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Altered EEG alpha and theta oscillations characterize apathy in Parkinson's disease during incentivized movement

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ABSTRACT

Apathy is a common non-motor symptom of Parkinson's disease (PD) that is difficult to quantify and poorly understood. Some studies have used incentivized motor tasks to assess apathy, as the condition is often associated with a reduction in motivated behavior. Normally event-related desynchronization, a reduction of power in specific frequency bands, is observed in the motor cortex during the peri-movement period. Also, alpha (8–12 Hz) and theta (4–7 Hz) oscillations are sensitive to rewards that are closely related to motivational states however these oscillations have not been widely investigated in relation to apathy in PD. Using EEG recordings, we investigated the neural oscillatory characteristics of apathy in PD during an incentivized motor task with interleaved rest periods. Apathetic and non-apathetic PD subjects on dopaminergic medication and healthy control subjects were instructed to squeeze a hand grip device for a monetary reward proportional to the subject's grip force and the monetary value attributed to that trial. Apathetic PD subjects exhibited higher alpha and theta powers in the pre-trial baseline rest period compared to non-apathetic PD subjects and healthy subjects. Further, we found that both resting power and relative power in alpha and theta bands during incentivized movement predicted PD subjects' apathy scores. Our results suggest that apathetic PD patients may need to overcome greater baseline alpha and theta oscillatory activity in order to facilitate incentivized movement. Clinically, resting alpha and theta power as well as alpha and theta event-related desynchronization during movement may serve as potential neural markers for apathy severity in PD.

1. Introduction

Apathy is a common and debilitating non-motor symptom of Parkinson's disease (PD), characterized by a reduction in motivated behavior and a decrease in reward sensitivity (Marin, 1991; Leentjens et al., 2008). It is poorly understood and difficult to quantify, resulting in a lack of targeted therapies and qualitative methods of diagnosis. Questionnaire-based rating scales are currently used to diagnose apathy, but the results have limited accuracy due to reporter subjectivity and variable diagnostic criteria of different scales (Pagonabarraga et al., 2015). Therefore, a neurological biomarker that could quantitatively assess apathy in PD would provide substantial improvements in apathy diagnosis and monitoring.

Apathy is also associated with a reduction in motivated behavior: prior studies have used incentivized motor tasks to measure apathy by detecting a reduction in motor response to rewards in apathetic individuals (Schmidt et al., 2008; Chong et al., 2015). Bradykinesia, a distinguishing motor symptom of PD, characterized by a slowness of movement, has been hypothesized to be related to motivational deficits associated with apathy (Mazzoni et al., 2007; Shiner et al., 2012).

Neural oscillations are known to play a vital role in modulating motor output and processing rewards but have not been extensively explored with respect to apathy. Normally, beta (12–30 Hz) and alpha (8–12 Hz) oscillations in the motor cortex desynchronize immediately prior to and during movement (Pfurtscheller and Lopes da Silva, 1999; Pfurtscheller et al., 2003). However, PD subjects off of their

Abbreviations: ACC, Anterior cingulate cortex; ANOVA, Analysis of variance; BDI, Beck's Depression Inventory; ICA, Independent component analysis; LARS, Lille Apathy Rating Scale; MEG, Magnetoencephalography; MoCA, Montreal Cognitive Assessment; MRI, Magnetic resonance imaging; MVC, Maximum voluntary contraction; PCA, Principal component analysis

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Table 1
Subject demographic and clinical characteristics[a].

	Apathetic patients	Non-apathetic patients	Healthy controls	*p*-value[c]
	Mean ± SD	Mean ± SD	Mean ± SD	
Gender (F/M)	(5/7)	(6/6)	(8/5)	–
Age (years)	70.1 ± 4.7	67.7 ± 5.3	69.9 ± 7.3	0.535
MoCA	26.2 ± 0.8	26.4 ± 0.6	26.2 ± 0.7	0.938
UPDRS III	27.8 ± 2.3	24.9 ± 2.4	–	0.645
BDI	13.3 ± 1.5	5.1 ± 1.3	4.9 ± 1.5	< 0.001
SAS	17.0 ± 0.9	6.9 ± 1.5	6.8 ± 1.5	< 0.001
LEDD[b]	877.7 ± 408.8	1015.1 ± 651.5	–	0.544
Antidepressant use (n, %)	5 (41.7)	5 (41.7)	–	1.000
Cholinesterase inhibitor use (n, %)	1 (8.3)	0 (0)	–	0.339

[a] MoCA, Montreal Cognitive Assessment; UPDRS III, Unified Parkinson's Disease Rating Scale; BDI, Beck's Depression Inventory; SAS, Starkstein Apathy Scale.
[b] LEDD, levodopa equivalent daily dosage in milligrams.
[c] Three group comparisons are done using one-way ANOVA, while two group comparisons are done using Student's *t*-tests.

dopaminergic medication tend to exhibit less prominent beta and alpha desynchronization compared to healthy individuals; these changes are suggested to contribute to the diminished mobility in PD (Heinrichs-Graham et al., 2014). Also, resting state electrophysiological recordings in humans and animal models of PD have revealed excessive synchronized oscillatory activity of neuronal populations in the cortico-basal ganglia network, particularly in the beta frequency range (Sharott et al., 2005; Kühn et al., 2006; Hammond et al., 2007; McCarthy et al., 2011), as a result of dopaminergic degeneration (Alexander and Crutcher, 1990; Parent and Hazrati, 1995).

Beta, alpha, and theta (4–7 Hz) oscillations have also been linked to the processing of rewards. In a magnetoencephalography (MEG) study of healthy individuals exerting physical effort on a hand grip device to win monetary rewards, the level of beta desynchronization was positively associated with incentive level and a decrease in rest duration, suggesting that beta desynchronization may act as a mechanism that speeds the initiation of effort production in the presence of greater rewards (Meyniel and Pessiglione, 2014). In an electroencephalography (EEG) study, monetary reward was found to be associated with better performance and greater reduction in alpha power prior to movement in a rapid visual detection task (Hughes et al., 2013). Theta band oscillations in the anterior cingulate cortex (ACC) and frontal cortex, are also sensitive to reward stimuli. In a primate model, reward was found to accentuate the increase of theta power in the medial prefrontal cortex and rostral ACC just prior to, and immediately after, movement (Tsujimoto et al., 2006). The joint association of beta, alpha, and theta oscillations with reward processing and movement makes them of interest when studying abnormalities in reward processing, such as apathy in PD.

Importantly, the majority of studies involving task-related neural oscillations report oscillatory activity as change of power relative to a baseline or resting power prior to a stimulus. Although this approach is useful in accounting for inter-individual variability of baseline oscillations, it does not take into consideration the possibility of abnormalities in resting oscillatory activity (Heinrichs-Graham et al., 2014). Investigating absolute oscillatory power may be particularly useful in PD, as the disease is characterized by abnormally high synchronous behavior of alpha and beta oscillations at rest. Despite the significance of resting oscillatory activity in PD subjects, a limited number of studies have considered absolute oscillatory power when investigating task-related neural oscillations in this patient population.

In the current study, we explored the behavioral and neural oscillatory characteristics associated with motivational deficits in apathetic people with PD. Specifically, we used EEG recordings to examine both absolute and relative event-related changes in neural oscillatory activity of apathetic patients, non-apathetic patients, and healthy individuals as they performed an incentivized motor task. We hypothesized that resting and event-related theta, alpha, and beta power will exhibit abnormalities during movement and processing of reward stimuli in apathetic patients with PD. We used a period before the start of the trial as a baseline to measure activity at rest and to assess event-related changes against that baseline.

2. Materials and methods

2.1. Subjects

We recruited 37 subjects with PD and 13 healthy control subjects for the study. Participants with PD were recruited from the University of British Columbia Movement Disorders Clinic while healthy subjects were either recruited from the community or were spouses of patients. Informed written consent was obtained and the study was approved by the University of British Columbia's Clinical Research Ethics Board and the Vancouver Coastal Health Ethics Committee. Participants with PD were classified as apathetic if they scored ≥14 on the Starkstein Apathy Scale (SAS). One individual from the apathetic patient group and one individual from the non-apathetic patient group were excluded from the analysis due to excessive artifacts in the EEG data. An additional non-apathetic individual was excluded due to device malfunction. The remaining analyses included 12 apathetic subjects, 12 non-apathetic subjects and 13 healthy control subjects. All subjects had normal or corrected-to-normal vision and all except one apathetic subject were right-handed. This was corrected for during subsequent analyses.

Inclusion criteria for subjects with PD included those prescribed with a stable dosage of an antiparkinsonian medication for at least 2 months prior to study enrollment and those showing satisfactory clinical response to the medication. Inclusion criteria for all subjects included those under 85 years of age and those without cognitive impairment. Criteria for the absence of cognitive impairment were set at a score of ≥26 on the Montreal Cognitive Assessment (MoCA). The Beck's Depression Inventory (BDI) was used to assess the presence of depression set at a score of ≥14. Patients were additionally administered the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) to assess disease severity related to motor symptoms. All demographic and clinical information are summarized in Table 1. The apathetic PD subject group had significantly greater depression scores than the non-apathetic subjects and control subjects. Therefore, depression score was included as a covariate in subsequent statistical analyses. All subjects were on their regular dopaminergic medication for the duration of the experiment.

2.2. Experimental setup

Subjects were seated comfortably in front of a 19″ computer screen in a noise-reduced room. They performed an incentivized squeeze grip task using a grip force transducer as described below (Fig. 1B; Hand

Fig. 1. Behavioral task. A) The task Sequence shown from left to right: First, subjects saw a visual display indicating either $1, $10 or $50 on the computer screen. Next, a graduated scale with the monetary value at the top appeared, which signaled subjects to squeeze the grip force transducer. At the end of the trial, the amount of money earned in the current trial and the cumulative money earned was presented as feedback. Each trial was followed by a 9 s rest period. Trials with different money values were presented in a randomized order B) Subjects were required to squeeze the corresponding grip force transducer to earn money.

Dynamometer Logger Sensor NUL-237, NeuLog, USA).

2.2.1. Maximum voluntary contraction calibration

Subjects were instructed to squeeze as hard as they could over three exertions using their dominant hand. The maximum force reached across the three exertions was recorded as the Maximum Voluntary Contraction (MVC). Subjects were then instructed to squeeze the grip force transducer so as to reach a red line on a graduated scale displayed on the computer screen, with real-time visual feedback. The red line corresponded to a target level of force that was either 40, 80, or 120% of the maximum force recorded previously. Each force level was presented three times in a randomized order, for a total of nine trials. The 120% level ensured that subjects were in fact squeezing to their maximum force. If this exceeded the maximum force recorded, the highest force reached over the three 120% trials was recorded as the new maximum force. If individuals reached or exceeded the red line indicating the 120% mark, subjects were required to repeat the procedure again. A one-way ANOVA was performed and no significant difference in MVC was found between the three subject groups ($p = .30$).

2.2.2. Behavioral task

Participants were told they would be given remuneration for an unspecified fraction of the amount of money they earned during the behavioral task. At the start of each trial, subjects were presented a monetary value ($1, $10, or $50) for two seconds, indicating the maximum amount they could earn for the trial (Fig. 1A). Next, they were shown a graduated scale with the target level of force at the top for four seconds. They were told that they would earn a monetary reward proportional to how hard they squeezed the grip force transducer using their dominant hand, with the maximum reward being the value presented at the beginning of the trial. At the end of each trial, feedback on the amount of money earned was displayed for two seconds, followed by nine seconds of rest. Each subject's MVC was set to 50% of the total monetary value on the scale. Therefore, when subjects exerted their MVC, they reached the midline and received half of the monetary incentive. This was done to avoid ceiling effects. The task consisted of 45 trials, with 15 trials per monetary incentive presented in a mixed and randomized order.

2.3. Behavioral analysis

Grip force data recorded at a sampling rate of 15 Hz was digitized and sent to a computer running MATLAB (Mathworks, Natick, USA). The maximum force value reached over each trial of the behavioral task was used to obtain each subject's grip force response (GFR) per trial. The GFR was then averaged over trials of each monetary value.

To assess the modulation of grip force, we performed a two-way mixed analysis of variance (ANOVA) with groups (apathetic subjects with PD, non-apathetic subjects with PD, and healthy control subjects) as the between factor and the lowest and highest monetary values ($1 and $50) as the within factor. Comparisons were made between only the lowest and highest values to obtain the largest potential differences in GFR. Subsequently, we performed post-hoc two-tailed *t*-tests for between-group comparisons and two-tailed paired *t*-tests for within-group comparisons.

2.4. EEG recording

EEG data were collected using 34 channels of a 64-channel EEG cap (Neuroscan Ltd.) and high impedance amplifier Neuroscan SynAmps^2 (Compumedics Neuroscan Ltd., VA, USA) at a sampling rate of 500 Hz. Impedances were kept below 20 kΩ using Electro-Gel (Electrode-Cap International, OH, USA). Recording electrodes were positioned according to the International 10–20 EEG System (Homan et al., 1987). Two additional pairs of surface electrodes were used to detect horizontal and vertical eye movements for subsequent artifact removal.

2.5. Preprocessing

EEG data were preprocessed offline using custom-written scripts in MATLAB, incorporating functions from the open-source MATLAB toolbox, EEGLAB (Delorme and Makeig, 2004). Continuous EEG recordings were segmented into eight second epochs, which included one second of rest before the start of the trial, two seconds of reward value presentation, four seconds of squeeze duration, and one second post squeezing. Each epoch was linearly detrended and band-pass filtered between 1 and 50 Hz. Epochs were then concatenated and band-pass filtered again between 1 and 50 Hz. Using the EEGLAB plug-in, *clean_rawdata*, channels containing continuous artifacts were removed and interpolated using spherical spline interpolation. Data were then re-referenced to average reference and any stereotypical artifacts, such as eye blinks, eye movements and muscle tension, were separately removed using an automatic artifact rejection method (Gomez-Herrero et al., 2006) based on the blind source separation algorithm, Independent Component Analysis (ICA) (Makeig et al., 1996). Finally, any trial containing data with an absolute amplitude exceeding 180 microvolts was removed as this trial was assumed to be corrupted by artifacts. On average, 2% of the trials were removed, which did not differ between subject groups (one-way ANOVA: $p = .40$). Electrodes designating the scalp distribution for the one left-handed subject were flipped over the sagittal plane to account for any lateralized differences. This method was previously described by Rossiter et al. (2014) on

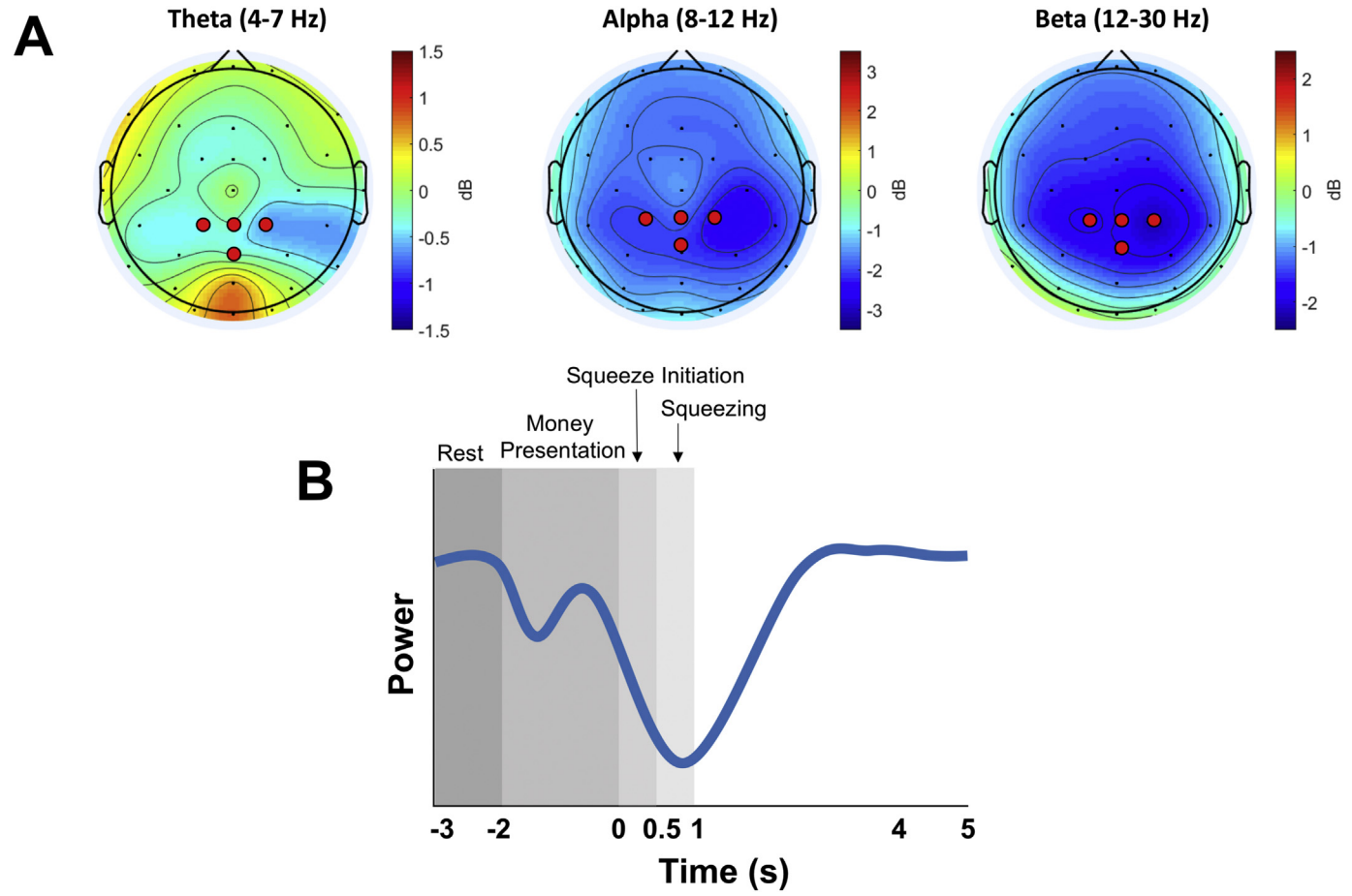

Fig. 2. Electrodes and time frames used in spectral data analysis. A) Average scalp distribution during the first 3 s of squeezing across all groups for relative theta, alpha, and beta power. Selected electrodes (CPz, CP1, CP2, Pz) for further analyses are shown in red. B) Schematic diagram of time frames used in spectral data analysis. Rest: −3 to −2 s; Money Presentation: −2 to 0 s; Squeeze Initiation: 0 to 0.5 s; Squeezing: 0.5 to 1 s. Blue line indicates the power evolution over time averaged over the frequency band of interest.

movement-related beta desynchronization.

2.6. EEG spectral analyses

Time-frequency analysis was performed on the preprocessed data by convolving each trial in the time domain with a seven-cycle complex Morlet wavelet for a frequency range of 1–50 Hz using the *cwt* function in MATLAB. Power for each time point and frequency was computed as the sum of squares for real and imaginary parts of the transformed signal and averaged over all trials for each subject, then averaged across subjects for each condition. *Absolute event-related power* was calculated as the 10*log10 of power post-event and *relative event-related power* was defined as 10*log10 of the power post-event relative to the average power in baseline defined as 1 s before the presentation of money. *Absolute resting power* was the absolute power calculated during this baseline period.

To identify the sensors showing the strongest changes in relative theta, alpha, and beta power, we plotted the grand average scalp distribution across all subjects as an average relative power over the first three seconds of squeeze duration for each of the theta (4–7 Hz), alpha (8–12 Hz), and beta (12–30 Hz) frequency ranges. Nine common centro-parietal electrodes were identified to have the highest theta, alpha, and beta desynchronization during squeezing: Cz, C4, CP5, CP1, CPz, CP2, CP6, Pz, and P4. These electrodes were also consistent with those found in previous literature to show movement-related desynchronization (Homan et al., 1987; Mcfarland et al., 2000; Zaepffel et al., 2013; Nelson et al., 2017; Pirondini et al., 2017).

2.7. Determining channels of interest

In order to determine the EEG channels with the greatest differences in theta, alpha, and beta power between subject groups during different time periods, we performed one-way multivariate analysis of variance (MANOVA) tests with subject group (apathetic subjects with PD, non-apathetic subjects with PD, and healthy control subjects) as the independent variable and each of the nine centro-parietal channels as a dependent variable separately for theta, alpha and beta bands. A MANOVA is particularly useful in detecting differences when dependent variables are correlated, as in the case of EEG channels. Specifically, we were interested in the 1 s of rest before the beginning of the trial and the first 3 s following squeeze onset. For the 1 s of rest, a one-way MANOVA was performed comparing absolute power in each of the theta, alpha, and beta bands separately. For the 3 s following squeeze onset, a one-way MANOVA was performed comparing relative power for beta, alpha, and theta bands separately. A total of six one-way MANOVA tests were performed. Subsequent one-way ANOVA tests were done to determine differences between groups for each channel and Tukey's Honest Significant Difference (Tukey HSD) post-hoc tests were done to determine differences between individual groups. We selected a group of channels that showed the highest number of significant differences as channels of interest and computed the averaged power in these channels for all further analyses.

2.8. Spectral statistics over the centro-parietal area

We performed separate two-way mixed ANOVAs for relative and absolute theta, alpha, and beta power, taken as averages across the defined channels of interest, including group as a between subject factor and time period as a within subject factor. Time periods were defined as: 'rest' (1 s before the start of the next trial), 'money presentation' (2 s duration of monetary incentive presentation on the computer screen), and 'squeezing' (0.5–1 s following onset of squeezing, during which the greatest event-related theta, alpha, and beta modulation occurred). The rest period was not included in any relative power analyses as it was always calculated as absolute power. Additionally, due to the presence of a momentary increase in theta power during the start of the squeeze period, an additional time period was included for the analysis of the theta band and was denoted the 'squeeze initiation' (0–0.5 s during the onset of squeezing) period (Fig. 2B). In summary, we ran statistical tests on absolute event-related power and relative event-related power in the time frames of interest (rest, money presentation, squeeze initiation, and squeezing). Tukey HSD post-hoc tests were subsequently performed to further investigate significant differences between individual groups and correct for multiple comparisons.

Principal component regression (PCR) was used to predict patient apathy scores from absolute power at rest and relative power during squeezing for each frequency band of interest as well as other demographic and clinically relevant factors. PCR was used to correct for the presence of predictor variables that were highly correlated. We first performed principal component analysis (PCA) on predictor variables to group highly correlated independent variables into independent principal components, then conducted a multiple linear regression of the response variable on the components. Each variable was normalized by its mean and standard deviation to account for differences in variance (Liu et al., 2003).

2.9. Spectral comparisons between $1 and $50 conditions

In order to compare spectral differences in response to different monetary values, we separated and grouped EEG trials into $1 and $50 trials. Paired *t*-tests were performed on the $1 and $50 trial spectral data for each time point of interest (rest, money presentation, and squeezing) and each group. Mean power was computed separately over the theta, alpha, and beta bands.

3. Results

3.1. Behavioral results

Two-way mixed ANOVA on GFR values, with subject groups as the between-subjects factor and monetary values as the within-subjects factor, revealed a significant main effect of group ($F(2,34) = 4.50$, $p = .018$), a significant main effect of monetary value ($F(1,34) = 21.60$, $p < .0001$), and no interaction between group and monetary value ($p > .05$). Paired *t*-tests showed that the GFR for the $50 condition was significantly higher than that of the $1 condition in all groups (apathetic patients: $t(12) = -2.49$; non-apathetic patients: $t(12) = -5.43$; healthy patients: $t(13) = -3.43$; all $p < .05$; Fig. 3). For the $1 condition, apathetic subjects with PD had lower GFR compared to non-apathetic subjects with PD ($t(24) = -1.99$, $p = .060$), however, this difference was not statistically significant. The GFR of apathetic subjects with PD was significantly lower than that of healthy control subjects for both the $1 ($t(25) = -2.91$; $p = .004$) and $50 ($t(25) = -2.82$; $p = .005$) conditions. No significant differences in GFR were found for other group comparisons, regardless of the monetary value (all $p > .05$).

3.2. Channels of interest

One-way MANOVA for absolute theta power at rest with subject group (apathetic PD, non-apathetic PD, and healthy control subjects) as the independent variable and each of the nine channels (Cz, C4, CP5, CP1, CPz, CP2, CP6, Pz, and P4) as a dependent variable showed a marginally non-significant difference between subject groups ($F(2,34) = 1.70$, $p = .068$; Pillai's Trace = 0.724, partial $\eta^2 = 0.362$). For the purposes of the study, we were most interested in the differences between apathetic and non-apathetic PD subjects and given the marginal insignificance of group effect, we carried out further post-hoc tests for absolute theta power. Individual comparisons using Tukey HSD post-hoc tests showed significant differences between the apathetic and non-apathetic patient groups in the CP1 and Pz electrodes (all $p < .05$) for absolute theta power at rest. MANOVA for relative theta during squeezing, showed no significant difference between subject groups ($p = .167$).

One-way MANOVA for absolute alpha power at rest with subject group as the independent variable and each channel as a dependent variable showed a significant difference between subject groups ($F(2,34) = 1.80$, $p < .05$; Pillai's Trace = 0.751, partial $\eta^2 = 0.38$). A similar MANOVA with relative alpha power during squeezing also showed a significant effect of group ($F(2,34) = 2.53$, $p = .005$; Pillai's Trace = 0.903, partial $\eta 2 = 0.45$). After post-hoc analyses, only absolute alpha power at rest in the CPz, CP1, CP2, and Pz electrodes was significantly greater in apathetic subjects with PD compared to both non-apathetic subjects with PD and healthy control subjects.

For absolute and relative beta power, MANOVA showed no significant difference between subject groups ($p = .45$).

Using these findings as a guide, we defined a common group of channels (CPz, CP1, CP2, Pz) with significant differences specifically between the apathetic and non-apathetic subject groups (Fig. 2A) and computed an average of these channels across each frequency band for all further analyses.

3.3. Theta power

A two-way ANOVA on absolute theta power averaged across CPz, CP1, CP2, and Pz revealed a significant main effect of group ($F(2,34) = 7.01$, $p = .003$) and a significant interaction between group and time frame (money presentation, squeeze initiation, and squeezing) ($F(2,68) = 2.12$, $p = .009$). Apathetic subjects with PD had a significantly higher absolute theta power compared to non-apathetic subjects with PD. Post-hoc *t*-tests showed that this effect was specific to the absolute power at rest ($p = .042$) (Fig. 4B).

For relative theta power, there was a significant main effect of group ($F(2,34) = 11.7$, $p = .0001$) and a significant interaction between group and time frame ($F(2,34) = 3.56$, $p = .040$). Post-hoc analyses revealed that, compared to non-apathetic subjects with PD, apathetic subjects with PD had significantly lower relative theta power during the money presentation period ($p = .017$), relative theta power during the squeeze initiation period ($p = .032$), and relative theta power during the squeezing period ($p = .005$) (Fig. 4A).

Overall, post-hoc analyses revealed no significant differences in absolute and relative theta power between non-apathetic subjects with PD and healthy control subjects during any time period.

3.4. Alpha power

For absolute alpha power averaged across CPz, CP1, CP2, and Pz (Fig. 5B), there was a significant main effect of group ($F(2,34) = 10.31$, $p < .0001$) and a significant interaction between group and time frame ($F(2,68) = 7.14$, $p < .0001$). Specifically during the squeezing period, non-apathetic subjects with PD exhibited a significantly higher absolute alpha power than healthy control subjects ($p = .026$). Compared to non-apathetic subjects with PD, apathetic subjects with PD had a

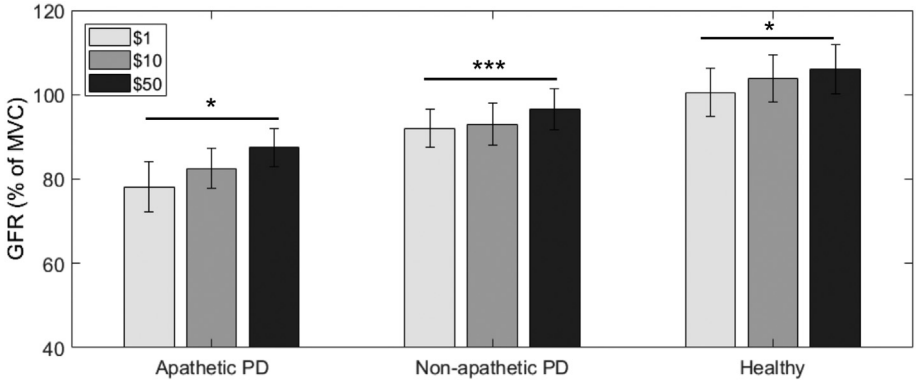

Fig. 3. Behavioral results. Mean grip force response (GFR) shown as a percentage of the total maximum voluntary contraction (MVC) for apathetic subjects with Parkinson's disease, non-apathetic subjects with Parkinson's disease, and healthy control subjects in response to $1, $10, and $50. Error bars are ± SEM. Asterisks indicate a significant difference (paired *t*-test) between $1 and $50 conditions. PD = Parkinson's disease. *$p < .05$, **$p < .005$, ***$p < .0005$.

significantly higher absolute power at rest ($p = .018$) and during money presentation ($p = .028$).

For relative alpha power, there was a significant interaction between group and time frame ($F(2,34) = 7.68$, $p = .002$). Similar to the pattern observed for theta power, apathetic subjects with PD exhibited significantly lower relative alpha power during the squeezing period compared to non-apathetic subjects with PD ($p = .041$) (Fig. 5A). There were no significant differences between non-apathetic subjects with PD and healthy control subjects in relative alpha power.

3.5. Predicting patient apathy scores using theta and alpha power

PCR using absolute theta power at rest, relative event-related theta power during squeezing, age, UPDRS-III scores, and depression scores showed that a two component model was able to significantly predict subject apathy scores ($R^2 = 0.592$, $F(24,21) = 15.3$, $p < .0001$). The first principal component significantly contributed to the model ($p < .0001$). Absolute resting theta power (combined PCA and regression β coefficient = 0.297), relative theta power during squeezing

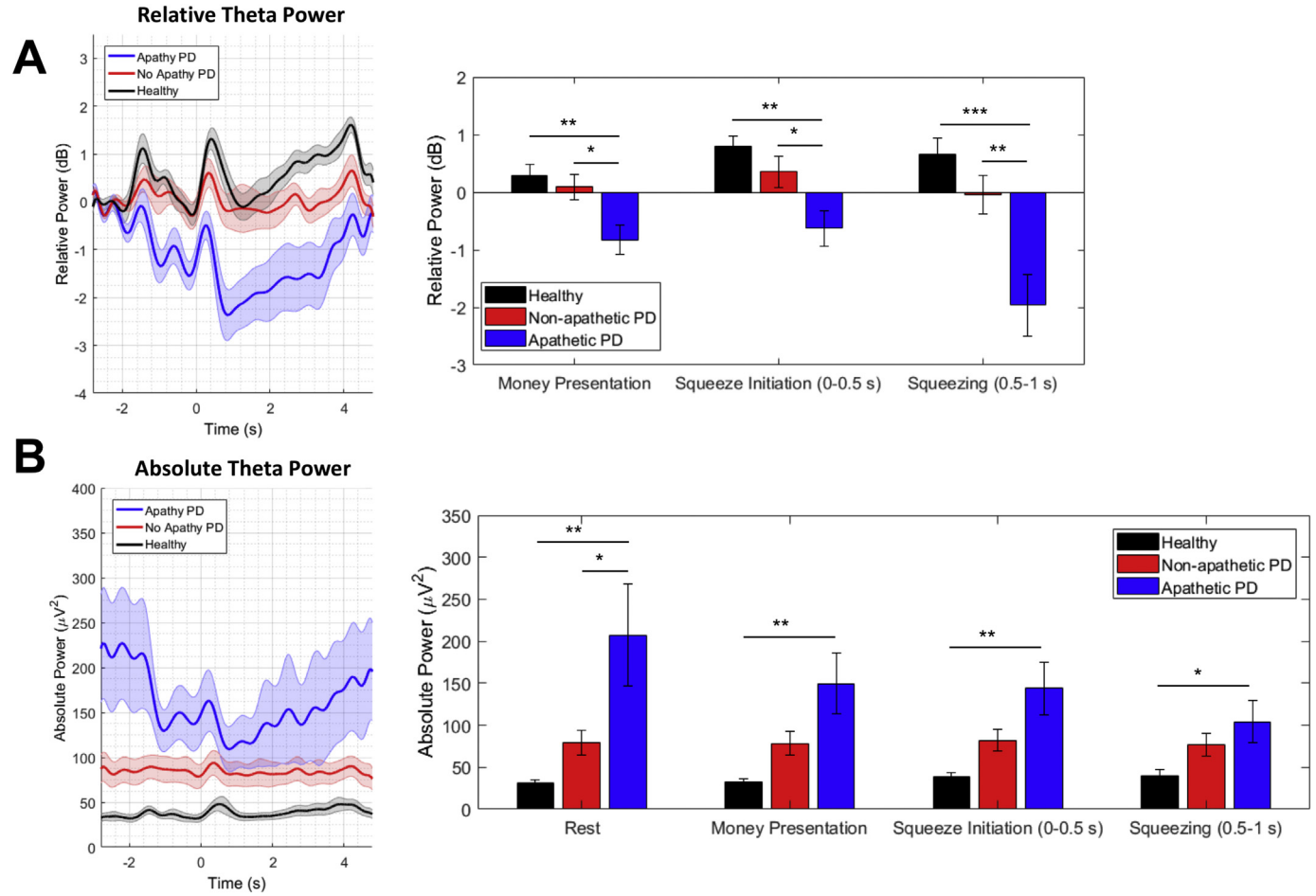

Fig. 4. Relative and absolute theta power over time. A) Left: Relative theta power time courses were extracted by taking the average relative theta power over the CPz, CP1, CP2, and Pz electrodes (represented in dB). -2 s is the time of money presentation and 0 s is the time of squeeze onset. Shaded areas denote the standard error of mean (SEM). Right: Average relative theta power was computed for each group during money presentation (−2 to 0 s), squeeze initiation (0 to 0.5 s), and squeezing (0.5 to 1 s). B) Left: Absolute theta power time courses were extracted by taking the average absolute theta power over the CPz, CP1, CP2, and Pz electrodes (represented in μV^2). Right: Average absolute theta power was computed for each group during rest (−3 to −2 s), money presentation (−2 to 0 s), squeeze initiation (0 to 0.5 s), and squeezing (0.5 to 1 s). PD = Parkinson's disease. *p < .05, **$p < .005$, ***$p < .0005$.

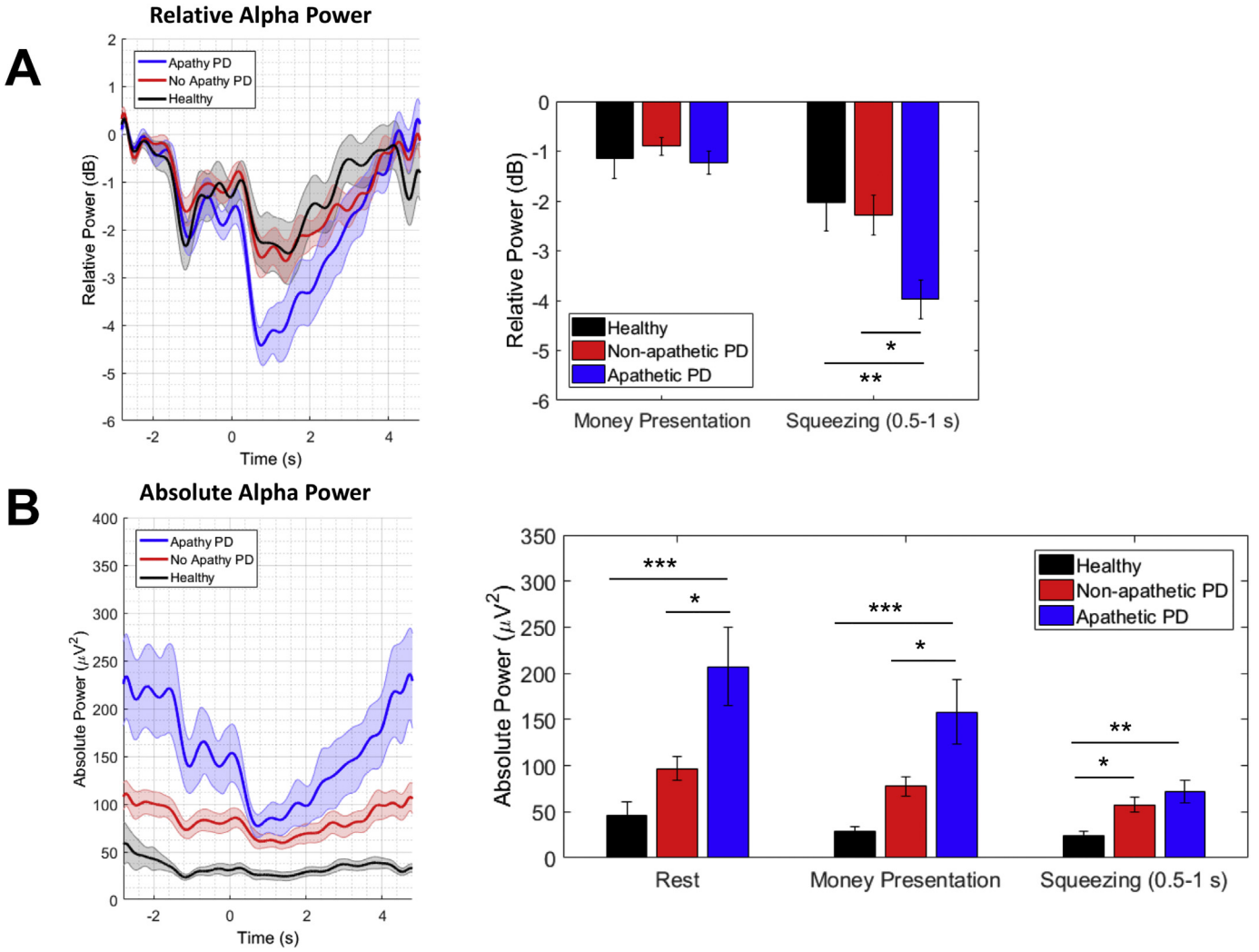

Fig. 5. Relative and absolute alpha power over time. A) Left: Relative alpha power time courses were extracted by taking the average relative alpha power over the CPz, CP1, CP2, and Pz electrodes (represented in dB). -2 s is the time of money presentation and 0 s is the time of squeeze onset. Shaded areas denote the standard error of mean (SEM). Right: Average relative alpha power was computed for each group during money presentation (−2 to 0 s), squeeze initiation (0 to 0.5 s), and squeezing (0.5 to 1 s). B) Left: Absolute alpha power time courses were extracted by taking the average absolute alpha power over the CPz, CP1, CP2, and Pz electrodes (represented in μV^2). Right: Average absolute alpha power was computed for each group during rest (−3 to −2 s), money presentation (−2 to 0 s), squeeze initiation (0 to 0.5 s), and squeezing (0.5 to 1 s). PD = Parkinson's disease. *p < .05, **p < .005, ***p < .0005.

(combined PCA and regression β coefficient = −0.234), and depression (combined PCA and regression β = 0.300) had the highest contribution to the component, with depression having the highest contribution in this model (Fig. 6; left).

PCR using absolute resting alpha power, relative event-related alpha power during squeezing, UPDRS-III scores, age, and depression scores as predictors also found that a two component model was able to significantly predict apathy scores (R^2 = 0.694, $F(24,21)$ = 23.8, p < .0001). The first principal component significantly contributed to the model (p < .0001). Combined PCA and regression coefficients showed the greatest contribution from absolute resting alpha power (combined PCA and regression β coefficient = 0.357) and relative alpha power during squeezing (combined PCA and regression β coefficient = −0.360) to the component. Depression also had a high, but slightly lower contribution, with a combined PCA and regression β of 0.290. This is consistent with previous knowledge that depression and apathy are highly correlated conditions (Fig. 6; right).

3.6. Spectral comparison between $1 and $50

Paired t-tests on the $1 and $50 condition for theta, alpha, and beta showed no significant difference was found between the two money value conditions for any group or time frame (p > .05).

4. Discussion

In the current study, we investigated the behavioral and neural oscillatory characteristics associated with apathy in PD using an incentivized squeeze grip paradigm. We determined that medicated PD subjects, regardless of the presence of apathy, were able to modulate their effort expenditure based on the level of reward. Although we did not observe distinct behavioral differences between cohorts, our EEG results demonstrate that apathetic individuals with PD exhibited a higher centro-parietal resting alpha and theta power and a greater reduction in event-related desynchronization, in alpha and theta power during squeezing compared to non-apathetic individuals with PD and healthy controls. Furthermore, absolute resting power and relative power during squeezing in the alpha and theta bands accurately predicted clinical PD apathy scores. Depression had a substantial contribution to the regression models, which is in line with the observation that apathy and depression have a high comorbidity with PD.

Higher theta and alpha power during rest was an overall feature of

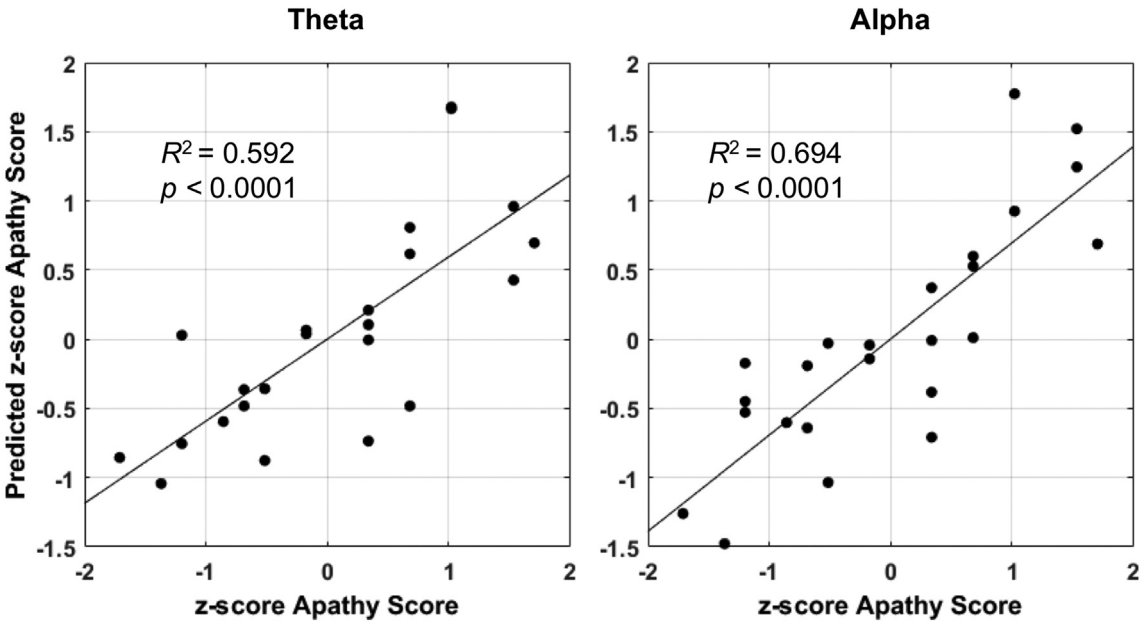

Fig. 6. Scatter plots of normalized predicted vs. actual apathy scores using principal component regression. Left: Normalized (z-score) predicted apathy score plotted against normalized (z-score) actual apathy score using absolute resting theta power, relative theta power during squeezing, age, UPDRS-III, and depression as predictors of apathy score. Right: Normalized (z-score) predicted apathy score plotted against normalized (z-score) actual apathy score using absolute resting alpha power, relative alpha power during squeezing, age, UPDRS-III, and depression as predictors of apathy score.

apathy in PD in our study. Previous studies have shown that theta and alpha oscillatory power over motor cortical areas are typically higher at rest in those with PD (Moazami-Goudarzi et al., 2008) and are positively associated with the presence of dementia (Stoffers et al., 2008). Similarly, the presence of apathy in PD has been linked to cognitive decline and accelerated onset of dementia (Dujardin et al., 2009; Fitts et al., 2015). Recently-diagnosed, drug-naive individuals also tend to show an overall increase in resting-state alpha power that is not strongly affected by disease progression nor levodopa treatment, suggesting contribution from non-dopaminergic and non-motor factors (Stoffers et al., 2008). However, the specific contribution of apathy to these aforementioned results was not evaluated in these studies. Taken together with our current findings, the observed increases in theta and alpha power may provide a link between cognitive decline and non-dopaminergic contributions observed in previous studies and apathy in PD.

There is an abundance of evidence relating alpha oscillations to processes that indirectly affect apathy. Levels of alpha power at rest may be a marker of cortical excitability (Romei et al., 2008) which may relate to both apathy and fatigue. In stimulation of the the primary motor cortex using transcranial magnetic stimulation (TMS), motor evoked potentials are shown to be elicited more easily when alpha power immediately preceding TMS is low, compared to when alpha power is relatively high (Sauseng et al., 2009). Using simultaneous EEG and magnetic resonance imaging (MRI), Laufs et al. (2003) reported a negative correlation between EEG alpha power and regional cerebral blood flow in parietal and frontal cortical regions associated with attentional processes. These findings suggest that high alpha activity is associated with low brain metabolism. Metabolic alterations in these brain regions have also been reported in subjects with PD and apathy (Robert et al., 2012). Apathy in other neurological diseases, such as Alzheimer's disease, is also correlated with decreased regional cerebral blood flow in frontal, temporal, and parietal regions (Kang et al., 2012). Apathy in PD is often accompanied by mental fatigue, which may result from an incongruity between the amount of effort invested into a task and potential rewards (Boksem and Tops, 2008), and is associated with an increase in occipital alpha and frontal theta (Aftanas and Golocheikine, 2001; Wascher et al., 2014).

We also observed significant differences in theta power in apathetic subjects with PD. Normally, theta power increases as a result of attention demanding processes preceding movement onset (Popivanov et al., 1999; Turak et al., 2001; Tsujimoto et al., 2006; Christie and Tata, 2009) and during conflict processing (Zavala et al., 2014). Here, we found an increase in theta power during reward presentation and motor initiation in response to reward, but apathetic subjects with PD exhibited significantly lower relative theta power compared to both non-apathetic subjects with PD and healthy control subjects in both cases (Fig. 4). Previously, theta oscillations in the subthalamic nucleus have been associated with conflict processing in PD (Ghahremani et al., 2018). Further, we found a direct relationship between resting alpha and theta oscillations and the magnitude of alpha and theta desynchronization during reward-related movement. Due to the increase in resting alpha and theta power in the motor cortex with apathy, these frequency bands may require greater modulation in order to reach a threshold required for movement execution (Heinrichs-Graham et al., 2014). The larger desynchronization we observed in individuals with higher apathy scores may be evidence of a neural compensatory effect to counteract the higher baseline alpha and theta power in apathetic patients. Thus, changes in relative and absolute theta power may be a potential neural marker for a blunted reward response in apathetic patients.

Interestingly, there were no significant differences in absolute resting beta power and beta desynchronization during motor execution between groups. This suggests that beta band oscillations may be more specifically related to motor function and is successfully controlled by dopamine medication (Little & Brown, 2014), whereas the alpha and theta band activity may be associated with a combination of motor function and neuropsychiatric characteristics, such as apathy and harder to control by dopaminergic medication. This is also supported by previous finding that movement-related suppression of local alpha power in the temporal cortex and subthalamic nucleus is independent of dopaminergic status (Oswal et al., 2013). Nonetheless, it would be worthwhile to investigate this oscillatory behavior further in apathetic subjects who are both on and off their normal dopaminergic medication. We specifically tested our patients on medication in order to probe medication-resistant apathy features.

Despite a significant effect of monetary value on GFR in all cohorts, our present results did not reveal significant differences between the highest and lowest money values in neural oscillatory behavior in any frequency band of interest. This is consistent with previous studies which have reported that the magnitude of beta and alpha desynchronization during movement does not change with the force applied (Anzak et al., 2012; Brücke et al., 2012; Joundi et al., 2012). Our finding supports the argument that the degree of desynchronization serves a permissive role, promoting movement initiation rather than the force applied during movement (Brown and Williams, 2005).

Finally, we found no difference between our apathy patients and other groups in terms of modulating their effort expenditure based on reward. We speculate that the successful modulation of effort based on reward in apathy might be due to the compensatory mechanisms we observed in alpha and theta. However, this is in contrast with a previous study showing that patients with auto-activation deficit (AAD) disorder, a subcategory of apathy characterized by a reduction in self-initiated behaviors, did not differ in their effort expenditure in response to reward whereas PD patients could still exert greater motor effort in response to higher monetary rewards (Schmidt et al., 2008). We believe this difference in results might be due to the effects of dopaminergic medication.

5. Conclusion

This is the first study to characterize abnormal oscillatory activity of apathy in PD. Our findings reveal that medicated apathetic patients with PD have distinct neural oscillatory characteristics despite showing similar behavioral responses to reward to non-apathetic subjects with PD. We demonstrate that apathetic subjects with PD exhibit a higher resting EEG theta and alpha power compared to non-apathetic subjects with PD. Furthermore, both resting power and relative event-related theta and alpha desynchronization during squeezing were able to predict patient apathy scores. Future research may examine the effects of dopaminergic medication on the behavioral and neural oscillatory differences in apathetic subjects with PD. As apathy is currently diagnosed using subjective questionnaire-based evaluation scales, determining potential neural markers of apathy in PD can be beneficial in increasing the reliability of its diagnosis and can aid in the development of more targeted therapies.

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Competing interests

There are no competing interests to report.

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