Neural correlates of impaired response inhibition in the antisaccade task in Parkinson’s disease

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ARTICLE INFO

Keywords:
Parkinson’s disease
Executive function
Inhibition control
Impulsivity
Antisaccade
Eye-tracking

ABSTRACT

Deficits in response inhibition are a central feature of the highly prevalent dysexecutive syndrome found in Parkinson’s disease (PD). Such deficits are related to a range of common clinically relevant symptoms including cognitive impairment as well as impulsive and compulsive behaviors.

In this study, we explored the cortical dynamics underlying response inhibition during the mental preparation for the antisaccade task by recording magnetoencephalography (MEG) and eye-movements in 21 non-demented patients with early to mid-stage Parkinson’s disease and 21 age-matched healthy control participants (HC).

During the pre-stimulus preparatory period for antisaccades we observed:

• a preparation-related increase in beta band activity in the right dorsolateral prefrontal cortex (DLPFC) of HC (n = 15) for antisaccades compared with prosaccades that was not detectable in the PD group (n = 17);
• a significant attenuation of the preparation-related increase in alpha band power in bilateral FEF and reduced alpha band connectivity between the right DLPFC and right FEF in the PD group compared with HC, suggesting reduced top-down control to inhibit pre-potent activation of FEF in PD; and
• a positive correlation between the magnitude of pre-stimulus beta desynchronization in FEF and subsequent antisaccade latency in PD and HC, indicating a relationship between preparatory beta band modulation and effectiveness of subsequent antisaccade execution.

Taken together, the results indicate that alterations in pre-stimulus prefrontal alpha and beta activity hinder proactive response inhibition and in turn result in higher error rates and prolonged response latencies in PD.

1. Introduction

1.1. Response inhibition in Parkinson’s disease

While James Parkinson stated in his original description of Parkinson’s disease (PD) that cognition was preserved in the condition, cognitive impairment is now regarded a central symptom that PD patients may present even in the earliest stages of the disease [1]. In earlier disease stages, a dysexecutive syndrome is the most common cognitive profile [3].

Within this set of executive functions, response inhibition is the ability to suppress habitual or prepotent reactions to stimuli, which can be achieved by postponing, with-holding, or cancelling the response [5]. Withholding prepotent reflexive responses and thereby allocating more resources to the task at hand is particularly challenging in PD due to a compromised ability to resist unnecessary or prepotent responses [1].

Abbreviations: PD, Parkinson’s disease; ACC, Anterior cingulate cortex; DLPFC, Dorsolateral prefrontal cortex; MEG, Magnetoencephalography; FEF, Frontal eye field.

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https://doi.org/10.1016/j.bbr.2022.113763
Received 15 September 2021; Received in revised form 12 January 2022; Accepted 15 January 2022
Available online 19 January 2022
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time to shape the behavioral strategy according to the context often leads to more favorable outcomes of our actions. Impaired response inhibition, on the other hand, results in impulsivity, i.e., the tendency of acting without delay, reflection, or voluntary directing, resulting in impulsive actions (in the motor domain) or choices (in the behavioral domain) [5]. In PD, impulse control disorders are common non-motor symptoms affecting around 14% of all patients [6] and bearing a relevant negative impact on quality of life [7].

The dynamic properties of the interactions between the prefrontal cortex and basal ganglia to proactively delay action selection when accuracy is favored over speed or when an action needs to be selected out of more than one simultaneously activated response sets are crucial for efficient and successful response inhibition [10,11]. As these mechanisms are modulated by the availability of dopamine in fronto-striatal networks, cognitive control capacity are particularly affected by the loss of dopaminergic innervation in PD [1]. For instance, response inhibition deficits have been associated with reduced striatal activation and connectivity which may be restored by dopamine replacement therapies in early disease stages [12].

Although many studies support deficits in response inhibition in PD [14,15], the underlying neural mechanisms are only partly understood. Studies in healthy individuals have revealed that response inhibition activates a network consisting of prefrontal and premotor regions as well as the basal ganglia [16] which are interconnected via frequency-specific synchronized neuronal oscillations. In brief, the main cortical areas involved in the response inhibition network include the inferior frontal gyrus, the medial and anterior cingulate cortex (ACC), and the dorsolateral prefrontal cortex (DLPFC) [17]. The anterior cingulate cortex is particularly involved in delaying responses whenever conflict or heightened need for cognitive control is detected to allow more time for successful action selection, i.e., it serves proactive response inhibition [18].

Fig. 1. Study workflow. Eye-tracking: sequence of a prosaccade (upper row) and antisaccade (lower row) trial; MRI: anatomical labels that defined the ROI on the cortical surfaces on the individual MRI scans. MEG: Raw MEG data were preprocessed with temporal signal space separation, cleaned from artifacts using independent component analysis and divided into epochs time-locked to the onset of the lateral eye-tracking stimulus. Time-frequency representations: Source construction using LCMV beamformer was followed by decomposition of the epoch’s signal in the time and frequency domains (6-38 Hz) using Morlet wavelets. Connectivity: alpha and beta band specific all-to-all connectivity analysis between the DLPFC, FEF and ACC ROI of both hemispheres. Statistical inference was done with non-parametric cluster-based permutation tests.
1.2. Cortical control of the antisaccade task

A successful experimental paradigm used to explore response inhibition is the antisaccade task. In this task, participants are instructed to suppress a reflexive eye movement in the direction of a presented stimulus and to execute a volitional saccade to the opposite direction instead (Fig. 1). To successfully perform an antisaccade, a reflexive saccade (also referred to as prosaccade) must be suppressed and consecutively a voluntary saccade (the antisaccade) to the opposite direction must be planned and executed.

Patients with PD tend to show higher rates of erroneous reflexive saccades made towards, instead of away from the stimulus than healthy controls [22–24], and these error rates have been found to correlate with their impairment in executive functions [25]. While preparation for both pros- and antisaccades activates the frontal and supplementary eye fields (FEF, respectively SEF) [26], the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) show higher activation in antisaccades than in prosaccades [27]. While the function of FEF during the antisaccade task seems to mainly be to trigger the voluntary saccade [28], the DLPFC is involved in the suppression of the pre-potent reflexive response [29].

DLPFC and ACC are considered key nodes of executive control across different modalities integrated in reciprocal fronto-striatal loops [30]. Transcranial magnetic stimulation of the DLPFC 100 ms before visual stimulus onset reduced antisaccade performance in healthy individuals, supporting the view that the critical interval for successful suppression of a reflexive saccade is actually during the preparatory phase of antisaccade, e.g., before the final direction of a saccade is even known [31]. Using magnetoencephalography (MEG), Hwang and colleagues found that the beta band power in the lateral PFC and the alpha band power in the frontal areas during the preparation for an antisaccade predicted the strength of synchronization in the theta and beta frequencies between FEF and ACC [29].

These studies suggest that correct performance of an antisaccade requires proactive inhibition of saccade-related activity in the FEF even before the saccade stimulus appears, which may be interpreted as a top-down inhibitory signal potentially originating from DLPFC or ACC.

1.3. Aim of this study

In summary, impaired response inhibition can be interpreted as an interface between motor, cognitive and motivational control and may serve as an intermediate phenotype in PD, i.e., as a cognitive process that links brain pathology to behavioral outcomes [4]. Revealing the mechanisms underlying impaired response inhibition might, therefore, help to gain a deeper understanding of PD pathology and behavior.

In early PD, it is particularly important to identify individuals who develop an increase in impulsivity and consecutively are at high risk for impulse control disorders. Further, a better understanding of the relationship between executive functions and behavioral impulsivity may also aid in identifying effective targets for symptom relief in the future.

In this study, we investigated the cortical correlates of deficits in response inhibition during the antisaccade task in patients with early to moderate stage PD by combining eye-tracking and MEG recordings.

2. Material and methods

2.1. Inclusion and exclusion criteria

The study was approved by the Swedish Ethical Review Authority (DNR 2019-00542) and followed the Declaration of Helsinki. All participants gave written informed consent before participating. The patients were recruited from the Parkinson’s Outpatient Clinic, Department of Neurology, Karolinska University Hospital, Stockholm, Sweden.

For both study groups, the following exclusion criteria were defined: signs of clinically relevant depression (Beck Depression Inventory > 14) or dementia (Movement Disorders Society task force criteria level I [33]), other neurological or psychiatric conditions, medications that may influence eye movements (for example benzodiazepines), or disorders of the eyes or visual system with reduced visual acuity. Of 30 patients with PD (Hoehn & Yahr stages 1–3, diagnosed according to [34]) and 30 age-matched healthy control subjects that were initially recruited for this study, we report data of 21 patients with PD and 21 control subjects that were included in the final analysis.

2.2. Clinical assessments

Patients with PD completed the study in “on” medication state, i.e., after intake of their regular dose of dopaminergic medication. Motor symptoms were assessed using the motor section of the Movement Disorder Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [35]. Levodopa equivalent daily doses were calculated according to [36]. Montreal Cognitive Assessment (MoCA) and the Frontal Assessment Battery (FAB) were used to assess general cognitive ability and executive functions [37,38]. Please see Table 1 for demographics and clinical characteristics.

2.3. Eye tracking procedure

Stimuli were presented in Presentation® (NeuroBehavioral Systems Inc., Berkeley, CA, USA) using a DLPFC projector (model FL35, Projection Design) and a back projection screen in a viewing distance of 100 cm. Eye movements were recorded with a video-based eye tracker EyeLink 1000 plus (SR Research Ltd.) that was connected and synchronized to the MEG system. The positions of both eyes were tracked with a sampling rate of 500 Hz. Sets of 8° horizontal prosaccades and antisaccades were presented in separate blocks to reduce the influence of task switching on trial outcome [39]. Participants first performed four blocks of 50 horizontal prosaccades (n = 200) followed by six blocks of 50 horizontal antisaccades (n = 300). To compensate for an expected rate of directive errors in the antisaccade task of up to 30% in healthy individuals [40] and up to 52% in cognitively intact patients with PD [41], the number of antisaccades was 30% higher than the number of prosaccade trials.

Each trial started with a central fixation cross that was presented for 1500 ms in the middle of the screen. It was followed by a blank screen (gap) for 200 ms. Thereafter, the stimulus, a white dot with a diameter of 1° located 8° left or right from the initial central fixation cross, appeared in a randomized order for 1000 ms. After an interstimulus interval that was randomized between 250 and 500 ms, the next trial started with a

| Table 1 | Demographics and clinical characteristics of the healthy control and the PD groups. |
|---------|---------------------------------|
|          | healthy controls | patients with PD |
| N = 21   | N = 21            |                   |
| % female | mean ± sd         | mean ± sd         | T statistic | p value |
| 42.9     | 61.8 ± 8.3        | 65.9 ± 9.0        | 1.531       | 0.135   |
| years of education (y) | 13.7 ± 2.0        | 14.6 ± 1.8        | 1.554       | 0.129   |
| FAB      | 16.7 ± 1.6        | 16.4 ± 2.0        | 0.642       | 0.525   |
| MoCA     | 25.9 ± 2.1        | 27.0 ± 2.9        | 1.298       | 0.202   |
| Hoehn & Yahr stage | /                | 1.7 ± 0.6         | /           | /       |
| MDS-UPDRS III | /                | 19.6 ± 9.5        | /           | /       |
| LEDD (mg) | /                | 581.0 ± 320.0     | /           | /       |
new fixation cross. The implementation of a gap period is known to facilitate fixation disengagement and, thereby, reduce saccade latency and increase errors in healthy individuals and patients with PD [42,43].

In prosaccade trials, participants were instructed to look at the lateral stimulus as fast and precisely as possible as soon as it was presented on the screen, respectively to look at the exact opposite direction of the lateral stimulus in antisaccade trials. This instruction also appeared on the screen at the beginning of each block. As an additional reminder of the current task, a green fixation cross indicated an upcoming prosaccade and red fixation crosses indicated an upcoming antisaccade trial throughout the experiment (Fig. 1). Ten practice trials were presented before the respective first prosaccade and antisaccade blocks.

2.4. Eye tracking data analysis

A parsing system incorporated in the EyeLink 1000 software intersected eye position data into visual events, i.e., saccades, fixations, and blinks. This event data set was analyzed in the statistical computing program R [44] with the eyelinker package [34] using a 40°/s peak velocity threshold for saccade detection and 60 ms for minimum fixation duration. Antisaccade latency was defined as the time from stimulus onset to the start of the first saccade. Trials in which an anticipated (latency < 90 ms) or express saccade (90 ms < latency < 130 ms), a directive error, or the first saccade after > 600 ms occurred were excluded from further analysis. Latencies of prosaccade and antisaccade trials as well as the error rate in the antisaccade task are reported as primary behavioral outcomes. Four subjects (three in the PD group and one control) had to be excluded from further analysis due to technical failure of the eye-tracking device.

2.5. MEG recording procedure

MEG data were recorded using an Elekta Neuromag TRIUX 306-channel MEG system, with 102 magnetometers and 102 pairs of orthogonal planar gradiometers inside a two-layer magnetically shielded room (model Ak3B, Vacuumshmelze GmbH), with internal active shielding to suppress electromagnetic artifacts. Data were recorded at 1000 Hz with an online 0.1 Hz high-pass filter and 330 Hz low-pass filter. Head-position indicator coils attached to subjects’ heads were used to measure the subjects’ position and movements inside the MEG scanner during the recordings. The location of the coils and additional points (anatomical landmarks and head contour) giving a representation of the subjects’ head shape were digitalized with a Polhemus Fastrak motion tracker prior to the experiment. The head shapes were later used to co-register MEG data and structural MRI. Horizontal and vertical electrooculogram (EOG), electrocardiogram (ECG) and eye tracking were recorded simultaneously with the MEG.

2.6. MEG data analysis

MEG data processing was performed in MNE Python [47]. First, MEG data were processed off-line by applying temporal signal space separation (tSSS) with a buffer length of 10 s and a cut-off correlation coefficient of 0.95 to suppress artifacts from outside the scanner helmet and to correct for head movements during the recordings [48]. Movement correction was done by shifting the head position to a position based on the median head position. Subsequently, raw data was low pass filtered at 40 Hz. An independent component analysis (ICA) was performed for each subject using the fastica algorithm [49] implemented in MNE-Python. Segments containing magnetometer responses greater than 4 pT or gradiometer responses greater than 500 pT/m were rejected, and components related to heartbeats were identified based on their correlation with ECG and removed. The noise covariance matrix was estimated from two minutes of empty room data recorded before the session and processed using the same parameters as the actual data.

Data were segmented into epochs time-locked to the onset of stimulus presentation containing 1000 ms leading up to the stimulus presentation. Since this study focused on the preparatory activity for the upcoming saccade task, the epochs were limited to the time window before the direction of the stimulus had been revealed to the participant. In this way, any brain activity related to the actual sensorimotor transformation, i.e., the process of translating the visual stimulus information into an oculomotor command [50], was excluded. Accordingly, the epochs included a time window of 800 ms in which the fixation cross was presented as well as the 200 ms gap period. Epochs that included eye movements or blink artefacts (EOG peak-to-peak amplitude > 250 μV) were excluded from further analysis (9.7 ± 7.9% of trials in the control group and 10.8 ± 9.2% of trials in the PD group).

Since trial numbers are a primary factor affecting the signal-to-noise ratio [51], equalization of trial numbers is recommended in within-subject comparisons between conditions [52]. Comparing trial numbers in a two-way ANOVA resulted in a significant main effect of task (F (1, 42) = 10.320, p = 0.003), but no effect of group (F (20, 42) = 0.790, p = 0.7) nor task-by-group interaction (F (20, 42) = 0.599, p = 0.9). The number of available trials in the final analysis was lower for prosaccades (healthy controls: 46.1 ± 23.5, range = (20, 109), PD: 47.1 ± 18.3, range = (21, 82)) than for antisaccades (73.1 ± 30.2 range = (34, 137), PD: 55.4 ± 24.3, range = (30, 141)) with significant post-hoc comparisons in the PD (t (40) = 2.303, p = 0.03) and the healthy control group (t (40) = 2.562, p = 0.01).

To maintain a reasonable signal-to-noise ratio, the minimum trial number was set at 30 per condition and subjects with lower trial counts were excluded from further analysis of the respective task, resulting in 21 participants per group for the antisaccades, and 15, respectively 17 subjects for the prosaccades.

MEG source reconstruction was applied using the linearily constrained minimum variance (LCMV) beamformer [53] consisting of a spatial filter that projects the sensor-level MEG data onto the points in the source space and suppresses contribution from all other sources and therefore making it less susceptible to potential residual eye movement artifacts. The spatial filters were estimated using all valid trials for which artifact-free eye-tracking data was available. The source space consisted of 5124 evenly spaced points sampled across the white matter surfaces. The surfaces were obtained with the automatic routine for extracting cortical surfaces in Freesurfer [54] from individual T1 weighted MRI obtained on a GE Discovery 3.0 T MR scanner. The inner skull boundary was used to create a single compartment volume conductor model to estimate the forward model. The cortical surface was then segmented into anatomical labels based on the automatic labeling algorithm in Freesurfer [55]. The time series for all epochs were extracted for five regions of interest (ROI). These labels were selected a priori based on previous studies about the involvement of the cortical regions in the antisaccade task (see Introduction): 1) the superior (number of vertices range (18,50)) and inferior parts (vertices range (17,44)) of the precentral sulcus defining the inferior and superior portions of FEF [56] 2) the middle frontal sulcus (vertices range (15,47)) defining DLPFC [57], and 3) the anterior (vertices range (29,58)) and middle anterior part (vertices range (24,45)) of the cingulate cortex defining the rostral, respectively dorsal portion of ACC (Fig. 1). Virtual channels were created by taking the sign-corrected dominant direction normal vector orientations of the source estimate within these labels in both hemispheres. This approach applied a singular value decomposition to the time course within the label with the first right-singular vector for the representative label time course. This signal was scaled so that its power matched the average power per vertex within the label, and sign-flipped to ensure that extracting the time courses did not result in 180° direction/phase changes.

Within the epochs’ time frame, the time window from – 1000 ms to – 500 ms before stimulus presentation was defined as baseline, under the assumption that fixations on the fixation cross were relatively stable during this period without expected saccade-related activity. The
averaged response was subtracted from every single trial for each subject to enhance sensitivity to non-phase locked responses [58]. Morlet wavelets with variable cycles (= frequency / 3) were used to decompose the signal within each of the ROI into frequencies between 6 and 38 Hz in steps of 1 Hz. The change in spectral power during the preparation period (−500 to 0 ms) is reported as percent change from the baseline period, averaged across trials for each task, and pooled across participants for statistical analysis.

Band-specific all-to-all connectivity between ROI time-series in the alpha (8–12 Hz) and beta (15–29 Hz) band was calculated as the weighted Phase Lag Index (wPLI) based on power spectral density estimates during the preparation period (−500 to 0 ms) averaged over all correct antisaccade trials and over subjects. Compared to other measures of phase synchronization, the Phase Lag Index (PLI) was designed to reduce the effect of volume conduction by correcting antisaccade trials and over subjects.

The asymmetric distribution of available trials between the tasks would have led to additional rejections of trials (and subsequently subjects) in a task-by-group mixed-effects model. To maintain as much data as possible and to avoid further reduction of statistical power, we ran two separate analyses of differences in time frequency representations exploring 1) the task effect (antisaccade versus prosaccades) assessed separately in both groups, and 2) the group effect (PD versus healthy controls) in the antisaccade task.

Statistical inference was done with cluster-based permutation tests [61] implemented in MNE-Python with 1000 permutations per test. The test corrects for multiple comparisons within time-frequency representations by identifying clusters of differences between conditions by summing adjacent significantly different time-frequency bins and comparing the cluster size to a distribution of largest cluster values obtained by randomly shuffling the conditional labels under the null-hypothesis. If the observed cluster statistics exceed 95% of the permutation distribution (corresponding to a critical alpha = 0.05) the null hypothesis was rejected.

First, we compared the cortical activation during mental preparation for the prosaccade task with the additional cortical control involved in the antisaccade task. 15 controls subjects and 17 subjects with PD with at least 30 correctly executed prosaccade trials were included in this comparison. One-sample cluster-based permutation t-tests were used to compare the time-frequency representations in each ROI on the difference between the antisaccade and prosaccade tasks within the respective group. For the paired test, the number of trials was equalized between the antisaccade and prosaccade trials to maintain a constant signal-to-noise-ratio within subjects. Excessive trials were randomly removed using the equalize function implemented in MNE Python.

Second, we compared the cortical activation during the preparation for subsequent correctly executed antisaccades between the PD and the healthy control group. Differences in the time-frequency representations of the ROI between the PD and the healthy control group in the antisaccade task were assessed using a cluster-based permutation t test. Based on the results in the time-frequency domains (see below), correlations with clinical and behavioral data (age, FAB score, MDS-UPDRS III score, antisaccade latency, antisaccade error rate) were tested for the averaged alpha (8–12 Hz) and beta (13–30 Hz) power changes during the preparatory period in bilateral inferior FEF and right DLPFC using Pearson’s correlation coefficients.

Differences in the all-to-all connectivity of the five ROI during the preparation for antisaccades between the PD and the healthy control group were assessed using a permutation t-test [62].

In all analyses, p-values < 0.05 were considered statistically significant.

3. Results

3.1. Saccade latency and directional accuracy

In the antisaccade task, saccade onset latencies were significantly increased in the PD group compared with the healthy control group (335 ms versus 294 ms, t(40) = 2.965, p = 0.005). The rate of directional errors tended to be higher in the PD group without reaching statistical significance (37% versus 28%, 95%-confidence interval (CI) of mean difference = (−1.7, 18.4), t(40) = 1.673, p = 0.1). PD antisaccades tended to be initiated both later and less accurate than those of healthy controls. Neither saccade latency of directional errors in the antisaccade task, nor saccade latency in the prosaccade task differed between the groups (Table 2).

3.2. Pre-stimulus activity in DLPFC

During the preparation for upcoming saccades, activity in the right DLPFC differed significantly between tasks (antisaccades versus prosaccades) in the healthy control group (n = 15), as informed by a cluster of difference in beta power (16–24 Hz) in the right DLPFC (p = 0.04). Compared with prosaccades, mental preparation for antisaccades was accompanied by a larger increase in beta power in a cluster ranging from approximately − 290 ms to − 120 ms before stimulus onset (Fig. 2A and C).

No corresponding significant task effect was found in the PD group (n = 17) (Figs. 2B and D). However, the between-groups comparison of the antisaccade task did not result in a significant difference in activation in the DLPFC between the healthy control and the PD group.

3.3. Pre-stimulus activity in FEF

During the preparation for antisaccades, the alpha (8–12 Hz) and lower beta (13–19 Hz) band power in left and right inferior FEF were lower in the PD group than in the control group (Fig. 3). The significant difference was defined by a single cluster starting at approximately − 300 ms and lasting until stimulus onset (0 ms), covering a frequency range from 9 Hz to 19 Hz (p = 0.02) in the left inferior FEF, respectively from approximately − 260 ms to stimulus onset (8–19 Hz) in the right inferior FEF (p = 0.03).

No significant differences in time frequency representations for DLPFC or ACC for the preparation for antisaccades were found between the PD and the healthy control group.

Table 2

|                     | healthy controls N = 21 | patients with PD N = 21 | T statistic | P value |
|---------------------|-------------------------|-------------------------|-------------|---------|
| prosaccade latency (ms) | 213.7 38.7             | 216.5 39.7             | 0.266       | 0.791   |
| antisaccade latency (ms) | 293.7 46.1             | 334.6 43.3             | 2.965       | 0.005   |
| antisaccade error rate (%) | 28.4 14.2             | 36.6 17.8             | 1.673       | 0.102   |
3.4. Correlations with clinical scores

While the alpha and lower beta power change in bilateral FEF diverged between the groups during the preparation phase for antisaccades, both groups showed a reduction of beta power during the gap period (Fig. 3). To further investigate potential relationships with clinical measures, the relative power change in the alpha and beta band in bilateral FEF as well as the beta power change in the right DLPFC during the preparatory period were averaged over all trials per subject and then correlated with motor and cognitive scores in both groups.

The change in beta band power in the right inferior FEF correlated with mean antisaccade latency in the healthy control (r = 0.569, CI = (0.183, 0.804), p = 0.007) and in the PD group (r = 0.566, CI = (0.178, 0.802), p = 0.007) whereby the slopes were parallel (F(38,1) = 0.476, p = 0.5) with distinct intercepts (F(39,1) = 15.400, p = 0.0003) (Fig. 4). In the PD group, the change in beta band power in the right inferior FEF also correlated with FAB score (r = 0.534, 95%-CI = (0.785, 0.133), p = 0.01).

For the left inferior FEF, changes in beta (r = 0.449, 95%-CI = (0.021, 0.738), p = 0.04) and alpha power (r = 0.495, 95%-CI = (0.080, 0.763), p = 0.02) correlated with antisaccade latency in healthy controls, but not in the PD group. No correlations were found between changes in cortical activation and age, motor symptom severity or dosage of dopamine replacement therapy. See Table 3 for complete results.

3.5. Pre-stimulus connectivity

The permutation t-test revealed reduced alpha band connectivity measured as wPLI between the right DLPFC and the right superior FEF (p = 0.03) in the PD group compared with healthy controls. Connectivity of the right DLPFC with left (p = 0.04) and right ventral ACC (p = 0.04), and with the left DLPFC (p = 0.04), on the other hand, was increased in the PD group (Fig. 5). No significant differences in beta band connectivity were observed.

4. Discussion

4.1. Summary of our results

In this study, we explored the cortical dynamics underlying response inhibition using the antisaccade task in patients with PD and healthy age-matched individuals. The combined recording of MEG and eye-tracking allowed us to analyze the behavioral performance (saccade latency and errors) in conjunction with the preceding brain activity during the mental preparation for the task and allowed us to explore the relationships between these measures and clinical scores of disease severity and cognitive functions.

During the pre-stimulus preparatory period, we observed an increased beta band activity in the right DLPFC for antisaccades compared with prosaccades in the healthy control group which was not detectable in the PD group. Direct comparison on a group level revealed
that the pre-stimulus increase in alpha band power in bilateral inferior FEF as well alpha band connectivity between the right DLPFC and right superior FEF were attenuated in the PD group compared with healthy controls. Further, both groups showed a pre-stimulus preparatory beta desynchronization in the inferior FEF whose magnitude correlated with the mean latency of correctly executed antisaccades.

4.2. Antisaccades performance in PD: a two-fold problem

The behavioral results of our study (increased antisaccade latency, unaltered prosaccades) are in line with several earlier studies of antisaccades in patients with PD [63,64]. The observation that patients with PD exhibit prolonged antisaccade latencies on the one hand side, and still tend to execute express saccades and fast reflexive antisaccade errors on the other hand, supports the hypothesis that antisaccade performance relies on two distinct mechanisms: withholding a reflexive saccade, e.g., response inhibition, and preparing and subsequently activating sensorimotor transformation to execute a voluntary saccade in the opposite direction. Deficits in these processes may at times be dissociated, not only in different PD cohorts, but also within the same subject [22], which implies that a two-fold control mechanism is needed for correct antisaccade execution [65]. Based on the results of our study, we will discuss in the following paragraphs that attenuated pre-stimulus alpha band activity in FEF during the preparatory period for antisaccades may reflect impaired oculomotor inhibition control, potentially caused by reduced top-down inhibition from DLPFC or ACC (see below), while attenuated or delayed beta desynchronization in FEF, on the other hand, may be a neural correlate of prolonged antisaccade latency in PD.

4.3. The role of DLPFC in inhibition of reflexive saccades

Our results replicate those of a previous study, showing that the antisaccade task induces higher preparatory beta band activity in the right DLPFC than the prosaccade task in healthy individuals [29]. The lateralization to the right DLPFC has been a recurrent finding in studies of response inhibition and, more specifically, in MEG, fMRI and PET studies on the antisaccade task [26,29,57,66]. Lesion studies and neuroimaging findings support the hypothesis that DLPFC is a crucial region involved in suppressing pre-potent reflexive responses [67–69]. In oculomotor control, DLPFC seems to exert its role via top-down control over FEF, as supported by the study by Hwang et al. which demonstrated directed beta-alpha coupling between these regions. [29].

Although there were no significant differences in the between-group comparison of the time-frequency representations in the DLPFC, the lack of task modulation in the right DLPFC in the PD group indirectly suggests a relative reduction of DLPFC recruitment, and subsequent lack of top-down control. However, one must emphasize that the lack of a
Fig. 4. Scatter plots for the combinations of clinical and behavioral measures and cortical power changes that resulted in a significant correlation in at least one of the two groups (see also Table 3). Only significant linear regressions (solid lines) and their 95% confidence intervals (dashed lines) are shown. A: relative change in beta power from baseline in the right inferior frontal eye field (FEF) and antisaccade latency (PD: $r^2 = 0.320$, HC: $r^2 = 0.324$), slopes are not significantly different between the groups; B: relative change in beta power from baseline in the left inferior frontal eye field (FEF) and antisaccade latency (PD: $r^2 = 0.122$, HC: $r^2 = 0.201$); C: relative change in beta power from baseline in the right inferior FEF and Frontal Assessment Battery (FAB) score (PD: $r^2 = 0.122$, HC: $r^2 = 0.003$); D: relative change in alpha power from baseline in the right inferior FEF and antisaccade latency (PD: $r^2 = 0.008$, HC: $r^2 = 0.245$). PD group in blue, healthy control group in red.

Table 3
Univariate linear correlations between the mean change in alpha and beta band power during the 500 ms preceding correct antisaccade trials and clinical and behavioral data. Significant correlations printed in bold/red. AS LAT – antisaccade latency, AS ERR – antisaccade error rate, DLPPC – dorsolateral prefrontal cortex, FAB – Frontal Assessment Battery, iFEF – inferior portion of the frontal eye field, HC – healthy control group, LEDD – levodopa equivalent daily dosage, MDS-UPDRS - Movement Disorders Society revised version of the Unified Parkinson’s Disease Rating Scale part III, PD - Parkinson group.

|                         | right iFEF change in beta power | left iFEF change in beta power | right DLPPC change in beta power |
|-------------------------|---------------------------------|-------------------------------|---------------------------------|
|                         | HC                              | PD                            | HC                              |
| Age                     | Pearson r | p          | Pearson r | p          | Pearson r | p          | Pearson r | p          | Pearson r | p          |
| FAB                     | -0.399    | 0.073      | 0.240     | 0.309      | -0.313    | 0.166      | 0.113     | 0.634      | 0.022     | 0.924      | 0.079     | 0.740      |
| MDS-UPDRS               | NA       | NA         | 0.364     | 0.115      | NA        | NA         | 0.159     | 0.503      | NA        | NA         | 0.376     | 0.102      |
| LEDD                    | NA       | NA         | -0.070    | 0.768      | NA        | NA         | -0.144    | 0.544      | NA        | NA         | 0.208     | 0.379      |
| AS ERR                  | 0.151     | 0.515      | 0.085     | 0.716      | -0.165    | 0.474      | 0.011     | 0.961      | 0.111     | 0.633      | 0.042     | 0.856      |
| AS LAT                  | 0.569     | 0.007      | 0.566     | 0.007      | 0.449     | 0.041      | 0.349     | 0.122      | 0.227     | 0.321      | 0.128     | 0.581      |

|                         | right iFEF change in alpha power | left iFEF change in alpha power | right DLPPC change in alpha power |
|-------------------------|---------------------------------|-------------------------------|---------------------------------|
|                         | HC                              | PD                            | HC                              |
| Age                     | Pearson r | p          | Pearson r | p          | Pearson r | p          | Pearson r | p          |
| FAB                     | 0.135    | 0.558      | 0.139     | 0.559      | -0.107    | 0.644      | -0.267    | 0.255      |
| MDS-UPDRS               | NA       | NA         | -0.407    | 0.075      | -0.106    | 0.647      | -0.031    | 0.898      |
| LEDD                    | NA       | NA         | -0.264    | 0.260      | NA        | NA         | -0.009    | 0.972      |
| AS ERR                  | 0.025     | 0.913      | -0.104    | 0.652      | -0.179    | 0.439      | 0.164     | 0.477      |
| AS LAT                  | 0.159     | 0.492      | 0.034     | 0.884      | 0.495     | 0.023      | 0.090     | 0.698      |
respective brain areas [72]. For instance, successful inhibition of a reflexive response might set the oculomotor network into a readiness state for sensorimotor activation. The dACC responds to salient stimuli and supports motor response inhibition, as indexed by SSRT, only.

**4.5. Preparatory beta power desynchronization in FEF and antisaccade latency**

During the second half of the preparatory period, beta power decreases in both healthy subjects and patients with PD. Given that beta band activity has been demonstrated to be a main neural correlate of motor control this finding may be interpreted as a correlate of proactive preparation in the sensorimotor system for the upcoming saccade. While beta power increases when movement is voluntarily suppressed [79], it decreases over the motor cortex during preparation and execution of a movement [80]. In PD, increased beta band power as well as a reduced ability of the primary motor cortex to disengage from these beta band oscillations during the execution of movements have been observed [81, 82].

As a decrease in beta power over prefrontal areas has been associated with readiness and alertness for an upcoming cognitive task [83], beta band modulation may serve a predictive role in preparation of future actions. In particular, several studies on motor and cognitive tasks [83-85] in healthy individuals found positive correlations of pre-stimulus beta power over the motor cortex with reaction times, suggesting that proactive preparation of sensorimotor areas might promote faster responses once a stimulus is presented. In fact, preparatory beta band desynchronization in FEF, respectively in fronto-central regions has been reported before in MEG [86] and EEG studies [87] of the antisaccade task in healthy individuals. Given that FEF can be interpreted as the oculomotor correlate of the supplementary motor area (SMA), the beta decrease during the preparation for an antisaccade might set the oculomotor network into a readiness state for sensorimotor transformation.

The notion that preparatory FEF activation contributes to antisaccade latency is further supported by findings that lesions as well as pre-stimulus transcranial stimulation of FEF result in an increase of antisaccade latency [88,89]. Here, we add to the literature that larger pre-stimulus beta desynchronization in FEF during the preparatory period is associated with shorter latencies of antisaccades in both healthy individuals as well as patients with PD. Further, the change in beta power during the preparatory period correlated with the FAB score in the PD group. Hence, subjects who showed the capacity for setting the
prefrontal cortex into a readiness state, measured as higher preparatory beta desynchronization in FEF, also performed better in predominantly frontal-based executive functions.

4.6. Limitations

While our results on the neural activation during preparation for antisaccades provide new insights into the role of prefrontal alpha and beta activity for proactive response inhibition in PD, we acknowledge several limitations to these results. First, the number of available trials after rejection of eye movement-related artifacts was much smaller than expected which also constrained the exclusion of participants and, in turn, reduced the statistical power of our study. In particular, the low trial numbers precluded us from a direct task-by-group comparison impeding straightforward interpretation of our findings in the DLPFC.

Another important limitation of our study is that the order of pre- and antisaccade trials was fixed. Thus, growing fatigue throughout the recordings may have influenced the performance in the antisaccade task.

Although not statistically significant, the PD group tended to be older than the control group. An effect of the mean difference of four years seems unlikely but cannot be excluded. The patients in the PD group were relatively early in the course of the disease and had normal cognitive functioning. This might be a reason why differences to the healthy control group did not reach statistical significance. Due to the long and challenging study protocol, inclusion of more severely affected subjects was not feasible.

We cannot dissociate potential medication effects on our results since the PD group did perform the study tasks after intake of their regular dose of dopaminergic medication. However, a recent trial concluded that antisaccade performance seems to be unaffected of levodopa intake [90]. Further, the alterations of brain activity in the PD group did not correlate with the levodopa equivalent daily dosage in our study which indirectly supports that the results are not primarily based on medication effects.

Since our study was driven by a clearly defined a priori hypothesis, we confined our analysis to five ROI and to brain activity in two predefined frequency bands. While this reduces the multiple comparison problem, we cannot exclude that other potentially relevant regions or frequency bands also contribute to the antisaccade behavior in PD. – Though we did not have prior hypotheses about where and how, so it will be up to future explorative studies to uncover this.

5. Conclusions

In summary, our study on the neural activation during the preparation for antisaccades provides new insights that alterations in prefrontal alpha and beta activity hinder proactive response inhibition and result in prolonged response latencies in PD. Based on our findings, we suggest that reduced top-down cognitive control from the DLPFC onto FEF via alpha band connectivity may result in relative attenuation of alpha band-mediated inhibition of FEF and the downstream oculomotor control network which, in turn, may lead to a higher probability for prepotent triggering of reflexive oculomotor responses in patients with PD. Analogous to preparatory activity in SMA during motor tasks, pre-stimulus beta desynchronization in FEF may facilitate the successful initiation of voluntary saccades by setting the oculomotor network into a readiness state for the upcoming sensorimotor transformation. As the magnitude pre-stimulus beta desynchronization in FEF during the preparatory period was predictive of the subsequent antisaccade latency, attenuated proactive preparation for the upcoming task may be a correlate of delayed oculomotor responses in PD.

Funding

This study, including the work of J.W., M.C.V., A.E., P.S., and D.L., was supported by the Swedish Foundation for Strategic Research, Sweden (SBE 13-0115).

CRediT authorship contribution statement

Josefine Waldthaler: Conceptualization, Methodology, Software, Investigation, Data curation, Formal analysis, Writing – original draft.
Mikkeli C. Vinding: Methodology, Software, Investigation, Data curation, Formal analysis, Writing – review & editing. Allisson Eriksson: Project administration, Investigation, Data curation, Writing – review & editing. Per Svenningsson: Resources, Supervision, Writing – review & editing. Daniel Lundqvist: Resources, Data curation, Supervision, Writing – review & editing.

Acknowledgements

Data for this study were collected at NatMEG, the National Facility for MEG (http://natmeg.se), Karolinska Institutet, Sweden.

References

[1] A. Kudlicka, L. Clare, J.V. Hindle, Executive functions in Parkinson’s disease: systematic review and meta-analysis, Mov. Disord. 26 (2011) 2305–2315, https://doi.org/10.1002/mds.23868.
[2] K.P. Pedersen, J.P. Larsen, O.B. Tynas, G. Alves, Natural course of mild cognitive impairment in Parkinson disease: a 5-year population-based study, Neurology 88 (2017) 767–774, https://doi.org/10.1212/WNL.0000000000003634.
[3] T.R. Goldberg, M.F. Egan, T. Gochside, R. Coppola, T. Weickert, B.S. Kolachana, D. Goldman, D.R. Weinberger, Executive subprocesses in working memory, Arch. Gen. Psychiatry 60 (2003) 880–886, https://doi.org/10.1001/archpsyc.60.9.880.
[4] A. Bari, T.W. Robbins, Inhibition and impulsivity: behavioral and neural basis of response control, Prog. Neurobiol. 108 (2013) 44–79, https://doi.org/10.1016/j.progneurobi.2013.06.005.
[5] D. Weintraub, J. Koester, M.N. Potenza, A.D. Siderowf, M. Stacy, V. Ouyang, J. Whetstone, G.R. Wunderlich, A.E. Lang, Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients, Arch. Neurol. 67 (2010) 589–595, https://doi.org/10.1001/archneurol.2010.58.
[6] V. Ouyang, T.C. Napier, M.J. Frank, V. Sambamurthy-Faure, A.A. Grace, M. Rodriguez-Oroz, J. Obeso, E. Bezdard, P.O. Fernagut, Impulse control disorders and levodopa-induced dyskinesias in Parkinson’s disease: an update, Lancet Neurol. 16 (2017) 238–250, https://doi.org/10.1016/S1474-4422(17)30004-2.
[7] D.M. Herz, S. Little, D.J. Pedrosa, G. Tinkhauser, B. Cheeran, T. Foltynie, R. Bogacz, P. Brown, Mechanisms underlying decision-making as revealed by deep-brain stimulation in patients with Parkinson’s disease, Curr. Biol. 28 (2018) 1169–1178, https://doi.org/10.1016/j.cub.2018.02.057.
[8] M.J. Frank, Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making, Neural Netw. 19 (2006) 1120–1136, https://doi.org/10.1016/j.neunet.2006.03.006.
[9] P. Manza, G. Schwartz, M. Masson, S. Kann, N.D. Volkow, C. Shan, R. Li, H. C. Leung. Levodopa improves response inhibition and enhances striatal activation in early-stage Parkinson’s disease, Neurobiol Aging 66 (2018) 12–22, https://doi.org/10.1016/j.neurobiolaging.2018.02.003.
[10] I. Obeso, L. Wilkinson, E. Canhoto, M.L. Brinas, M. Alvarez, L. Alvarez, N. Pavon, M.C. Rodriguez-Oroz, R. Macias, J.A. Obeso, M. Jahanshahi, Deficits in inhibitory control and conflict resolution on cognitive and motor tasks in Parkinson’s disease, Exp. Brain Res 212 (2011) 371–384, https://doi.org/10.1007/s00221-010-2736-6.
[11] P. Manza, M. Amadrola, V. Tatindenri, C.R. Li, H.-C. Leung, Response inhibition in Parkinson’s disease: a meta-analysis of dopaminergic medication and disease duration effects, npj Parkin. Dis. 3 (2017) 23, https://doi.org/10.1038/s41531-017-0024-2.
[12] M.C. Stevens, K.A. Kiehl, G.D. Pearlson, V.D. Calhoun, Functional neural networks underlying response inhibition in adolescents and adults, Behav. Brain Res. 181 (2007) 22–27, https://doi.org/10.1016/j.bbr.2007.03.023.
[13] T. Hinsult, K. Larcher, N. Zanurowski, J. Gotman, A. Daghet, Spatio-temporal patterns of cognitive control revealed with simultaneous electroencephalography and functional magnetic resonance imaging, Hum. Brain Mapp. 40 (2019) 80–97, https://doi.org/10.1002/hbm.24536.
[14] L. Ma, J.L. Chan, K. Johnston, S.G. Lomber, S. Everling, Macaque anterior cingulate cortex deactivation impairs performance and alters lateral prefrontal oscillatory activities in a rule-switching task, PLoS Biol. 17 (2019), e3000045, https://doi.org/10.1371/journal.pbio.3000045.
[15] S. van Stockum, M. MacAskill, T. Anderson, J. Dalrymple-Alford, Don’t look now or look away: two sources of saccadic disinhibition in Parkinson’s disease, Neuropsychologia (2008) https://doi.org/10.1016/j.neuropsychologia.2008.07.002.
[16] J. Waldthaler, P. Tausi, P. Svenningsson, Vertical saccades and antisaccades: complementary markers for motor and cognitive impairment in Parkinson’s disease, npj Park. Dis. 5 (2019) 11, https://doi.org/10.1038/s41531-019-0083-7.
[17] C.A. Antoniades, N. Demeyere, C. Kennard, G.W. Humphreys, M.T. Hu, Antisaccades and executive dysfunction in early drug-naive Parkinson’s disease.
an eye-tracking and fMRI study, Brain Res. 1648 (2016) 469–484, https://doi.org/10.1016/j.brainres.2016.07.037.

[75] K. Johnston, H.M. Levin, M.J. Koval, S. Everling, Top-down control-signal dynamics in anterior cingulate and prefrontal cortex neurons following task switching, Neuron 53 (2007) 453–462, https://doi.org/10.1016/j.neuron.2006.12.023.

[76] P. Manza, S. Hu, H.H. Chao, S. Zhang, H.C. Leung, C. Shan, R. Li, A dual but asymmetric role of the dorsal anterior cingulate cortex in response inhibition and switching from a non-salient to salient action, Neuroimage 134 (2016) 466–474, https://doi.org/10.1016/j.neuroimage.2016.04.055.

[77] J. Pa, S. Dutt, J.B. Minkly, H.W. Heuer, P. Keselman, E. Kong, A. Trujillo, A. Gazzaley, J.H. Kramer, H.W. Seeley, B.L. Miller, A.L. Boxer, The functional oculomotor network and saccadic cognitive control in healthy elders, Neuroimage 95 (2014) 61–68, https://doi.org/10.1016/j.neuroimage.2014.03.051.

[78] C. Shen, S. Ardil, D. Kaping, S. Westendorf, S. Everling, T. Womelsdorf, Anterior cingulate cortex cells identify process-specific errors of attentional control prior to transient prefrontal-cingulate inhibition, Cereb. Cortex 25 (2015) 2213–2228, https://doi.org/10.1093/cercor/bhu028.

[79] Y. Zhang, Y. Chen, S.L. Bressler, Y. Chen, M. Ding, Prestimulus cortical activity is correlated with speed of visuomotor processing, J. Cogn. Neurosci. 20 (2008) 1915–1925, https://doi.org/10.1162/jocn.2008.20132.

[80] B.R. Cornwell, S.C. Mueller, R. Kaplan, C. Grillon, M. Ernst, Anxiety, a benefit and detriment to cognition: behavioral and magnetoencephalographic evidence from a mixed-saccade task, Brain Cogn. 78 (2012) 257–267, https://doi.org/10.1016/j.bandc.2012.01.002.

[81] I. Cordones, C.M. Gómez, M. Escudero, Cortical dynamics during the preparation of antisaccadic and prosaccadic eye movements in humans in a gap paradigm, PLoS One 8 (2013) 63751, https://doi.org/10.1371/journal.pone.0063751.

[82] S. Hanslmayr, A. Aslan, T. Staudigl, C.S. Herrmann, K.H. Bauml, Prestimulus oscillations predict visual perception performance between and within subjects, Neuroimage 37 (2007) 1465–1473, https://doi.org/10.1016/j.neuroimage.2007.07.041.

[83] B. Pollok, V. Krause, W. Martsch, C. Grillon, M. Ernst, Anxiety, a benefit and detriment to cognition: behavioral and magnetoencephalographic evidence from a mixed-saccade task, Brain Cogn. 78 (2012) 257–267, https://doi.org/10.1016/j.bandc.2012.01.002.

[84] I. Cordones, C.M. Gómez, M. Escudero, Cortical dynamics during the preparation of antisaccadic and prosaccadic eye movements in humans in a gap paradigm, PLoS One 8 (2013) 63751, https://doi.org/10.1371/journal.pone.0063751.

[85] B. Pollok, V. Krause, W. Martsch, C. Grillon, M. Ernst, Anxiety, a benefit and detriment to cognition: behavioral and magnetoencephalographic evidence from a mixed-saccade task, Brain Cogn. 78 (2012) 257–267, https://doi.org/10.1016/j.bandc.2012.01.002.

[86] I. Cordones, C.M. Gómez, M. Escudero, Cortical dynamics during the preparation of antisaccadic and prosaccadic eye movements in humans in a gap paradigm, PLoS One 8 (2013) 63751, https://doi.org/10.1371/journal.pone.0063751.

[87] S. Hanslmayr, A. Aslan, T. Staudigl, C.S. Herrmann, K.H. Bauml, Prestimulus oscillations predict visual perception performance between and within subjects, Neuroimage 37 (2007) 1465–1473, https://doi.org/10.1016/j.neuroimage.2007.07.041.

[88] B. Pollok, V. Krause, W. Martsch, C. Grillon, M. Ernst, Anxiety, a benefit and detriment to cognition: behavioral and magnetoencephalographic evidence from a mixed-saccade task, Brain Cogn. 78 (2012) 257–267, https://doi.org/10.1016/j.bandc.2012.01.002.

[89] I. Cordones, C.M. Gómez, M. Escudero, Cortical dynamics during the preparation of antisaccadic and prosaccadic eye movements in humans in a gap paradigm, PLoS One 8 (2013) 63751, https://doi.org/10.1371/journal.pone.0063751.

[90] S. Hanslmayr, A. Aslan, T. Staudigl, C.S. Herrmann, K.H. Bauml, Prestimulus oscillations predict visual perception performance between and within subjects, Neuroimage 37 (2007) 1465–1473, https://doi.org/10.1016/j.neuroimage.2007.07.041.