TMT, previous studies have reported a link between fronto-parietal theta and executive functions (Sauseng et al., 2005; Chen et al., 2016). Nevertheless, the correlations were only exploratory (without corrections for multiple comparison) and deserve future investigations.

Our approach allowed to directly investigate how distinct electrocortical signatures to errors are differently affected by dopamine balance in PD. Among the strengths of the present study is that we used an ecological and short (~ 20 minutes) task which, thanks to immersive

virtual reality, made possible to test the brain reaction to errors in PD, without confounds due to movement speed or difficulty (Ozkan & Pezzetta, 2018). We acknowledge, however, some potential limitations. One may observe that PD were tested twice, whereas the HCs only one. Yet, in keeping with previous studies (Singh et al., 2018) we can reasonably exclude a learning effect, because the adopted task involves simple action-observation, and it is not related to the acquisition of task-specific abilities. A second limitation is that other neurotransmitters might play a role in the performance monitoring, either through direct modulation of the ACC or by virtue of their influence on the DA system (Calabresi et al., 2006; Singh et al., 2018). Future studies should take into consideration the role of neurotransmitters like serotonin, norepinephrine, GABA and adenosine in cooperating with dopamine to orchestrate error processes (Jocham & Ullsperger, 2009) in samples with different phenotypes (Van Nuland et al., 2021).

In conclusion, we expanded research in old adults and neurological populations, by providing novel support to the idea that error-related signals (theta and oPe) may reflect distinct structural, functional and biochemical paths within the complex architecture of the performance monitoring system (Di Gregorio et al., 2018; Krigolson & Holroyd, 2007; Steinhauser & Yeung, 2010). The error-related modulation of theta activity contingent upon dopamine depletion reported in our study may pave the way to future studies on neurophysiological biomarkers related to prediction processing and model updating (Klein et al., 2007; Friston et al., 2012; Masina et al, 2022) that may ultimately help to understand higher-order cognitive control in Parkinson's Disease.

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Author Contributions

Conceptualization of the idea and the design: R.P. and S.M.A. Patients recruitment and neuropsychological assessment: S.Z., S.T. Neurological assessment: A.P. Virtual reality implementation and setup, and video production: G.T. Data collection: R.P., D.G.O., V.E., G.T. Data analysis and figures: R.P. Data interpretation: R.P., V.E., S.M.A. Writing the original draft: R.P., S.M.A. Revision of the manuscript and final approval: all the Authors. Supervision of the project: A.C., C.C., S.M.A.

Paradigm video

https://www.youtube.com/watch?v=F-NEbOT1nh4

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