Corticostriatal Beta Power Changes Associated with Cognitive Function in Parkinson's Disease

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Abstract

Cognitive impairment (CI) is the most frequent nonmotor symptom in Parkinson's Disease (PD) and is associated with deficits in executive functions such as working memory. Previous studies have demonstrated that caudate beta power underlies learning and working memory. Decreased dopamine in motor cortico-striato-thalamo-cortical (CSTC) circuits results in increased beta power and PD motor symptoms. Analogous changes in cognitive CSTC circuits, including the caudate and dorsolateral prefrontal cortex (DLPFC), may contribute to PD CI. A better understanding of anatomic structures and neurophysiologic changes associated with working memory deficits is needed to develop potential neuromodulatory treatment strategies for PD CI. The objective of our study is to evaluate neurophysiologic changes underlying cognitive dysfunction in PD patients via direct local field potential recordings during deep brain stimulation surgery. Fifteen patients were included, one of which only completed 2 minutes of resting state data collection while the other fourteen completed resting state collection and task based data collection with a verbal working memory 2-back task with feedback. LFP signals from DLPFC (50 channels) and caudate (25 channels) were sampled at 1000Hz, demeaned by channel and aligned to task events of encoding and feedback. Correlations of resting state beta power and pre-operative neuropsychological testing as well as caudate volumes were performed. Beta power decreased in both DLPFC and caudate during encoding and was significantly different for correct and incorrect trials, whereas beta power increased in DLPFC and caudate during feedback and was significantly different for correct and incorrect trials. Lower beta power during encoding correlated with better memory scores on pre-operative neuropsychological testing. Understanding neurophysiologic correlates of cognitive dysfunction within cognitive CSTC circuits will aid in development of novel neuromodulatory therapies for patients with PD CI and other cognitive disorders.

Introduction

Parkinson's disease (PD) is a movement disorder that affects approximately 1 million people in the US and 10 million people worldwide, the prevalence of which is expected to double by 2030 [1]. Although PD is predominantly considered a movement disorder with cardinal symptoms of bradykinesia, rigidity and tremor, the clinical spectrum of this disorder encompasses many non-motor symptoms, the most common of which is cognitive impairment (CI), present in approximately 9-19% of all PD patients within 2 years of initial diagnosis [2–4],

50% at 5-10 years after diagnosis [5,6], and up to 75% of patients at the time of death. PD CI is a major contributor to patient disability, ultimately decreasing quality of life and increasing disease-related mortality [7]. Current first line therapies for PD CI include behavioral therapy, acetylcholinesterase inhibitors and memantine, however further therapies beyond this are limited in number and efficacy. An improved understanding of the mechanisms of PD CI can aid in formulating effective, novel interventional treatment options, particularly with neuromodulation.

While the pathophysiology underlying motor symptoms in PD is well-studied, analogous mechanisms underlying PD CI are less understood and require further study. The striatum which includes the nucleus accumbens, caudate and putamen, is somatotopically organized into three parallel cortico-striato-thalamo-cortical (CSTC) circuits which contribute to motor, cognitive and limbic functions [8]. Dopamine related dysfunction in motor CSTC circuits leads to common cardinal motor symptoms of PD, notably reflected in beta range (15-30 Hz) neural signal oscillation changes [9–11]. However, dopaminergic effects on analogous cognitive CSTC circuits, in which the dorsolateral prefrontal cortex (DLPFC) and caudate are core structures, remain unclear. Structural imaging studies have demonstrated that caudate volume and dopamine levels directly correlate with the degree of PD CI [12,13]. Functional MRIs have demonstrated blood oxygen level dependent (BOLD) signal changes in cognitive CSTC regions with decreased caudate activation and decreased caudate-DLPFC connectivity in patients with CI [14,15], however the temporal resolution of this modality is limited and it is an indirect measure of brain activity. Previous human neurophysiologic studies have demonstrated caudate beta power changes associated with enhancements in learning and memory [16]. Direct neurophysiologic recordings allow for improved spatial and temporal resolution of functional networks, yet these recordings have not yet been leveraged to study PD CI and one of its primary domains, working memory.

Working memory is a vital human executive function, allowing us to store and update relevant information central to decision making. The purpose of the present study is to assess neurophysiologic changes related to deficits in cognitive impairment and executive function, specifically verbal working memory, via direct human local field potential recordings from cognitive CSTC circuit structures during deep brain stimulation (DBS) surgery. Our hypothesis is that dopamine-mediated dysfunction of the cognitive CSTC circuits will be reflected in beta power changes and contribute to working memory deficits. Ultimately, the goal of this neurophysiologic analysis is to better understand PD CI disease pathophysiology and thereby support development of novel interventional therapies, such as adaptive or responsive DBS.

Methods

Subject Selection

Fifteen PD patients who underwent awake DBS surgery of the subthalamic nucleus (STN) or globus pallidus internus (GPi) for treatment of primary motor symptoms participated in our study. All patients undergoing new DBS implantation, regardless of baseline cognitive status, were eligible to be included in our study and those who were agreeable provided written informed consent. Patients were excluded from the study if they declined participation and

channels were excluded from analysis if they were not within the targeted region on post-operative imaging or the signal was contaminated by significant artifact. This prospective study was reviewed and approved by the Vanderbilt University Medical Center Institutional Review Board prior to initiation. Demographic, behavioral, and clinical data from all subjects were collected from the electronic medical record and are reported in **Table 1**.

Surgical and Task Description

During the electrode implantation stage of DBS surgery, patients are kept awake to undergo clinical testing and research. A custom-made mini-stereotactic frame (FHC Inc., Bowdoin, ME) is mounted and microelectrodes with macrocontacts are implanted and advanced to a targeted cognitive CSTC structure (DLPFC or caudate) along the trajectory to the treatment target. This setup allows for bilateral simultaneous recordings collected via the FHC Guideline 5 system. At the initiation of the research component, two minutes of classic resting state local field potential (LFP) data was collected while subjects rested with their eyes closed [17]. Subjects subsequently participated in a verbal 2-back working memory task [18], during which they were prompted to determine if a word presented during the current trial matched the word presented two trials prior and were given feedback on correct or incorrect answer selections **(Figure 1)**. Subjects completed two 75-trial blocks of this task.

LFP data with a sampling rate of 1000 Hz was recorded from cognitive CSTC structures along the clinically planned electrode trajectory using single-channel recording microelectrodes with macrocontacts. Nine subjects had recording electrodes that traversed the caudate, and thirteen subjects had electrodes that traversed the cortex.

Preoperative Evaluation

All subjects received preoperative magnetic resonance imaging brain scans and underwent thorough preoperative motor and neuropsychological cognitive testing. Motor function on and off PD medications was graded by the Unified Parkinson's Disease Rating Scale (UPDRS). The neuropsychological battery included a test of premorbid functioning, the Montreal Cognitive Assessment (MoCA), the Wechsler Adult Intelligence Scale (WAIS) IV Digit Span Test, Trail Making Tests A and B, the Delis–Kaplan Executive Function System (D-KEFS) Color-Word Interference Test, the Action Fluency Test, the F-A-S Letter Fluency Test, the Animals Category Fluency Test, the Neuropsychological Assessment Battery (NAB) Naming Test (Form 1), the NAB Visual Discrimination Test (Form 1), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Line Orientation Test (Form A), the Rey Auditory Verbal Learning Test, and the Wechsler Memory Scale (Fourth Edition Logical Memory).

Data and Statistical Analysis

LFP analysis was performed offline via MATLAB (MathWorks, Natick MA). Data was bandpass filtered at 60 Hz to remove line noise, demeaned by channel, and aligned to task events

using digital event triggers. Beta range (15-30Hz) power was calculated with the Morlet wavelet time-frequency transformation in the Fieldtrip MATLAB toolbox (Oostenveld et al., 2011).

To analyze caudate and DLPFC power during the encoding and feedback periods of the working memory task respectively, we examined beta power during the 500-1000msec period after stimulus presentation and 250-750msec period after feedback presentation. We then analyzed the average caudate and DLPFC beta power from all subjects during these periods of interest for correct and incorrect trials.

Statistical analysis was also performed in MATLAB. We used the Wilcoxon signed-rank test to assess the mean beta power differences between correct and incorrect trials during encoding and after feedback. We also used the Wilcoxon signed-rank test to compare beta power during working memory encoding and feedback versus the 500 ms baseline period prior to stimulus and feedback onset, respectively.

To examine the relationship between beta power changes and cognitive function, we categorized each test from our pre-DBS neuropsychological assessment battery under the cognitive domains of executive function, attention, processing speed, memory, language, or visuospatial function. For each subject, we Z-scored and averaged assessment scores within each cognitive domain to create a domain-specific composite score.

We calculated the Pearson correlation coefficient to evaluate the significance of a linear correlation between each subject's composite cognitive scores across different domains and their beta power during working memory encoding and feedback. We also analyzed the correlation between subjects' composite cognitive scores and their average resting state beta power. We then calculated the Pearson correlation coefficient between each subject's caudate volume, normalized by intracranial volume (ICV), and their task-based and resting state beta power.

Lastly, we conducted a multivariate analysis using subjects' age, UPDRS Off score, Levodopa medication dosage, caudate volume, and either caudate or DLPFC beta power during resting state, task encoding, or task feedback in a normally distributed generalized linear model. We created six generalized linear models, and each model had beta power from a different alignment and structure as its final predictor variable. The response variable assessed was either subjects' composite scores in the memory domain or their performance on the 2-back task.

Results

Of the 15 subjects who participated in the study, 13 were male and 2 were female, 14 were right-handed and 1 was left-handed, 10 had bilateral STN implants and 5 had bilateral GPi implants. Mean age at time of surgery was 63±6.6 years (mean ± standard deviation), mean duration from PD diagnosis to surgery was 8.4±2.9 years, mean UPDRS off score of 45.8±12.0, mean UPDRS on score of 20.4±12.1, and mean Levodopa equivalent dose of 1407.9±601.2. Fourteen subjects completed both resting state data collection and the verbal working memory task, while one subject completed only resting state data collection. Across all subjects, 25 caudate and 50 DLPFC channels were included in the resting state analysis, while 21 caudate and 50 DLPFC channels were included in our task-based analysis. For the 14 patients that completed

the 2-back task, task performance was 75.8±11.7% correct, 21.2±8.7% incorrect, 3.0±4.3% unanswered. These findings are summarized in **Table 1** and **Figure 2**.

EVENT-RELATED BETA POWER CHANGES

During Encoding

Both caudate and DLPFC exhibited a decrease in beta power during working memory encoding 500 to 1000 ms following stimulus presentation for trials during which information was encoded correctly. We defined correct encoding trials as occurring two trials prior to a correct response. Average beta power during this period for correct trials was significantly lower than the average beta power during baseline [p=0.0026 and p=0.0039, respectively] (**Figure 3**). For incorrect encoding trials, this decrease was only significant in DLPFC [p=1.4E-06]. There was a significant difference between average beta power during correct and incorrect trials for both caudate and DLPFC [p=0.0051 and p=1.40E-04, respectively] (**Figure 4)**. In caudate, correct trials exhibited greater beta power decreases than incorrect trials, whereas the opposite was true for DLPFC.

During Feedback

In contrast, average caudate and DLPFC beta power increased significantly compared to baseline during the 250 to 750 ms following feedback presentation for trials where subjects responded correctly [p=0.0010 and p=0.0013] (**Figure 5**). This increase was not seen following feedback for incorrect trials. There was a significant difference between average beta power of correct and incorrect trials in both caudate and DLPFC during this period [p=1.1E-04 and p=6.8E-05] (**Figure 6)**. For both caudate and DLPFC, average beta power exhibited greater increases after correct trials than after incorrect trials.

WITHIN-GROUP CORRELATIONS WITH BETA POWER

We found a significant negative correlation between the minimum of each subject's caudate beta power during encoding for correct trials and memory function, as measured by composite cognitive scores in the memory domain [r =-0.97, p=9.1E-05], with a greater decrease in beta power corresponding with better memory function (**Figure 7)**.

DLPFC beta power during encoding did not exhibit a significant linear relationship with memory function. Neither caudate nor DLPFC beta power during encoding exhibited a significant relationship with subjects' task performance or with cognitive function in domains outside of memory.

Peak caudate beta power during task feedback exhibited a significant negative correlation with language function [r= -0.70, p=0.03], indicating that a greater increase in beta power following task feedback correlated with worse cognitive function in the language domain. DLPFC beta power during feedback was not significantly associated with cognitive function in any domain. Likewise, there was no significant relationship between task performance and either caudate or DLPFC beta power during feedback.

Average caudate and DLPFC resting state beta power exhibited no correlation with cognitive function or task performance. There was also no correlation between caudate and DLPFC resting state beta power and beta power during either encoding or feedback. For both caudate and DLPFC, we found no significant relationship between reaction time and beta power during resting state, task-based encoding, or task-based feedback. We also found no significant correlation between caudate volume and either caudate or DLPFC beta power during resting state, task encoding, or task feedback.

MULTIVARIATE ANALYSIS

Our generalized linear models showed that there was a significant linear relationship between the minimum of each subject's caudate beta power during encoding for correct trials and memory function [p=0.031]. However, the relationship between DLPFC beta power during encoding for correct trials was not significant, and there was also no linear relationship between task performance and either caudate or DLPFC beta power during encoding.

Age, UPDRS Off score, Levodopa medication dosage, and caudate volume did not have a significant linear relationship with either memory function or task performance when evaluated together with task-based caudate or DLPFC beta power as a predictor variable.

However, when caudate resting state beta power was used as a predictor variable, we found a significant linear relationship between task performance and UPDRS Off score, Levodopa dosage, and caudate volume, and caudate resting state beta power [p=0.031, p=0.031, p=0.029, and p=0.015, respectively].

The significance of this linear model was not replicated when DLPFC resting state beta power was used as a predictor variable for task performance. Neither DLPFC nor caudate resting state power as a predictor variable created models with any significant linear relationships with memory function. Age did not show a significant linear relationship with memory function or task performance in any of the multivariate analyses performed.

Discussion

Analysis of task event-related caudate and DLPFC beta power changes showed that beta power in both structures decreased during working memory encoding for correct trials and peaked shortly after task feedback during correct trials. We found that greater beta power suppression in the caudate during encoding correlated with better memory function, while higher beta power following task feedback correlated with greater impairment in the language domain. There was no correlation between resting-state beta power and cognitive impairment or task performance in either the caudate or DLPFC.

Elevated cortical and basal ganglia beta synchrony has been shown to be a biomarker of PD [8,19], with research on both human subjects and animal models indicating that dopamine depletion leads to pathologic increases in resting-state beta power [20,21,22,23]. Beta power has been proposed to indicate the active maintenance of a "status quo" state of neuronal activity [19,24,25], and decreased beta power has been shown to play a crucial role during movement planning and

execution [26]. While the link between elevated beta power in PD and motor symptoms of rigidity and bradykinesia has been well-documented, beta power has also been shown to be involved in cognitive functions such as executive control, working memory, and attention [24]. Widespread abnormalities in beta band oscillations have also been shown to characterize PD CI, with PD subjects with CI having higher resting-state beta and gamma (30-100 Hz) power compared to PD subjects without CI [27].

Our findings confirm previous research on the relationship between cortical beta neural oscillations and working memory encoding. Primate studies demonstrated that DLPFC beta bursting decreased during working memory encoding and increased following a task response [28–30], suggesting that beta suppression is necessary for information encoding and that elevated beta activity correlates with a working memory content being cleared out or reallocated once stored information is no longer needed [24]. Compared to healthy controls, PD subjects have been shown to exhibit both impaired memory strength and reduced global beta power decrease during deep-semantic encoding of a verbal working memory task [31]. Within the PD subject group, greater beta power suppression in left frontal regions correlated with greater memory strength [31]. Although there is evidence that event-related beta suppression is involved in the planning and execution of motor tasks[32], we found no relationship between reaction time and either caudate or DLPFC beta power during encoding. Thus, the beta power suppression we observed during encoding is likely a feature of cognitive function instead of motor action.

While most previous research on the role of beta neural oscillations during working memory focuses on cortical beta activity, our results show that caudate beta power suppression during encoding of correct trials exhibits a stronger correlation with cognitive impairment in the memory domain than DLPFC beta power. This supports that PD cognitive impairment results from the dysfunction of cognitive CSTC circuitry and provides evidence that the striatum gates information to the DLPFC by modulating disinhibition of excitatory CSTC loops [33]. Computational models have demonstrated that beta power in the basal ganglia can be generated by inhibitory striatal input to the globus pallidus externus (GPe) or excitatory cortical and subcortical inputs to the STN [24,34]. Drug-naive PD patients exhibit transient underactivation of caudate nuclei, putamen, and globus pallidus during working memory updating [35]. Although no changes in activation were observed in the DLPFC, basal ganglia under-recruitment disrupts striatal D2-dependent gating mechanisms to cortical regions and contributes to executive and cognitive dysfunction [35].

Our observations of increased caudate and DLPFC beta power following task feedback are also consistent with previous research into the role of caudate and DLPFC beta power during reinforcement learning [16]. Both caudate and DLPFC beta power have been shown to increase significantly following feedback for correct trials during a learning task, with DLPFC beta power correlating with learning over time [16]. There is evidence that caudate dopamine binding correlates with learning-related activation in the DLPFC, which then allows for DLPFC to optimize task performance [36]. However, the correlation we found between language impairment

and caudate beta power following correct trial feedback suggests that caudate beta power in this case may not be directly attributable to successful reinforcement learning.

Understanding of the neurophysiologic biomarkers and dynamics associated with PD CI can clinically translate into development of neuromodulation interventions for patients with medically refractory PD 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 certain designated biomarker is present, which prolongs battery life and minimizes stimulation-related side effects. The Medtronic Percept PC system has closed-loop stimulation capabilities that leverage beta power peaks within GPi or STN, noted to correlate with PD motor symptom severity, to initiate timing and cessation of stimulation [37]. Analogously, this closed-loop capability could be applied to cognitive CSTC circuit structures such as the caudate or DLPFC with electrodes that span both motor and cognitive targets. Other studies have reported efficacy of DBS for memory enhancement, although with alternative targets such as mesial temporal lobe structures [38] and the hypothalamus/fornix [39]. However, the efficacy of targeting cognitive CSTC structures for memory improvement in CI patients remains to be determined.

There are several limitations of our study worth mentioning. First, our sample size is small with 15 patients and 75 channels total, which limits the power of our study. Additionally, channels with significant artifact or channels out of the target region on post-operative imaging were excluded, which leads to inevitable selection bias. There is no control group of healthy subjects, which limits our ability to generalize these results outside of PD patients or to determine features of PD-specific CI. We also limited our analysis to the beta band given prior research demonstrating its value in PD motor symptoms, learning, and memory. Furthermore, LFPs have inherent limitations in spatial resolution of neural signaling and could be improved with single unit recordings.

Future directions of this work may include analysis of power changes in other frequency bands such as gamma, as gamma bursting has also been implicated in working memory and is thought to inversely correlate with beta bursting [28–30]. Other analyses of beta band activity, such as beta burst rate, beta coherence, and beta-gamma phase-amplitude coupling, could be performed to further examine the role beta oscillations play in CSTC circuitry. Higher resolution recordings could also be pursued with single unit recordings. Neurophysiologic analyses could be paired with functional neuroimaging to pair structural and functional connectivity.

Conclusion

Dopaminergic depletion in PD leads to altered neurophysiology within the cognitive CSTC circuit structures such as the caudate and DLPFC, which may contribute to working memory deficits and PD CI. Understanding of neurophysiologic correlates of PD CI can inform development of novel neuromodulatory interventions for medically refractory PD patients with comorbid CI.

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Tables/Figures

Table 1 - Patient Demographic and Disease Related Information

Patient Number	Age (years)	Sex	Race	Handedness	Duration of Disease (years)	Target	Caudate Channels	Cortex Channels	UPDRS score - off	UPDRS score - on	Levadopa equivalent dose
1 (0001)	56	M	White	Right	5	STN, bilateral	2	3	49	30	1400
2 (0002)	*68*	*M*	*White*	*Right*	*9*	*STN, bilateral*	*4*	*0*	*35*	*9*	*800*
3 (0006)	62	M	White	Right	9	STN, bilateral	3	2	53	28	1240
4 (0008)	60	F	White	Right	11	STN, bilateral	3	3	49	35	1600
5 (0014)	58	M	White	Right	11	STN, bilateral	0	6	60	5	2450
6 (0017)	62	M	White	Left	5	STN, bilateral	2	3	41	10	2050
7 (0021)	56	M	White	Right	6	STN, bilateral	2	3	71	N/A	100
8 (0023)	64	M	White	Right	8	STN, bilateral	2	3	30	2	1900
9 (0026)	60	M	White	Right	7	STN, bilateral	3	0	32	24	1200
10 (0028)	66	M	White	Right	9	GPI, bilateral	0	6	44	28	500
11 (0029)	56	M	White	Right	15	GPI, bilateral	0	5	47	25	1300
12 (0030)	57	M	White	Right	5	GPI, bilateral	0	5	33	12	1945
13 (0032)	76	M	White	Right	9	GPI, bilateral	2	3	60	45	2000
14 (0034)	67	M	White	Right	5	STN, bilateral	2	3	30	10	1333.34
15 (0038)	77	F	White	Right	12	GPI, bilateral	0	5	53	23	1300
Total/Avg	63.0	13M/2F	White	14R/1L	8.4	10STN/5GPI	25	50	45.8	20.4	1407.9

Figure 1 - Depiction of 2-back Verbal Working Memory Task

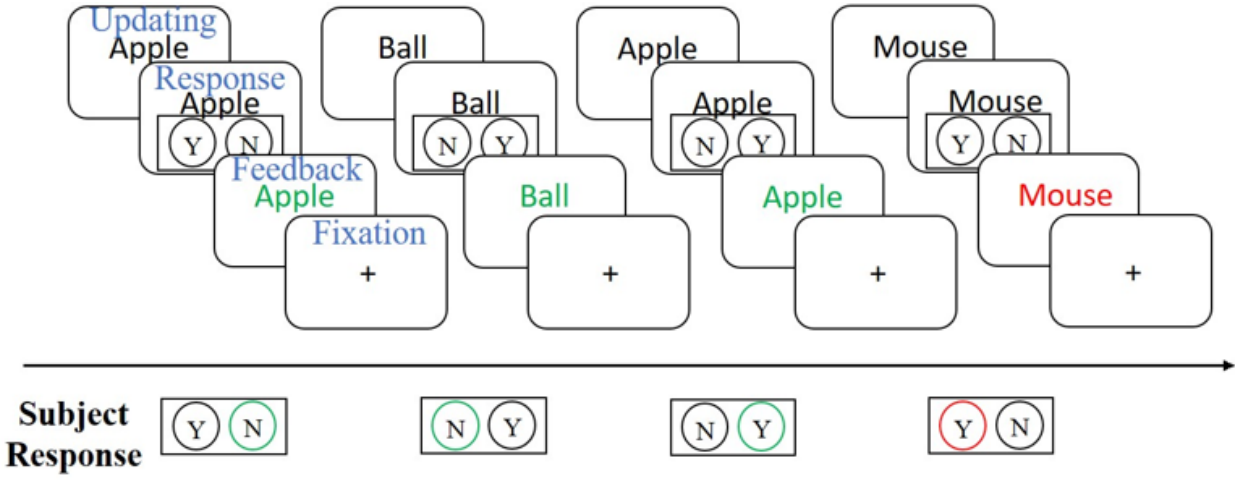

Fig 1: 2-back working memory task. The subject will be presented with a word, and after a pause a response cue will appear prompting the subject to answer whether the current word matches that from 2 trials prior. Following the response visual feedback will be presented. Green represents correct response, red represents incorrect response. Y=yes, N=no

Figure 2 - Task Performance Per Patient

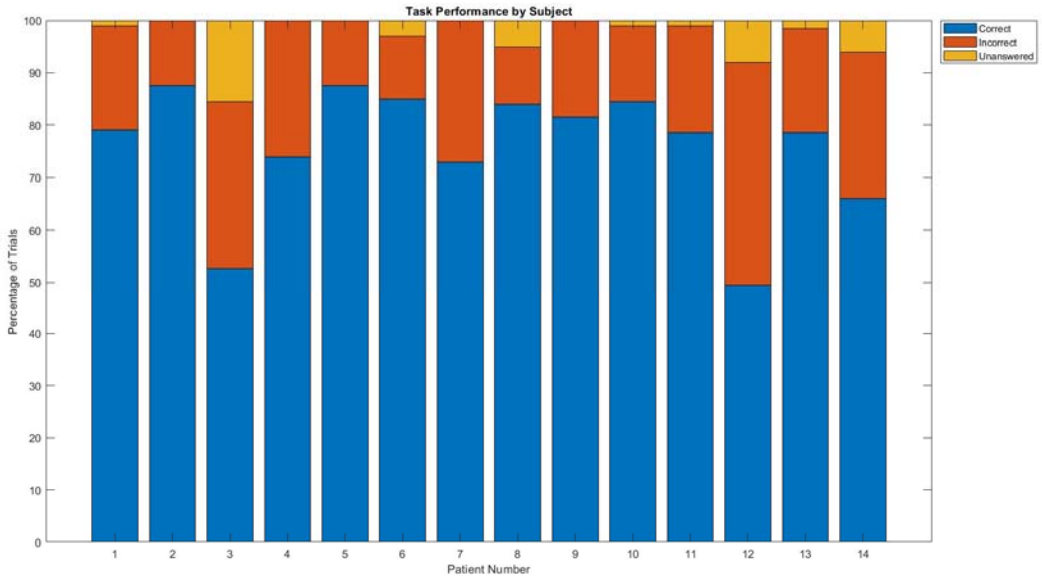

Figure 3 - Caudate and DLPFC Beta Power After Correct Encoding Trials Compared to Baseline

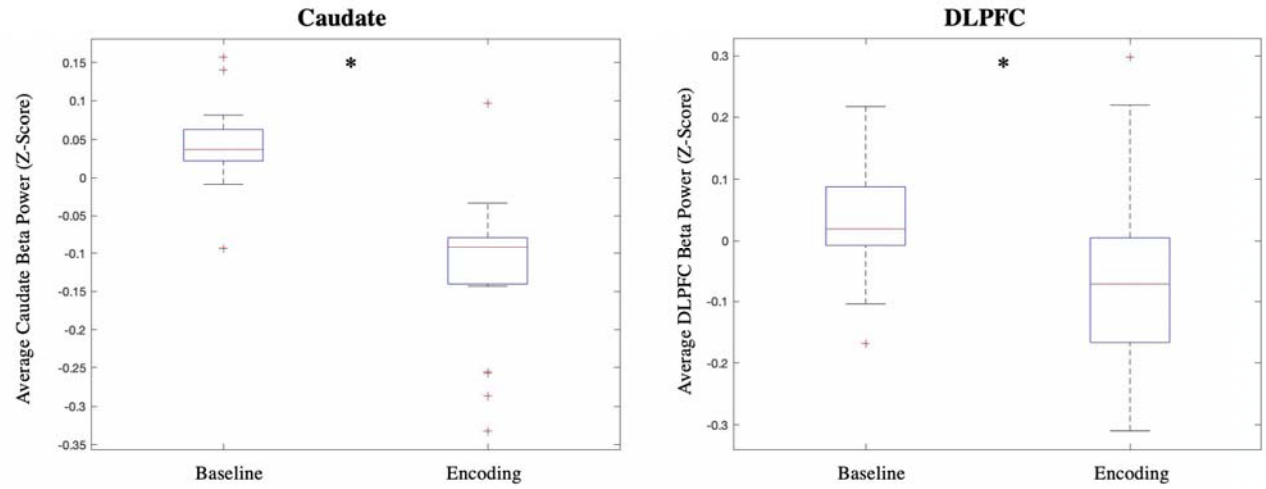

Figure 4 - Caudate and DLPFC Beta Power Line Graphs After Encoding for Correct vs Incorrect Trials and Spectrograms per Channel after Correct Trials

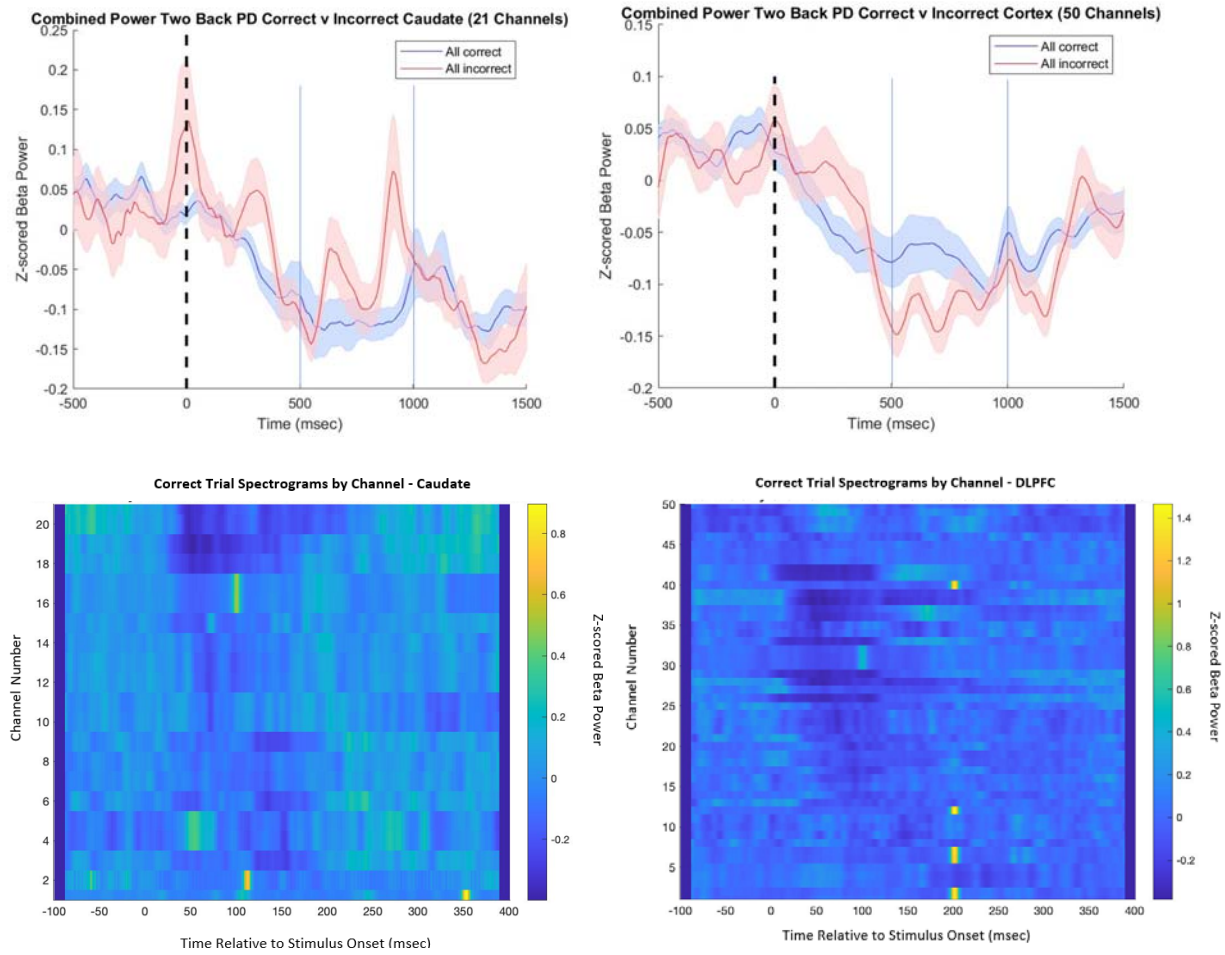

Figure 5 - Beta Power After Feedback Compared to Baseline

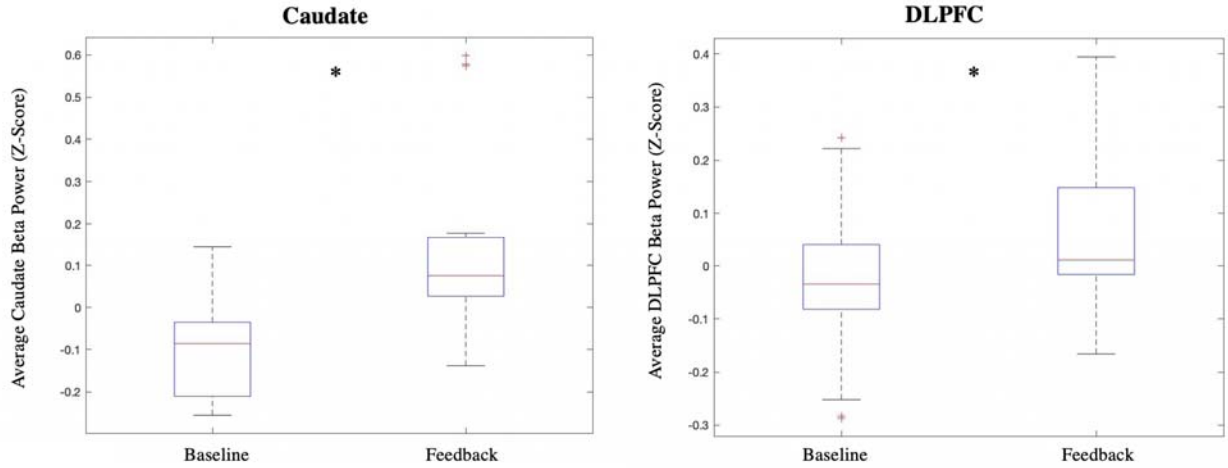

Figure 6 - Caudate and DLPFC Beta Power After Feedback for Correct vs Incorrect Trials

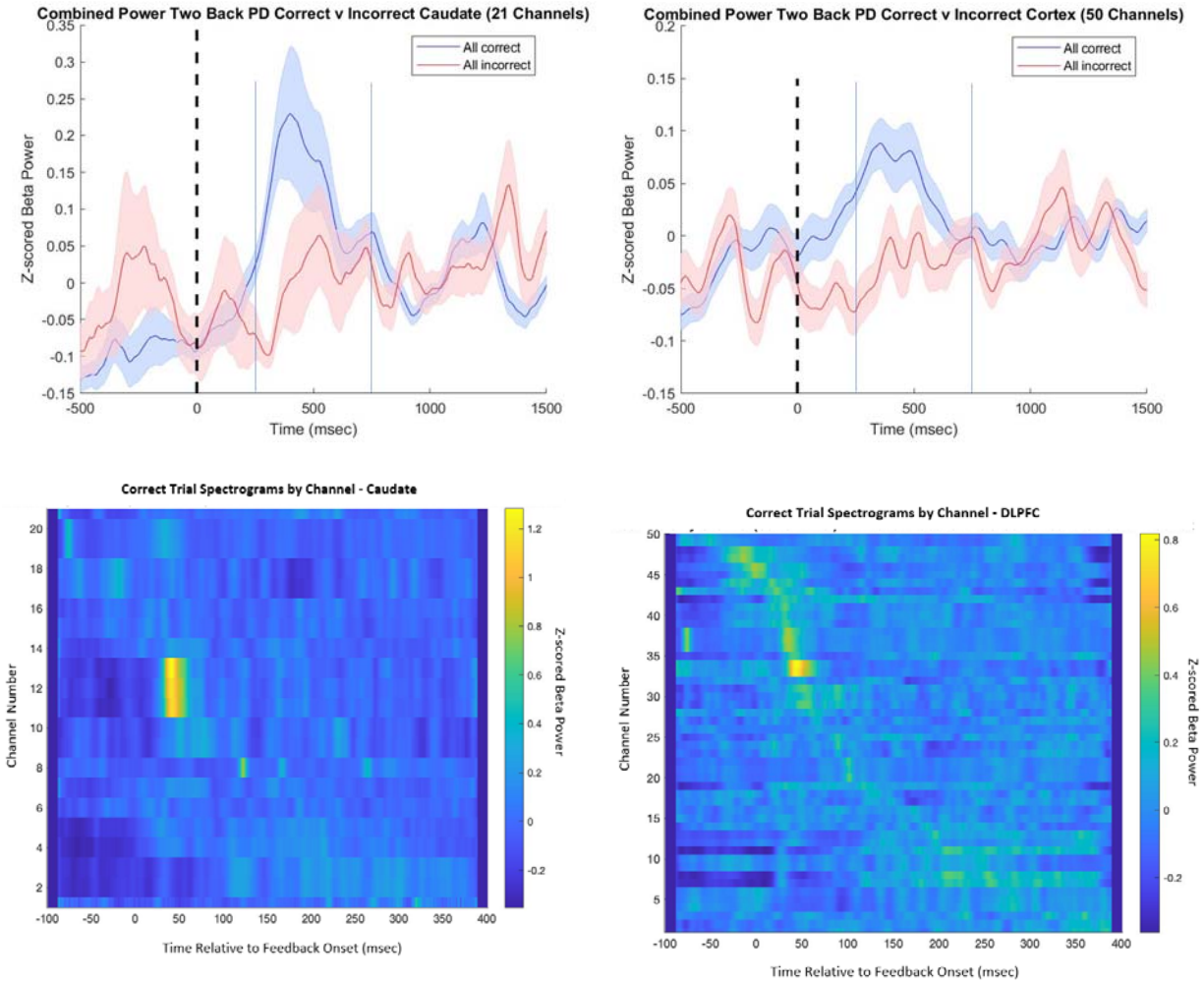
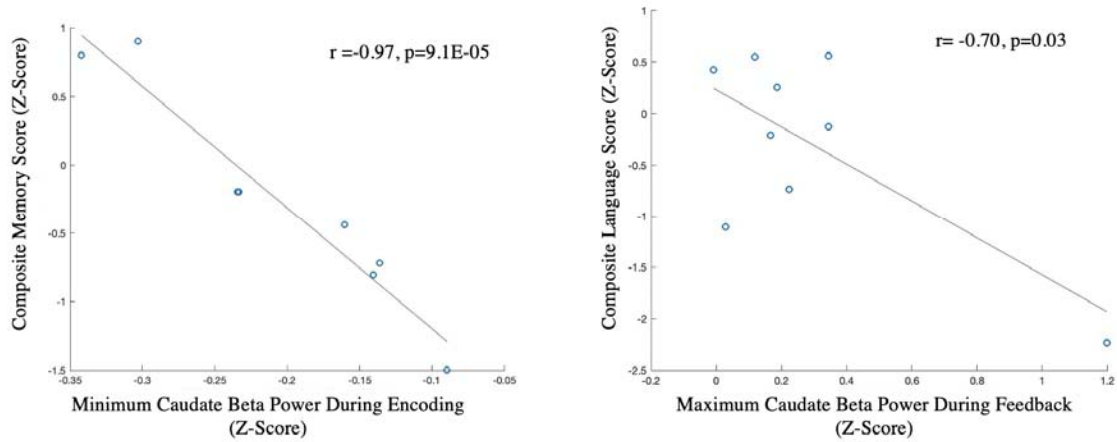
Figure 7 - Correlations of Caudate Beta Power and Cognitive Function