BRAIN
ORIGINAL ARTICLE

Corticostriatal beta oscillation changes associated with cognitive function in Parkinson's disease

Danika L. Paulo,[1,†] Helen Qian,[1,2,†] Deeptha Subramanian,[1] Graham W. Johnson,[1,3] Zixiang Zhao,[1] Kilian Hett,[4] Hakmook Kang,[5] C. Chris Kao,[1] Noah Roy,[1] Jessica E. Summers,[4] Daniel O. Claassen,[4] Kaltra Dhima[4] and Sarah K. Bick[1,6,7]

[†]These authors contributed equally to this work.

See Mansoureh Fahimi Hnazaee and Vladimir Litvak (https://doi.org/10.1093/brain/awad273) for a scientific commentary on this article.

Cognitive impairment is the most frequent non-motor symptom in Parkinson's disease and is associated with deficits in a number of cognitive functions including working memory. However, the pathophysiology of Parkinson's disease cognitive impairment is poorly understood. Beta oscillations have previously been shown to play an important role in cognitive functions including working memory encoding. Decreased dopamine in motor cortico-striato-thalamo-cortical (CSTC) circuits increases the spectral power of beta oscillations and results in Parkinson's disease motor symptoms. Analogous changes in parallel cognitive CSTC circuits involving the caudate and dorsolateral prefrontal cortex (DLPFC) may contribute to Parkinson's disease cognitive impairment.

The objective of our study is to evaluate whether changes in beta oscillations in the caudate and DLPFC contribute to cognitive impairment in Parkinson's disease patients. To investigate this, we used local field potential recordings during deep brain stimulation surgery in 15 patients with Parkinson's disease. Local field potentials were recorded from DLPFC and caudate at rest and during a working memory task. We examined changes in beta oscillatory power during the working memory task as well as the relationship of beta oscillatory activity to preoperative cognitive status, as determined from neuropsychological testing results. We additionally conducted exploratory analyses on the relationship between cognitive impairment and task-based changes in spectral power in additional frequency bands.

Spectral power of beta oscillations decreased in both DLPFC and caudate during working memory encoding and increased in these structures during feedback. Subjects with cognitive impairment had smaller decreases in caudate and DLPFC beta oscillatory power during encoding. In our exploratory analysis, we found that similar differences occurred in alpha frequencies in caudate and theta and alpha in DLPFC.

Our findings suggest that oscillatory power changes in cognitive CSTC circuits may contribute to cognitive symptoms in patients with Parkinson's disease. These findings may inform the future development of novel neuromodulatory treatments for cognitive impairment in Parkinson's disease.

1 Department of Neurological Surgery, Vanderbilt University Medical Center, Nashville, TN 37212, USA
2 Department of Neuroscience, Vanderbilt University, Nashville, TN 37212, USA
3 School of Medicine, Vanderbilt University, Nashville, TN 37212, USA
4 Department of Neurology, Vanderbilt University Medical Center, Nashville, TN 37212, USA
5 Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN 37212, USA
6 Department of Biomedical Engineering, Vanderbilt University, Nashville, TN 37212 USA
7 Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN 37212, USA

Received January 11, 2023. Revised May 08, 2023. Accepted May 16, 2023. Advance access publication June 16, 2023

Correspondence to: Danika L. Paulo
Vanderbilt University Medical Center
Department of Neurological Surgery
1500 21st Avenue South
Suite 4333, Nashville, TN 37212, USA
E-mail: Danika.L.Paulo@vumc.org

Keywords: cognitive impairment; neurophysiology; Parkinson's disease; working memory

Introduction

Cognitive impairment (CI) is the most common non-motor symptom of Parkinson's disease and is a major contributor to patient disability, decreased quality of life and increased disease-related mortality. The cognitive domains of executive function, which includes working memory, attention and memory, are most prominently affected in early Parkinson's disease,[1-3] while visuospatial function and global cognitive deficits occur by mid-stage of the disease.[4-6] Current first-line therapies for Parkinson's disease CI have limited efficacy, and improved understanding of the pathophysiology underlying Parkinson's disease CI is needed to support the development of novel treatment modalities.

Dysfunction of cortico-striato-thalamo-cortical (CSTC) circuits may contribute to both motor and cognitive symptoms in patients with Parkinson's disease. The striatum, which includes the nucleus accumbens, caudate and putamen, receives dopaminergic input and is somatotopically organized into parallel circuits that contribute to motor, cognitive and limbic functions.[7] Parkinson's disease motor symptoms are associated with dopamine-modulated pathological changes in the motor CSTC circuit including the putamen, subthalamic nucleus (STN) motor division, globus pallidus internus (GPI) and primary and supplementary motor cortex.[8-13] Imaging studies have suggested parallel cognitive CSTC circuit structures including the caudate and dorsolateral prefrontal cortex (DLPFC) play a role in Parkinson's disease CI, with cognitively impaired patients having decreased caudate volumes, activity, dopamine transporter levels and caudate-DLPFC connectivity.[14-17] Corticostriatal changes may be particularly important in early executive function deficits such as working memory impairment seen in Parkinson's disease CI. Corticostriatal structures including the caudate and DLPFC have well-established roles in the working memory of healthy subjects.[18-27] Parkinson's disease patients with CI have decreased caudate and DLPFC activity during a working memory task,[16] with caudate activity specifically decreased during working memory encoding.[26]

The pathophysiology of Parkinson's disease CI has largely been studied with structural and functional imaging techniques, which have limited spatial and temporal resolution to elucidate specific neural changes associated with pathological processes.[28,29] One way of overcoming these limitations is with direct, invasive neurophysiologic recordings routinely obtained during deep brain stimulation (DBS) implantation surgeries. Corticostriatal neurophysiological changes resulting in primary Parkinson's disease motor symptoms have been well-characterized and are under study for use in closed-loop DBS stimulation paradigms to improve the treatment of Parkinson's disease motor symptoms.[30] In motor CSTC circuits, decreased dopamine input to the putamen leads to beta (15–30 Hz) oscillatory changes with increased spectral power, bursting and coherence of beta oscillations in structures including STN, GPI and primary motor cortex which result in primary Parkinson's disease motor symptoms of bradykinesia and rigidity.[31-33] These beta oscillatory changes are reversed by medical and surgical therapies that improve Parkinson's disease motor symptoms.[34-38] The parallel cognitive CSTC circuit similarly has decreased dopaminergic input in Parkinson's disease; however, analogous neurophysiologic changes contributing to Parkinson's disease CI have not been previously studied via human intracranial local field potential (LFP) recordings.

Spectral power of beta oscillations, also referred to as beta power, in the caudate and DLPFC has been associated with normal cognitive functions. Primate studies have shown that DLPFC beta oscillation bursting and power are suppressed during working memory encoding, while gamma (30–100 Hz) power and bursts are induced.[39-41] Previous research in human subjects participating in a learning task found increased caudate and DLPFC beta power during feedback following correct trials, with DLPFC beta power correlating with learning.[42] Whether beta oscillation changes in cognitive CSTC circuits contribute to Parkinson's disease CI, however, remains unknown.

The primary objective of this study is to evaluate whether caudate and DLPFC beta oscillation changes contribute to CI in Parkinson's disease. We hypothesize that caudate and DLPFC beta oscillations play a role in Parkinson's disease cognitive deficits and are altered in Parkinson's disease patients with CI compared to those with normal cognition. To study this, we collected intraoperative LFP recordings from caudate and DLPFC at rest and during a verbal two-back working memory task in Parkinson's disease patients during DBS surgery. We report caudate and DLPFC beta power changes during working memory that differ in patients with CI, and in an exploratory analysis found that these differences extend to alpha power in the caudate and theta and alpha power in the DLPFC. These findings increase our understanding of the pathophysiology of Parkinson's disease CI and may inform future development of novel neuromodulation strategies to improve treatment of this common, debilitating symptom of Parkinson's disease.

Materials and methods

Subjects

Fifteen patients with Parkinson's disease undergoing bilateral DBS surgery of the STN or GPI under local anaesthesia at our institution from 2021–22 and with planned electrode trajectories that traversed caudate and/or DLPFC participated in this study. All Parkinson's disease patients undergoing new DBS implantation, regardless of baseline cognitive status, were eligible to participate. This prospective study was approved by the Vanderbilt University Medical Center Institutional Review Board prior to initiation and all subjects provided written informed consent. Demographic, behavioural and clinical data from all subjects were collected from their electronic medical records.

Preoperative evaluation

Routine DBS preoperative workup includes a preoperative CT, MRI and formal motor and neuropsychological testing. Motor function ON and

OFF Parkinson's disease medications was graded by the Unified Parkinson's Disease Rating Scale (UPDRS). Neuropsychological evaluation included tests to measure functioning within cognitive domains frequently impaired in Parkinson's disease: executive functioning, processing speed, attention, memory, visuospatial function and language (Supplementary Table 1). We categorized patients as cognitively impaired if they scored within impaired ranges on at least two individual task measures, per the Movement Disorder Society Task Force's level II criteria for Parkinson's disease mild cognitive impairment.[43] A neuropsychological test score was classified within the impaired range when falling below the 9th percentile.[44]

For subjects who consented to participate in this research study, the planned DBS electrode trajectory was examined using clinical planning software (WayPoint Navigator, FHC Inc., Bowdoin, ME), and the relationship of the trajectory to the caudate and DLPFC was noted. For trajectories that traversed the caudate, the distance of caudate entry relative to the planned target was calculated to determine the depth along the trajectory at which to perform intraoperative research recordings.

Surgery

All patients who participated in this study underwent bilateral DBS electrode implantation surgery under local anaesthesia with clinical microelectrode recordings. Dopaminergic medications were held the night prior to surgery according to standard clinical protocol to facilitate intraoperative motor testing. A custom-made mini-stereotactic frame (FHC Inc.) was mounted with two microdrives, each with three microelectrodes with macro contacts on the microelectrode protective tube 10 mm from the micro tip to allow recording of LFPs (FHC Inc.) (Supplementary Fig. 1). This setup allowed for simultaneous bilateral recordings. The microelectrodes were advanced through a rigid insertion tube along the planned clinical trajectory to the treatment target until the macro contact was within the structure to be recorded from (caudate or DLPFC). LFP recordings were performed from the macro contact of the clinical microelectrodes (Supplementary Fig. 1) and recorded via the FHC Guideline 5 system with a sampling rate of 1000 Hz. For cortical recordings, the rigid insertion tubes and microelectrodes were advanced to just above the uncoagulated cortical surface, the microelectrode tip was advanced through the pia, and the protective tube with macro contact was advanced over this until the macro contact was just inside the cortex by visual inspection. A similar method has previously been reported to perform single neuron recordings in the cortex using microelectrodes.[45] Per standard clinical protocol, saline and gelatin compressed sponges (Gelfoam) were then placed around the electrodes to minimize CSF egress. Following research recordings, the rigid insertion tubes were advanced, and the micro electrodes and protective tubes were advanced to target depth to perform clinical recordings and stimulation per standard clinical protocol. Because the electrode design is such that the microelectrode tip and macro contact are separated by 10 mm, we were not able to record simultaneous single unit recordings and LFPs from the same structures and focused our analysis on LFPs alone. Ten subjects had recording electrodes that traversed the caudate, and 13 subjects had electrodes that traversed the DLPFC. As there were three microelectrodes per side, often we recorded from multiple channels within each structure, but only one brain region was recorded per side.

Task

At the beginning of the research session, 2 min of LFP data were recorded while subjects rested quietly with their eyes closed.[46] Subjects subsequently participated in a verbal two-back working memory task,[47] during which they were sequentially visually presented with a series of words. Following a pause, a response cue appeared prompting them to respond whether the word presented during the current trial matched the word presented two trials prior by pressing a button. The side of the button assigned to yes versus no response was randomly assigned on a trial by trial basis and indicated by 'Y' and 'N' on the screen, which served as the response cue, to help control for motor-related effects and isolate the encoding task epoch from motor planning by preventing motor planning until the response cue appeared. Following the response, they were given visual feedback on whether their response was correct or incorrect (Fig. 1A). Subjects completed two 75-trial blocks of this task. The task was run using MonkeyLogic task presentation software (NIMH MonkeyLogic), with transistor-transistor logic (TTL) pulses sent to the FHC Guideline 5 neurophysiology system to allow alignment of task events with neural recordings.

Imaging

Following surgery, patients underwent postoperative CT as part of standard clinical protocol. This CT was then merged with their preoperative MRI using WayPoint software to evaluate final electrode placement and confirm positioning of recording microelectrodes. Recordings from any microelectrode tracts that were determined by two neurosurgeons (D.L.P., S.K.B.) to be out of the region of interest for this study were excluded from analysis.

Given the previously reported relationship between caudate volume and cognition in Parkinson's disease patients, we computed caudate volume to determine whether this was related to beta power. Estimation of caudate volumes was obtained by feeding subjects' preoperative T_1-weighted MRIs into a deep-learning approach based on a large ensemble of fully convolutional neural networks.[48] This method provides automatic parcellation of 133 brain structures following the Desikan-Killiany-Tourville protocol.[49] All caudate volumes were given in the T_1-weighted native space after total intracranial volume normalization.

Neurophysiology and statistical analysis

LFP analysis was performed offline using MATLAB (MathWorks, Natick MA) and MATLAB FieldTrip toolbox.[50] Recordings were visually examined for noise and excluded if the signal was contaminated by significant artifact. Data were notch filtered at 60 Hz to remove line noise, high-pass filtered at 1 Hz and aligned to task events using digital event triggers. Spectral power was calculated using the Morlet wavelet time-frequency transformation in MATLAB FieldTrip Toolbox. Task-based power was z-scored across all trials for each channel and frequency, while resting-state power was log transformed by base 10 and averaged over time. Power was then averaged into delta (1–4 Hz), theta (3–8 Hz), alpha (8–15 Hz), beta (15–30 Hz) and gamma (30–100 Hz) frequency bands. We did not find a significant difference between left and right-sided recordings and therefore combined bilateral channels in our analysis to increase statistical power.

To examine working memory related beta oscillation changes, we divided the task into several epochs. For working memory encoding, we examined beta power during the 1000 ms the word stimulus appeared on the screen, prior to the appearance of the response cue. For feedback, we examined the 500 ms when visual feedback was given. For each channel we recorded from, we averaged beta power within these time periods for correct and incorrect

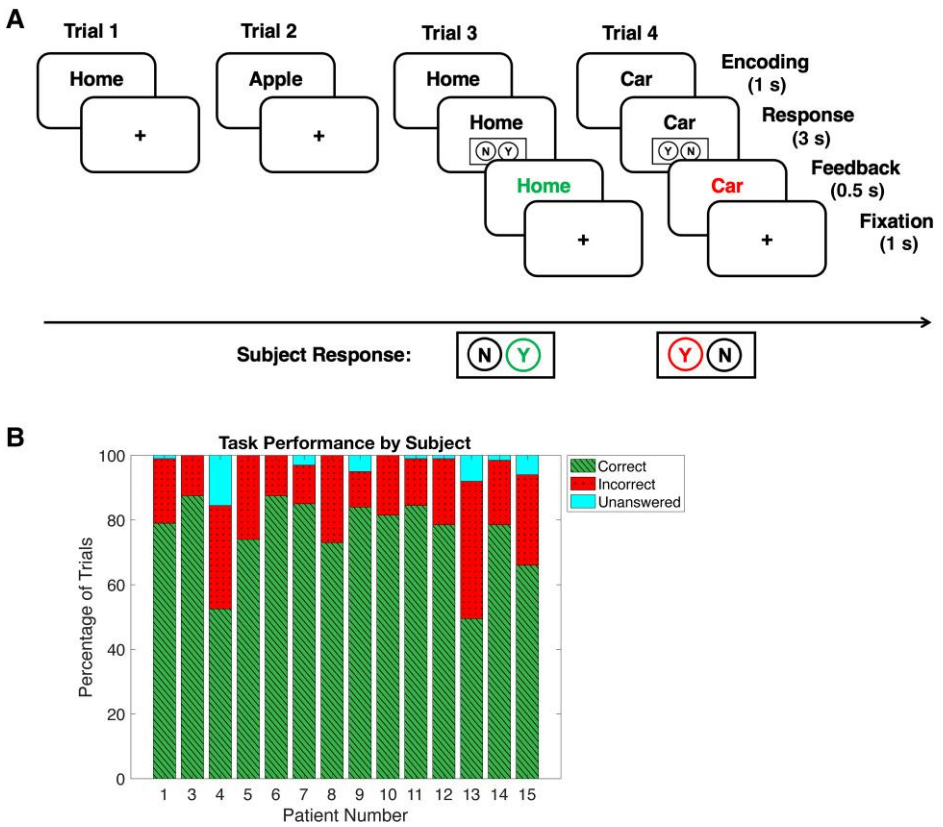

Figure 1 Working memory task. (**A**) Two-back Verbal Working Memory Task: The subject is presented with a word, and after a pause, a response cue appears prompting the subject to answer whether the current word matches that from two trials prior. Side of buttons corresponding to yes/no response is randomly assigned on a trial-by-trial basis. Following the response, visual feedback is presented. Green represents correct response, red represents incorrect response. Y = yes, N = no. (**B**) Task Performance By Subject: percentage of correct (green), incorrect (red) and unanswered (cyan) trials per subject, averaged across blocks. Patient 2 did not complete intraoperative tasks and is thus excluded from this graph.

trials. We also computed resting-state beta power for each channel and averaged it over the full 2-min recording period.

Statistical analysis was performed in MATLAB. Our primary hypothesis was that beta oscillation changes during working memory would be altered in Parkinson's disease patients with CI. To examine changes in power with working memory encoding and feedback we used the Wilcoxon signed-rank test to compare beta power during working memory encoding and feedback to beta power during the 500 ms baseline period just prior to stimulus and feedback onset. We also used the Wilcoxon signed-rank test to assess the mean beta power differences between correct and incorrect trials during encoding and feedback periods, to determine whether these changes were related to task performance. To examine the relationship between beta oscillatory power changes and cognitive function, we used the Wilcoxon rank sum test to assess whether recordings from cognitively impaired and non-impaired patients exhibited differences in average caudate and DLPFC beta power during working memory encoding for correct trials, feedback for correct trials and resting-state. We used a Pearson correlation to examine the relationship between each subject's caudate volume normalized by intracranial volume and their task-based and resting-state beta power. We also used a Pearson correlation to evaluate the relationship between resting-state and task-associated beta power and motor response times.

In addition to our primary analysis examining beta oscillation spectral power changes, we conducted an exploratory analysis of whether oscillatory power changes in the delta, theta, alpha and gamma bands during encoding and feedback are related to CI status. Since previous studies have reported different changes in high beta (21–30 Hz) and low beta (15–20 Hz) frequency oscillations related to Parkinson's disease motor symptoms, we also performed an exploratory analysis of spectral power in these sub bands.[34,51-54] We used the Wilcoxon rank sum test to analyse how average resting-state oscillatory power in these frequency bands differed between cognitively impaired and non-impaired patients. To test whether task-related power changes were different between patients with and without CI during the encoding and feedback periods, we first averaged power within each frequency band and across correct trials for each channel. We then performed cluster-based permutation testing, using a two-sample *t*-test to generate a T-value for comparison between patients with and without CI for power within the frequency band at each time point, then summing the T-values within clusters above the statistical significance threshold of 0.05 for at least four consecutive time points. The labels designating channels as from cognitively impaired or non-impaired subjects were then randomly reassigned 1000 times with the T-statistic similarly determined. Significant clusters were defined as those with summed T-values greater than that of 95% of the randomly determined comparisons. We used the 1000 ms word stimulus presentation period and the 500 ms feedback presentation period as our respective time windows of interest for working memory encoding and feedback analyses. This exploratory analysis was Bonferroni-corrected for multiple comparisons of all frequency bands examined.

Data availability

Raw data were generated at Vanderbilt University Medical Center. Derived data supporting the findings of this study are available from the corresponding author on reasonable request.

Results

Fifteen subjects participated in the study. Demographic and clinical characteristics are shown in Table 1. Fourteen subjects completed both resting-state data collection and the verbal working memory task, while one subject completed only resting-state data collection. Bilateral recordings were performed in all subjects. For resting-state recordings, 10 subjects had recordings from a total of 12 caudate nuclei (25 total channels), while 13 subjects had recordings from 18 DLPFC (50 total channels). For task-based recordings, nine subjects had recordings from a total of 10 caudate nuclei (21 total channels) and 13 subjects had recordings from 18 DLPFC (50 total channels) (Supplementary Table 2). For the 14 patients that completed the two-back task, mean task performance was 75.8 ± 11.7% correct, 21.2 ± 8.7% incorrect, 3.0 ± 4.3% unanswered (Fig. 1B). Nine patients met criteria for CI, while six patients exhibited normal cognition, one of whom was not included in our task-based analysis.

Caudate and DLPFC beta oscillations

In our primary analysis to test our hypothesis about beta oscillations, both caudate and DLPFC exhibited local peaks in beta power at rest (Supplementary Fig. 2A). During working memory encoding, both caudate and DLPFC exhibited a decrease in the spectral power of beta oscillations (Fig. 2A and B and Supplementary Fig. 3A). Average beta power during the 1000 ms encoding period for words subsequently recalled correctly was significantly lower than average beta power during the baseline period prior to stimulus presentation ($P = 0.0033$, $z = 2.9$ caudate and $P = 9.8 \times 10^{-5}$, $z = 3.9$ DLPFC) (Fig. 2C). Caudate beta power during the encoding period of incorrect trials was not significantly different from that in the baseline period prior to stimulus presentation ($P = 0.34$, $z = 0.96$), while average DLPFC beta power during encoding for incorrect trials was significantly decreased compared to this baseline ($P = 8.36 \times 10^{-5}$, $z = 3.9$). There was a significantly greater decrease in beta power during encoding of correct compared to incorrect trials for caudate ($P = 0.0057$, $z = -2.8$), but not DLPFC ($P = 0.28$, $z = 1.1$) (Fig. 2D).

During feedback, both caudate and DLPFC exhibited an increase in the spectral power of beta oscillations (Figs 3A and B and Supplementary Fig. 3B). Average beta power during the 500 ms feedback period following correct trials was significantly higher than baseline ($P = 0.0013$, $z = -3.2$ caudate and $P = 0.00029$, $z = -3.6$ DLPFC) (Fig. 3C). There was no significant change from baseline in caudate or DLPFC beta power during feedback following incorrect trials ($P = 0.77$, $z = -0.30$ caudate and $P = 0.20$, $z = 1.3$ DLPFC). Beta power in both caudate and DLPFC was significantly greater following correct compared to incorrect trials during this period ($P = 0.011$, $z = 2.6$ caudate and $P = 1.2 \times 10^{-7}$, $z = 5.3$ DLPFC) (Fig. 3D).

To explore whether the association between cognitive performance and beta oscillatory power was related to motor function, we examined correlations between resting-state and task-based beta power and working memory task reaction time. We found there was no relationship between average caudate or DLPFC resting-state, encoding or feedback beta power and reaction time (Supplementary Table 3). We also evaluated the relationship between caudate and DLPFC beta power and caudate volume to determine whether observed beta power changes were related to caudate atrophy. We found there was no relationship between average caudate or DLPFC resting-state, encoding or feedback-related beta power and caudate volume (Supplementary Table 4). These findings are summarized in Table 2.

Relationship between beta oscillations and cognitive impairment

Average spectral power of beta oscillations during the resting-state did not significantly differ between subjects with normal cognition and cognitively impaired subjects for both caudate and DLPFC

Table 1 Patient demographic and disease-related information

Patient number	Age, years	Sex	Handedness	Disease duration, years	Target	UPDRS score		Levodopa equivalent dose	Cognitive impairment
						OFF	ON		
1	56	M	Right	5	STN	49	30	1400	Impaired
2	68	M	Right	9	STN	35	9	800	Non-impaired
3	62	M	Right	9	STN	53	28	1240	Non-impaired
4	60	F	Right	11	STN	49	35	1600	Impaired
5	58	M	Right	11	STN	60	5	2450	Non-impaired
6	62	M	Left	5	STN	41	10	2050	Impaired
7	56	M	Right	6	STN	71	N/A	100	Impaired
8	64	M	Right	8	STN	30	2	1900	Impaired
9	60	M	Right	7	STN	32	24	1200	Non-impaired
10	66	M	Right	9	GPI	44	28	500	Impaired
11	56	M	Right	15	GPI	47	25	1300	Non-impaired
12	57	M	Right	5	GPI	33	12	1945	Impaired
13	76	M	Right	9	GPI	60	45	2000	Impaired
14	67	M	Right	5	STN	30	10	1333	Non-impaired
15	77	F	Right	12	GPI	53	23	1300	Impaired
Total/Avg ± SD	63 ± 6.6	13 M/2 F	14 R/ 1 L	8.4 ± 2.9	10 STN 5 GPI	46 ± 12.0	20 ± 12	1408 ± 601	9 I/6 NI

F = female; GPI = globus pallidus internus; I = impaired; M = male; NI = non-impaired; SD = standard deviation; STN = subthalamic nucleus.

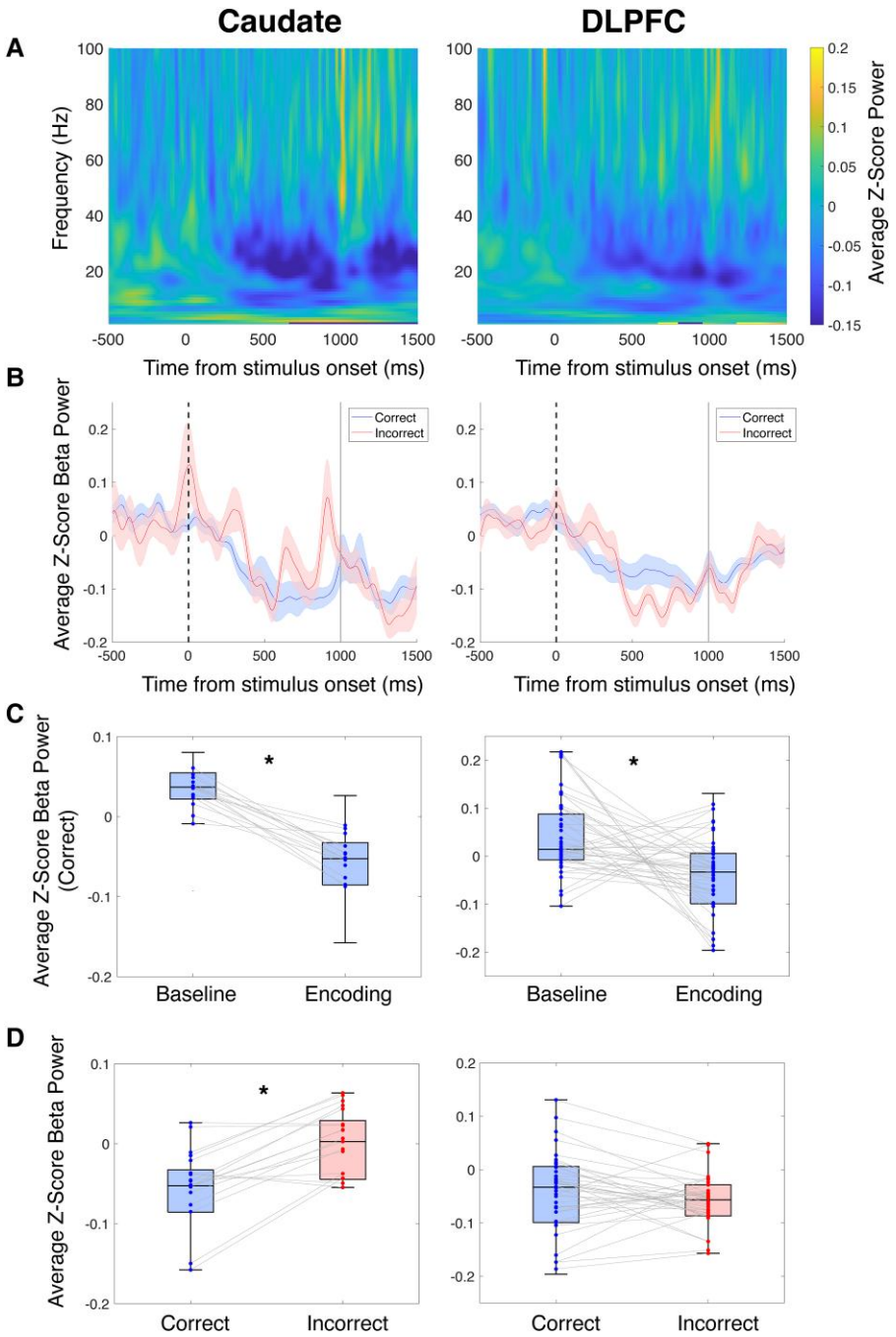

Figure 2 Caudate and DLPFC power during encoding. (**A**) Spectrograms of z-scored caudate and DLPFC power averaged over correct trials for all subjects, aligned to stimulus onset (encoding period). For correct trials, there was a significant decrease in power during working memory encoding centred in the beta band for both caudate (*left*) and DLPFC (*right*). (**B**) Time courses of caudate (*left*) and DLPFC (*right*) average beta power during encoding for correct and incorrect trials. Shading around the average line indicates standard error. Dotted line indicates word presentation onset and solid line indicates end of encoding period and appearance of the cue to select a response. (**C**) Box and whisker plots comparing average z-scored beta power at baseline and during encoding for correct trials in caudate (*left*) and DLPFC (*right*). Both caudate ($P = 0.0033$, $z = 2.9$) and DLPFC ($P = 9.8 \times 10^{-5}$, $z = 3.9$) beta power significantly decreased during encoding. Black line denotes median, box denotes interquartile range, whiskers denote range of minimum to maximum values. Grey lines denote paired subjects. (**D**) Box and whisker plots comparing average z-scored beta power during encoding of correct and incorrect trials in caudate (*left*) and DLPFC (*right*). Caudate beta power was significantly lower for correct trials ($P = 0.0057$, $z = -2.8$), while DLPFC beta power was not significantly different between correct and incorrect trials ($P = 0.28$, $z = 1.1$). *$P < 0.05$. DLPFC = dorsolateral prefrontal cortex.

($P = 0.08$, $z = -1.8$ caudate and $P = 0.83$, $z = -0.22$ DLPFC) (Supplementary Figs. 2B and C). Caudate and DLPFC beta power decreases during working memory encoding were related to cognitive function, with cognitively impaired subjects having smaller beta power decreases during encoding compared to those with normal cognition ($P = 0.0053$, $z = 2.8$ caudate and $P = 0.00024$, $z = 3.7$ DLPFC) (Fig. 4A and B). Caudate and DLPFC beta power during feedback following correct trials was not different between patients with

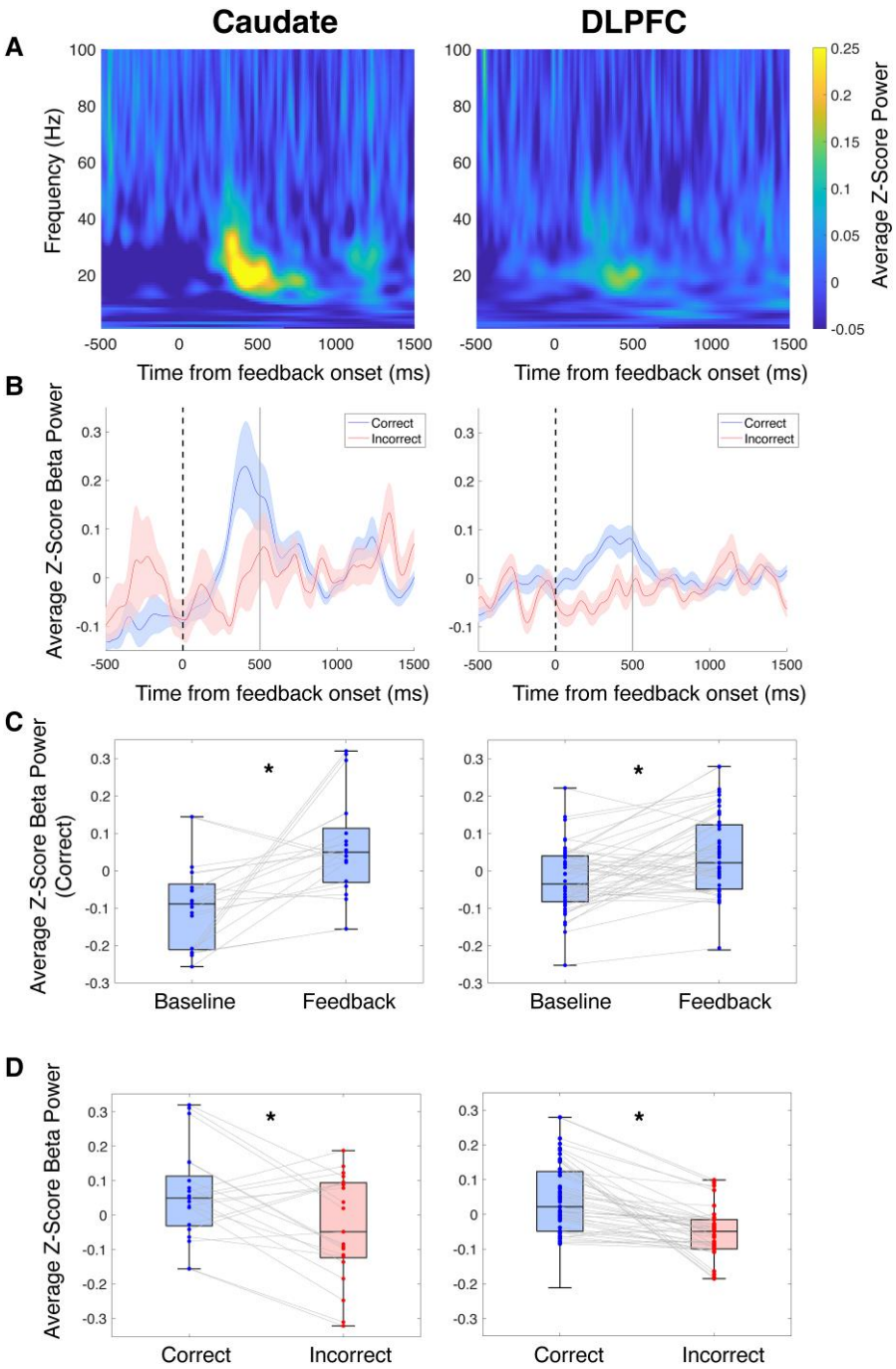

Figure 3 Caudate and DLPFC power during feedback. (**A**) Spectrograms of z-scored caudate (*left*) and DLPFC (*right*) power averaged over correct trials for all subjects, aligned to feedback onset. There was a significant increase in power during 500 ms of feedback for correct trials, centred in the beta band for both caudate (*left*) and DLPFC (*right*). (**B**) Time courses of average caudate and DLPFC beta power during feedback for correct and incorrect trials. Shading around the average line indicates standard error. Dotted line indicates feedback presentation onset and solid line indicates end of feedback period. (**C**) Box and whisker plots comparing average z-scored beta power at baseline and during feedback for correct trials in caudate (*left*) and DLPFC (*right*). Both caudate ($P = 0.0013$, $z = -3.2$) and DLPFC ($P = 0.00029$, $z = -3.6$ DLPFC) beta power significantly increased during feedback. Black line denotes median, box denotes interquartile range, whiskers denote range of minimum to maximum values (excluding outliers). Grey lines denote paired subjects. (**D**) Box and whisker plots comparing average z-scored beta power for feedback after correct and incorrect trials in caudate (*left*) and DLPFC (*right*). Both caudate ($P = 0.011$, $z = 2.6$) and DLPFC ($P = 1.2 \times 10^{-7}$, $z = 5.3$ DLPFC) beta power were significantly greater during correct trials. $^*P < 0.05$. DLPFC = dorsolateral prefrontal cortex.

cognitive impairment and patients with normal cognition ($P = 0.16$, $z = 1.4$ caudate and $P = 0.12$, $z = 1.5$ DLPFC) (Fig. 4C and D). Clinical and demographic metrics measured were not significantly different between cognitively impaired and normal cognition groups (Table 3).

Exploratory analysis of additional oscillatory frequency bands

In a secondary, exploratory analysis, we examined whether there was a relationship between resting-state or task-related oscillatory

Table 2 Summary of findings for beta power changes in caudate and DLPFC during encoding and feedback

	Caudate			DLPFC		
	Baseline	Task	Cognitive impairment	Baseline	Task	Cognitive impairment
Encoding	Beta power is higher at baseline than during encoding	Beta power is lower during encoding of correct trials than incorrect trials	Beta power during task encoding is lower for patients with normal cognition than for patients with cognitive impairment	Beta power is higher at baseline than during encoding	Beta power is not different for correct and incorrect trials	Beta power during task encoding is lower for patients with normal cognition than for patients with cognitive impairment
Feedback	Beta power is lower at baseline than during feedback	Beta power is higher during feedback of correct trials than incorrect trials	Beta power during task feedback is not different for patients with normal cognition than for patients with cognitive impairment	Beta power is lower at baseline than during feedback	Beta power is higher for correct trials than incorrect trials	Beta power during task feedback is not different for patients with normal cognition than for patients with cognitive impairment

power in delta, theta, alpha or gamma frequency bands and cognitive status. We also examined high and low beta frequency bands as previous studies have reported differences between high and low beta power as it relates to Parkinson's motor symptoms.[34,51-54]

Compared to patients with normal cognition, patients with CI exhibited significantly lower resting-state delta band spectral power ($P = 0.031$, $z = -2.8$, Bonferroni-corrected) in the caudate and significantly lower spectral power in the theta ($P = 0.0085$, $z = -3.2$, Bonferroni-corrected), alpha ($P = 0.020$, $z = -2.9$, Bonferroni-corrected) and low beta frequency bands ($P = 0.0059$, $z = -3.3$, Bonferroni-corrected) in the DLPFC (Fig. 5A). Caudate power was not significantly different between patient groups in the theta ($P = 0.22$, $z = -2.1$, Bonferroni-corrected), alpha ($P = 3.4$, $z = -0.57$, Bonferroni-corrected), low beta ($P = 0.90$, $z = -1.4$, Bonferroni-corrected), high beta ($P = 0.73$, $z = -1.6$, Bonferroni-corrected) or gamma frequency bands ($P = 0.22$, $z = -2.1$, Bonferroni-corrected), and DLPFC power did not significantly differ in the delta ($P = 2.1$, $z = -0.95$, Bonferroni-corrected), high beta ($P = 5.6$, $z = 0.094$, Bonferroni-corrected) or gamma ($P = 5.0$, $z = -0.22$, Bonferroni-corrected) frequency bands (Fig. 5A).

During working memory encoding, similar to the effects we observed in beta oscillations, we found that patients with CI had higher spectral power in alpha, low beta and high beta frequency bands in the caudate during working memory encoding, while in the DLPFC, CI was associated with higher power in theta, alpha, low beta and high beta frequency bands (Fig. 5B). In the caudate, time periods of significant difference were 200–1000 ms ($P = 0.0060$, Bonferroni-corrected) after stimulus appearance for alpha oscillatory power, 350–1000 ms ($P = 0.018$, Bonferroni-corrected) for low beta oscillatory power and both 500–730 ms ($P = 0.018$, Bonferroni-corrected) and 740–1000 ms ($P = 0.012$, Bonferroni-corrected) for high beta oscillatory power. In the DLPFC, a significant difference was seen from 250–1000 ms after stimulus appearance ($P = 0.0060$, Bonferroni-corrected) for theta power, 120–740 ms ($P = 0.012$, Bonferroni-corrected) for alpha power, 130–1000 ms ($P = 0.012$, Bonferroni-corrected) for low beta power and 210–1000 ms ($P = 0.0060$, Bonferroni-corrected) for high beta power. There were no time clusters during which delta or gamma power in either caudate or DLPFC differed between patients with CI and patients with normal cognition.

During the 500 ms feedback presentation period for correct trials, there were no time clusters during which caudate oscillatory power in any frequency band significantly differed between patients with and without CI. In the DLPFC, alpha oscillatory power was significantly higher for patients with CI compared to patients with normal cognition throughout the full feedback presentation period (0–500 ms) ($P = 0.012$, Bonferroni-corrected) (Fig. 5C).

Discussion

In this study, we report that the caudate and DLPFC exhibit decreases in the spectral power of beta oscillations during encoding and increases during feedback of a working memory task. We found that beta oscillatory power in these structures was altered in patients with CI, with cognitively impaired patients having attenuated caudate and DLPFC encoding-related beta oscillatory power decreases. In our secondary analysis, we found that these differences extended to alpha frequencies in the caudate and theta and alpha frequencies in the DLPFC. Patients with CI also exhibited significantly greater alpha oscillatory power in the DLPFC during feedback presentation for correct trials compared to patients with normal cognition. To our knowledge, this is the first study to report caudate and DLPFC oscillatory power changes in Parkinson's disease CI. These findings support a role for cognitive CSTC power changes in Parkinson's disease CI, similar to the beta power changes seen in parallel motor CSTC circuitry.

Beta oscillations are known to play a crucial role in movement planning and execution, decreasing during motor planning and movement and increasing following movement cessation.[13] In Parkinson's disease, decreased dopamine leads to increased beta oscillations in motor CSTC circuits and impairs this process, resulting in motor symptoms of rigidity and bradykinesia.[7,11,55-58] As the caudate is part of the cognitive striatum, decreased caudate volume and dopamine levels have been associated with CI in Parkinson's disease patients.[14,15] We report that Parkinson's disease patients with CI had greater caudate and DLPFC alpha and beta power during working memory encoding than those with normal cognition. Beta power was not correlated with reaction time and occurred before the cue appeared indicating which side button corresponded to a yes/no answer to allow the subject to plan motor response, suggesting that our findings are related to a cognitive rather than a motor process. Our findings support a role for cognitive CSTC circuit structure alpha and beta oscillations in working memory and alteration of this as a contributing factor to Parkinson's disease CI.

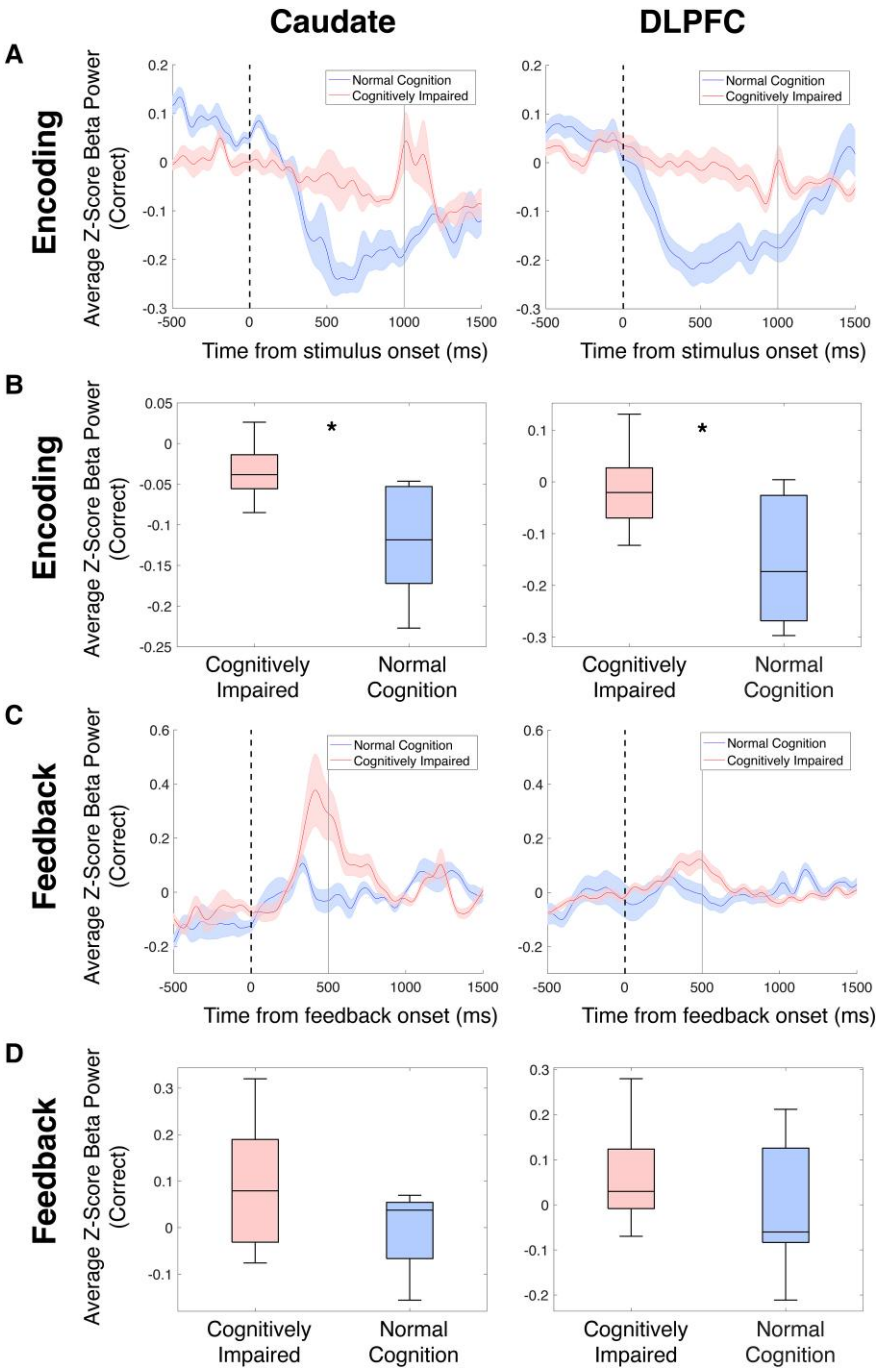

Figure 4 Caudate and DLPFC beta power is altered in patients with cognitive impairment. (**A**) Time course of caudate (*left*) and DLPFC (*right*) average z-score beta power during encoding for cognitively impaired (red) and normal cognition (blue) patients. (**B**) Box and whisker plots comparing caudate (*left*) and DLPFC (*right*) average z-score beta power during encoding (1000 ms word presentation period) for cognitively impaired (red) and normal cognition (blue) patients. Average beta power decreases during working memory encoding are significantly less for subjects with cognitive impairment ($P = 0.0053$, $z = 2.8$ caudate and $P = 0.00024$, $z = 3.7$ DLPFC). (**C**) Time course of caudate (*left*) and DLPFC (*right*) average z-score beta power after feedback for cognitively impaired (red) and normal cognition (blue) patients. (**D**) Box and whisker plots comparing caudate (*left*) and DLPFC (*right*) average z-score beta power during feedback (500 ms feedback presentation period) for cognitively impaired (red) and normal cognition (blue) patients. Average caudate and DLPFC beta power are not significantly different for subjects with cognitive impairment and subjects with normal cognition ($P = 0.16$, $z = 1.4$ caudate and $P = 0.12$, $z = 1.5$ DLPFC). *$P < 0.05$. DLPFC = dorsolateral prefrontal cortex.

Alpha and beta oscillations have also been shown to play an important role in cognitive functions such as executive control, working memory and attention in healthy subjects.[59] Primate studies have demonstrated that lateral prefrontal cortex beta oscillation bursting decreases during working memory encoding and increases following a task response.[39-41] Similarly, global alpha power has been shown to decrease during working memory encoding in human subjects.[60] Both alpha and beta power have been proposed to reflect a gating mechanism for information updating between the basal ganglia and prefrontal cortex, with suppression

Table 3 Demographic comparisons between cognitively impaired and normal cognition groups

	Cognitively impaired Mean ± SD (nine subjects)	Normal cognition Mean ± SD (six subjects)	Wilcoxon rank sum P-value
Age, years	64 ± 8	62 ± 5	0.94
Disease duration, years	7.8 ± 3	9.3 ± 3	0.44
UPDRS Score: OFF	48 ± 13	43 ± 12	0.55
UPDRS Score: ON	23 ± 14	17 ± 10	0.33
Levodopa equivalent dose	1421 ± 696	1387 ± 555	0.47
Caudate volume	0.41 ± 0.0	0.39 ± 0.04	0.27
Task performance (% correct)	72 ± 14	82 ± 5	0.36

SD = standard deviation.

allowing for encoding of new information in prefrontal cortex.[59,60] Our finding that caudate and DLPFC beta oscillation power decreases during working memory encoding suggests that these findings extend to humans and are also seen in the caudate, which, together with the DLPFC, comprises part of the cognitive CSTC circuit.

Non-invasive methods such as scalp EEG and magnetoencephalography have demonstrated widespread changes in oscillatory power in Parkinson's disease patients. At rest, global beta and gamma power have been reported to be higher in Parkinson's disease patients with mild CI but decreased in Parkinson's disease patients with dementia.[61,62] Increases in cortical spectral power of lower frequencies, including the delta and theta bands, have also been associated with both mild CI and dementia in Parkinson's disease patients.[61,62] We found that DLPFC resting-state low beta power was significantly lower for patients with mild CI. Resting-state spectral power in the delta band for the caudate and in the theta and alpha bands for the DLPFC was also significantly lower for cognitively impaired patients. The differences between our findings and those previously reported may be related to the mild degree of CI in our patient population who were all undergoing DBS, for which dementia is an exclusion criteria, or the specific anatomic regions we recorded from (caudate and DLPFC) compared to global cortical power values previous reported in scalp EEG studies. Parkinson's disease patients have also been shown to exhibit reduced global cortical alpha and beta power decrease during working memory encoding compared to healthy controls.[60,63,64] We found that Parkinson's patients with CI had smaller decreases in caudate and DLPFC alpha and beta power during working memory encoding than those with normal cognition, suggesting that these alpha and beta encoding related power changes previously reported in Parkinson's patients correlate with cognitive status and localize to specific anatomic structures.

Our observations of increased caudate and DLPFC beta power following task feedback are consistent with previous findings of caudate and DLPFC beta oscillation changes during cognitive processes.[42] Both caudate and DLPFC beta power have been shown to increase significantly following feedback for correct trials during an associative learning task, with DLPFC beta power correlating with learning over time.[42] In the present study, we similarly found beta power increased during feedback following correct but not incorrect trials, suggesting that this may be a reward-related signal. Dopamine is released in the caudate in response to reward,[65] and primate studies have shown that single neurons in both caudate and lateral prefrontal cortex encode reward prediction errors.[66] The increased beta power that we observed during correct feedback may be similar to a positive reward prediction error and was not associated with cognitive performance. We found that patients with CI had greater alpha power increases in DLPFC during feedback for correct trials, perhaps reflecting dysfunction of reward or motivational processes that may contribute to cognitive performance, though further study is needed to understand the etiology and significance of these findings.

While previous research has suggested that decreased caudate volume may be associated with Parkinson's disease CI[67-69] and lower caudate volume is linked with greater beta oscillatory power in motor CSTC structures,[70] we did not find any significant relationship between caudate volume and either task-based or resting-state caudate or DLPFC beta power or cognitive status in our patient population. We anticipated that caudate volume might be associated with beta power as our underlying hypothesis is that decreased dopaminergic input and increased atrophy contribute to altered beta oscillations. Our failure to detect a relationship may indicate that caudate atrophy does not contribute to altered beta oscillations. However, one limitation of our study population is that because it is confined to patients undergoing DBS surgery, the cognitive heterogeneity is somewhat limited, as patients with more severe CI or dementia are not candidates for DBS. It is possible that there is less variability in caudate volume in our patient population because of this, which contributed to our inability to detect a difference in caudate volume between patients with and without CI or a relationship between caudate volume and beta oscillations.

Understanding the neurophysiologic biomarkers and dynamics associated with Parkinson's disease CI may have implications for the development of neuromodulation interventions for patients with medically refractory Parkinson's disease and comorbid CI to improve quality of life and reduce disease-related mortality. Newer technological advancements in DBS devices allow for closed-loop adaptive or responsive stimulation, applying stimulation only at times when a designated biomarker is present, which prolongs battery life and minimizes stimulation-related side effects. Several device systems have closed-loop stimulation capabilities that leverage beta oscillations within GPI or STN to initiate onset and cessation of stimulation to improve Parkinson's disease motor symptoms.[71] Analogously, this closed-loop capability could be applied to cognitive CSTC circuit structures such as the caudate or DLPFC to improve Parkinson's disease cognitive symptoms. Other studies have reported some initial promise of DBS for memory enhancement with alternative targets such as mesial temporal lobe structures,[72] hypothalamus/fornix,[73] and nucleus basalis of Meynert.[74] Previous studies in primates and human epilepsy patients have suggested that specifically timed caudate stimulation may enhance learning.[42,75] STN and GPI stimulation have been shown to decrease beta oscillations with these decreases corresponding to improvement in motor symptoms.[34,36] Future studies are required to determine whether the stimulation related improvements in learning previously reported were similarly related to alterations in caudate beta power. Our results suggest that the caudate may be a neuromodulation target to consider for treating CI in Parkinson's disease patients, and that caudate alpha and beta and DLPFC theta, alpha and beta power changes may be biomarker candidates for the development of closed loop stimulation strategies to treat Parkinson's disease CI.

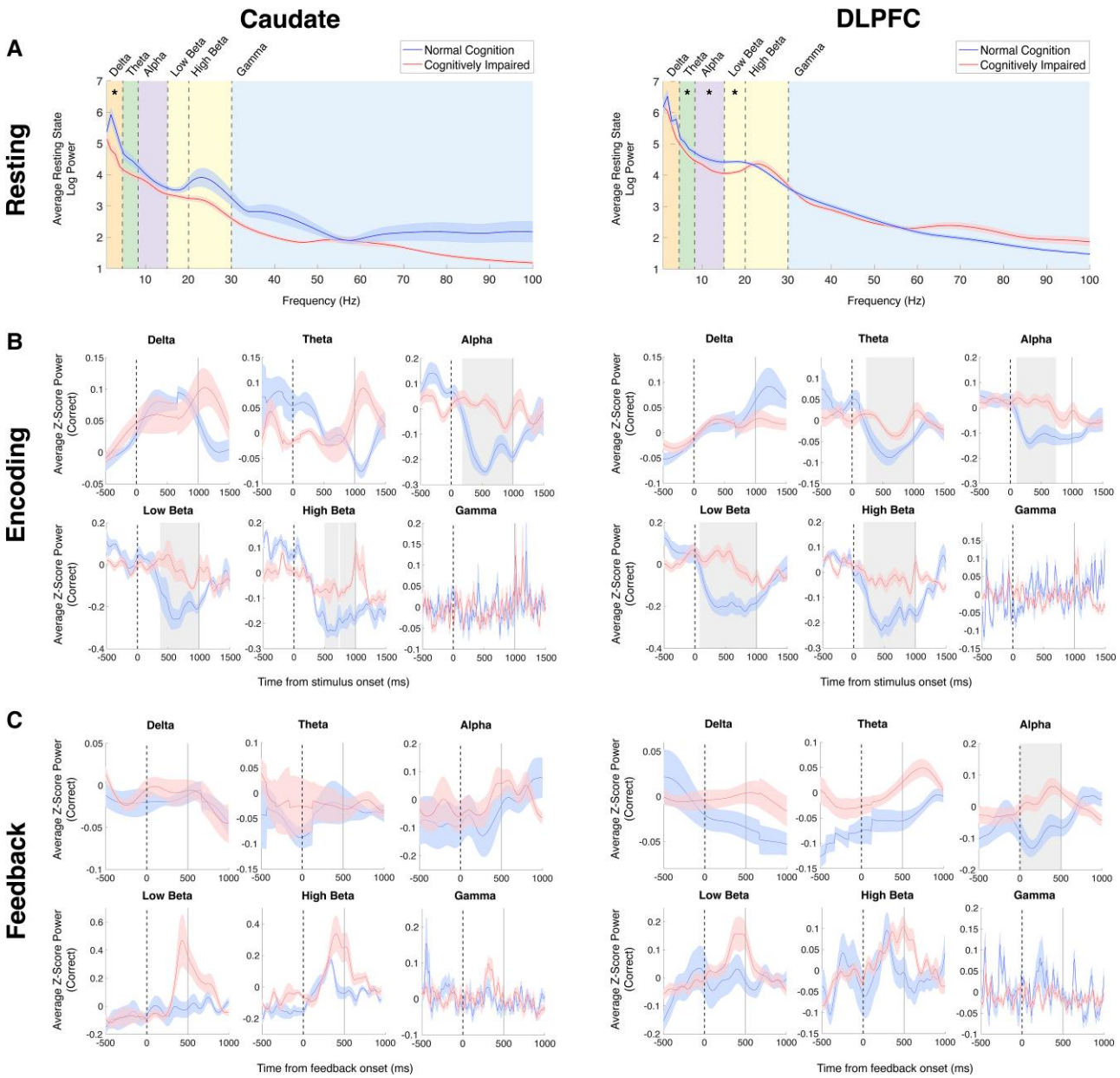

Figure 5 Caudate and DLPFC power in additional frequency bands. (**A**) Average caudate (*left*) and DLPFC (*right*) resting power (log-transformed by base 10) over 1–100 Hz for cognitively impaired (red) and normal cognition (blue) patients. Shading around the average line indicates standard error. Patients with cognitive impairment exhibited significantly lower average delta band spectral power ($P = 0.031$, $z = -2.8$, Bonferroni-corrected) in the caudate and significantly lower spectral power in the theta ($P = 0.0085$, $z = -3.2$, Bonferroni-corrected), alpha ($P = 0.020$, $z = -2.9$, Bonferroni-corrected) and low beta frequency bands ($P = 0.0059$, $z = -3.3$, Bonferroni-corrected) in the DLPFC. (**B**) Time course of caudate (*left*) and DLPFC (*right*) average z-score delta, theta, alpha, high beta, low beta and gamma power during encoding for cognitively impaired (red) and normal cognition (blue) patients. Grey shaded boxes indicate time clusters within the time window of interest where power was significantly different between patient groups ($P < 0.05$). Patients with normal cognition exhibited significantly lower caudate alpha power [$P = 0.0060$ (200–1000 ms)], low beta power [$P = 0.0018$ (350–1000 ms)] and high beta power [$P = 0.018$ (500–730 ms), $P = 0.012$ (740–1000 ms)] and significantly lower DLPFC theta power [$P = 0.0060$ (250–1000 ms), Bonferroni-corrected], alpha power [$P = 0.0012$ (120–740 ms)], low beta power [$P = 0.012$ (130–1000 ms)] and high beta power [$P = 0.0060$ (210–1000 ms)]. (**C**) Time course of caudate (*left*) and DLPFC (*right*) average z-score delta, theta, alpha, high beta, low beta and gamma power during feedback for cognitively impaired (red) and normal cognition (blue) patients. Grey shaded boxes indicate time clusters within the time window of interest where power was significantly different between patient groups ($P < 0.05$). Patients with cognitive impairment exhibited significantly higher DLPFC alpha power [$P = 0.012$ (0–500 ms)]. *$P < 0.05$. DLPFC = dorsolateral prefrontal cortex.

There are several limitations of our study. First, our sample size is relatively small with 15 patients, which limits the power of our study to detect differences between subgroups. There is no control group comparison to healthy subjects, which limits our ability to generalize these results outside of Parkinson's disease patients or to determine features of Parkinson's disease-specific CI. Furthermore, patients with severe CI are generally considered to be poor surgical candidates for DBS, which limits our ability to capture the entire clinical spectrum of Parkinson's disease CI. Lastly, patients are off all dopaminergic medications for surgery, which

may confound their neural signals as well as our ability to assess their 'native' cognitive state while on medications.[76,77]

Conclusion

Our findings demonstrate that caudate and DLPFC theta, alpha and beta oscillatory power changes occur during working memory and correlate with cognitive function in Parkinson's disease patients. These findings support a role for cognitive CSTC oscillatory power changes in Parkinson's disease CI and may inform the future development of novel treatment strategies for this disorder.

Funding

This work was supported by the Neurosurgery Research and Career Development Program (NRCDP) [NIH NINDS K12 NS080223] and the Mid-career Investigator Award in Patient-Oriented Research Program [NIH NIA 5K24AG064114]. H.Q. received funding from the Parkinson's Foundation [PF-SSF-940498] and the SyBBURE Searle Undergraduate Research Program.

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at Brain online .

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