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Altered prefrontal theta and gamma activity during an emotional face processing task in Parkinson's disease

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ABSTRACT

Parkinson's disease patients often experience non-motor symptoms including cognitive deficits, depression, and anxiety. Cognitive and affective processes are thought to be mediated by prefrontal cortico-basal ganglia circuitry. However, the topography and neurophysiology of prefrontal cortical activity during complex tasks are not well characterized. We used high-resolution electrocorticography in the prefrontal cortex of Parkinson's disease and essential tremor patients, during implantation of deep brain stimulator leads in the awake state, to understand disease-specific changes in prefrontal activity during an emotional face processing task. We found that Parkinson's patients had less task-related theta-alpha power and greater task-related gamma power in the dorsolateral prefrontal cortex, inferior frontal cortex, and lateral orbital frontal cortex. These findings support a model of prefrontal neurophysiological changes in the dopamine-depleted state, in which focal areas of hyperactivity in prefrontal cortical regions may compensate for impaired long-range interactions mediated by low frequency rhythms. These distinct neurophysiological changes suggest that non-motor circuits undergo characteristic changes in Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is a movement disorder that is also characterized by non-motor symptoms, such as cognitive deficits, depression, and anxiety . These non-motor symptoms are an integral component of the disease itself, comprising the prodromal stage and advancing with disease progression . A specific deficit in affective and cognitive functioning is the impaired ability to recognize emotional face images . However, neural activity during ~~and~~ emotional face recognition tasks remains poorly understood.

Unlike non-motor circuits, the physiology of motor networks in PD have been studied extensively. High spatio-temporal resolution human brain recording techniques have informed the "oscillatory model" of the Parkinsonian hypokinetic phenotype . This model posits that cardinal motor signs of PD are related to changes in oscillatory synchronization within and between structures in the motor network. Electrocorticography (ECoG) and subcortical local field potential (LFP) recordings have been implemented acutely during deep brain stimulation (DBS) surgeries to study canonical motor regions . These methods have the capability of assessing low frequency rhythms important for inter-region communication , as well as broadband high frequency activity that assays local cortical activation at very fast time scales . However, these tools have not yet been widely applied to the study of non-motor circuits in PD.

Here we utilized high-resolution ECoG over lateral prefrontal and orbitofrontal regions, in patients undergoing surgery for DBS lead implantation in the awake state, to understand disease-specific changes in prefrontal cortical activity during an emotional face processing task. The prefrontal cortex is thought to be involved in cognitive and affective processes, including the appraisal of emotional stimuli . In order to determine whether PD is characterized by distinct prefrontal physiology during a complex task, we compared PD patients to a cohort of ET patients. While essential tremor is also associated with psychiatric and other non-motor symptoms , they are generally milder than in PD and are unlikely to be connected to dopamine

depletion. We found that PD patients had less task-related theta-alpha and more gamma activity during an emotional face processing task, suggesting prefrontal neurophysiological changes characteristic of the dopamine-depleted state.

MATERIALS AND METHOD

Subjects

Subjects with idiopathic PD or ET were recruited from the University of California San Francisco or the San Francisco Veterans Affairs Medical Center. Diagnoses were confirmed by movement disorders neurologists, and motor evaluations were conducted prior to DBS surgery using the Unified Parkinson's Disease Rating Scale (UPDRS) for PD patients. All PD patients had neuropsychiatric evaluations conducted by a psychiatrist or clinical psychologist as a part of routine clinical care. Inclusion criteria for PD patients included: primary rigid-akinetic motor phenotype, UPDRS-III $\geq$ 30, and motor fluctuations on vs. off dopaminergic medications. Inclusion for ET patients included tremor that was inadequately responsive to medication. All patients consented to have a temporary, subdural ECoG strip placed intraoperatively, during their DBS surgeries, on the prefrontal cortex for research purposes. All patients provided informed consent prior to surgery, per protocol approved by the Institutional Review Board.

DBS and ECoG placement

PD patients had DBS electrodes targeted to the STN or globus pallidus internus (GPi) and ET patients had DBS electrodes placed in the thalamic ventralis intermedius. DBS electrodes were placed under standard surgical protocol . A temporary, high-resolution, subdural ECoG strip (Ad-tech, Racine, WI) was inserted through the same burr hole used for DBS implantation . The 28-contact ECoG strip consisted of 2 rows of 14 contacts, and each contact was 1.2 mm in diameter, spaced 4 mm center-to-center. The strip was targeted to one of three prefrontal regions: dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), or inferior frontal cortex (IFC). For unilateral DBS patients, the ECoG strip was placed ipsilateral to the DBS electrode, and for bilateral DBS patients, ECoG was placed over the hemisphere contralateral to the first side implanted with a DBS lead. Targeting and placement were guided by surgical planning software (Medtronic Framelink v5.1, Minneapolis, MN), which provided image guidance with intraoperative CT fused to the preoperative MRI.

Electrode localization

Postoperative image analyses were performed to localize each ECoG contact. FreeSurfer was used to reconstruct cortical surface models from the preoperative T1 MRI, and then the individual cortical surfaces were fit to the Desikan-Killiany atlas brain to generate cortical anatomy labels . The *img_pipe* toolbox was used to fuse the intraoperative CT and preoperative MRI, project ECoG contacts onto the cortical surface mesh, and obtain the anatomic locations of each ECoG contact . We implemented an electrode projection method using surface vectors , which visually minimized the distortion of projected strip electrodes and improved estimates of electrode location. Code for imaging analyses can be found at https://github.com/MichaelLebrand/img_pype.

Emotional face processing task
Subjects performed Tap That Emotion (Posit Science, San Francisco, CA), an emotional go/no-go task developed for the iPad (Apple, Cupertino, CA) (Figure 1). Six patients performed the task before DBS lead insertion and 6 patients after DBS lead insertion. An iPad was positioned 2 feet in front of the subject, and patients were presented with 50-100 images of emotional face images. 40% of trials were happy faces, 40% were sad faces, and 20% were neutral faces. Trial order was randomized. Subjects were instructed to identify the emotion type for each image and to respond as follows: for happy and sad faces, press a button on the iPad, and for neutral faces, withhold movement. Images were presented for 500 ms, with a variable inter-trial interval between 500 and 1500 ms. The maximum period for response was 1000-2000 ms before the trial timed out. Of note, this task was designed to be easily and quickly performed in the stressful environment of the operating room, not to maximally challenge the subject with difficult or subtle distinctions.

Signal recordings
ECoG potentials were recorded on the Neuro Omega (Alpha Omega, Nazareth, Israel) or the TDT PZ5 (Tucker Davis Technologies, Alachua, FL) acquisition systems. The Neuro Omega signals are recorded at a 22 KHz sampling rate and 0.075-3500 Hz bandpass filtered. The TDT signals are recorded at 3 kHz and 0.45-1350 Hz bandpass filtered. All ECoG potentials were recorded referenced to an ipsilateral scalp needle, which was placed subcutaneously over the vertex.

Neural data analysis
Custom MATLAB scripts were used to analyze electrophysiology data. Task-related data were downsampled to 1000 Hz. Spectral power at rest was calculated using the Welch periodogram method (MATLAB function pwelch) using a Fast Fourier Transform of 512 points. Task-related spectrograms were generated using wavelets . In a single patient, ECoG potentials for each channel were filtered with Gabor Wavelets into 128 center frequencies ranging from 2.5-250 Hz. Epochs of data were time-locked to the image onset (for emotional face task) or go/no-go cue presentation (for go/no-go task) of each trial, and all epochs were averaged. Each frequency in the spectrogram was baseline corrected by subtracting the average power of the 500 ms preceding the cue, corresponding to the inter-trial interval. Spectrograms were z-score normalized with bootstrapping. First, a distribution of 10,000 surrogate spectrograms were generated using permutations of the task spectrograms at random time points. Then, each point on the task spectrogram was transformed into a z-score using the mean and standard deviation generated from the surrogate spectrogram distribution. Within patients, an average spectrogram per anatomic region was calculated by averaging all contacts within the same region. All trial types (happy, sad, and neutral face images) were included. Grand averaged spectrograms were generated by averaging patients. To quantify task-related power, the average value of task-related power from image onset (0 ms) to the mean reaction time for all patients was calculated for the following frequency ranges: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), low gamma (30-50 Hz), and high gamma (50-150 Hz).

Statistical Analyses

Factorial analyses of variance (ANOVA) were performed to compare task-related power between disease groups and between anatomic regions. Post-hoc Bonferonni tests were conducted for pair-wise comparisons. A Bonferonni corrected p-value <0.05 was considered statistically significant for grouped data.

RESULTS

Subjects

Twelve patients were enrolled in this study: 7 PD (3 male/4 female) and 5 ET (4 male/1 female) subjects (Table 1). The mean age of the PD and ET patients were 61.7 ± 10.0 years and 69.0 ± 6.4 years, respectively. The average disease duration for PD patients was 8.1 ± 4.6 years and for ET patients was 35.0 ± 12.8 years. Four out of 7 PD subjects and 2 out of 5 ET subjects were prescribed medications for psychiatric symptoms (Table 1).

ECoG potentials were recorded from the right hemisphere in 7 patients and from the left hemisphere in 5 patients. A total of 300 ECoG electrodes covering the frontal lobe were analyzed (Table 1; Fig 2a). Forty one electrodes were on the IFC pars triangularis, 56 electrodes on the IFC pars orbitalis, 167 electrodes on the superior frontal gyrus (dlPFC), and 36 electrodes on the lateral OFC. In 4 subjects, a total of 36 channels were not included in the analyses due to electrical noise or equipment failure during recording.

PD patients have reduced prefrontal theta-alpha and increased prefrontal gamma activity during an emotional face processing task

Behaviorally, PD and ET patients performed similarly on the emotional face processing task. Mean reaction times for PD and ET patients were and 968 ± 287 ms and 1139 ± 201 ms, respectively, and mean task accuracy was 72 ± 14% and 72 ± 16% respectively. There were no statistical differences in reaction time (Wilcoxon rank sum, p=0.27) or task accuracy (Wilcoxon rank sum, p=0.96) between the two groups. We compared ECoG potentials between PD and ET patients at rest and during the emotional face processing task (Fig 2b,c). At baseline during rest, there were no differences in prefrontal spectral power in any frequency range (Wilcoxon rank sum; Fig 3a). To compare task-related cortical physiology between the two groups, we computed the grand averaged spectrograms time-locked to cue presentation. We quantified task-related activity per frequency band from cue presentation to all patients' average reaction time, 1039 ms. PD patients have lower task-related low frequency activity in the theta band ($F(1,21)=5.87$, $p=0.0246$; Figure 3b,c) and alpha band ($F(1,21)=4.75$, $p=0.0409$; Figure 3b,c). PD patients also had greater task-related prefrontal high gamma than ET patients ($F(1,21)=4.73$, $p=0.0412$; Figure 3b,c). The main effect was driven by disease, and there were no significant interactions between disease and cortical location in any frequency range. We assessed whether the task-related high gamma had a topographic focality in the prefrontal cortex. We found that task-related high gamma was not restricted to individual contacts of the 28 contact strip and occurred over a broad cortical region (Fig 3d).

We then assessed whether there were differences in prefrontal cortical physiology in response to the different emotional valences of the stimuli. We generated spectrograms for happy, sad, and neutral images per subject, and then averaged subjects together for the valence-specific grand spectrograms. To control

for the differences in trial numbers per trial type, we randomly subselected a constant number of trials to generate valence-specific spectrograms for each subject. We found no differences in prefrontal task-related activity by trial type (data not shown).

DISCUSSION

We utilized high-resolution intraoperative ECoG, in patients undergoing DBS implantation in the awake state, to characterize prefrontal activity during an emotional face processing task in PD and ET patients. We targeted the dlPFC, IFC, and OFC because functional imaging studies have implicated these regions of the prefrontal cortex in emotional and cognitive processing . In all regions studied, we found that PD patients have lower theta-alpha and greater high gamma during an emotional face processing task compared to ET patients. Our results show that the dopamine-depleted state is associated with distinct prefrontal neurophysiology during an emotional face processing task, suggesting that cognitive and affective circuits may undergo disease-specific changes in Parkinson's disease.

Deficit in theta reactivity may affect circuit integration in non-motor networks
The emotional face processing task likely recruits various simultaneous processes for attention recruitment, assessment of emotional valence, conflict resolution, decision-making, and motor output generation or inhibition. The neural circuits underlying these processes must be synchronized to complete the task properly. Low frequency oscillations are thought to synchronize neural networks by temporally coordinating excitability in different brain regions. This mechanism, known as "communication through coherence," permits integration of distributed brain areas required to perform complex tasks . Functional connectivity between the prefrontal cortex and other brain structures, such as the amygdala, is required for emotional processing and regulation . The prefrontal cortex exerts top-down control of stimulus processing and these top-down control mechanisms may be mediated by inter-region theta coherence . In cognitive networks, theta oscillations have been shown to orchestrate prefrontal cortical and subcortical structures during learning, memory, and attentional processes . In PD, theta is similarly involved in complex cognitive functions including conflict and error monitoring, particularly between the medial prefrontal cortex and STN . Furthermore, scalp EEG recording in humans with PD and optogenetic studies in rodent models show that mid-frontal theta in the dopamine-depleted state is diminished during cognitive control, suggesting that deficits in low frequency modulation may underlie cognitive deficits in PD.

Consistent with a prominent role for theta band activity in non-motor functioning, we show prefrontal theta modulation during an emotional face processing task that invokes a variety of cognitive and affective processes. The task-related increase in theta-alpha frequencies was diminished in PD patients compared to ET patients, and this attenuated prefrontal theta reactivity in PD may reflect a disease-specific deficit arising from dopamine depletion. Given the diverse roles of the prefrontal cortex, the deficits in theta reactivity in PD may produce impairments in the recognition and regulation of emotional states, as well as in cognitive processes required to perform task. The involvement of theta oscillations in Parkinsonian non-motor functioning suggests new therapeutic strategies aimed at

restoring task-related theta increases. In non-Parkinsonian patients with depression, for example, deep brain stimulation in the limbic striatum boosts theta activity during a cognitive task performed in the presence of emotional distractors and improves task performance .

PD patients may compensate for oscillatory deficits by excessive activation of the prefrontal cortex

In healthy subjects, functional imaging studies suggest that various prefrontal regions are engaged during emotional processing tasks, but there is no consensus on topography . Behaviorally, PD patients have deficits in the ability to assess the valence of emotional face images . Assessments of gray matter volume in PD patients suggest that bilateral OFC gray matter volume is positively correlated with facial emotion recognition performance . Furthermore, functional imaging suggests compensatory prefrontal activity to counteract behavioral deficits. Subclinical *Parkin* mutation carriers have a hyperactive right pars opercularis during emotional face processing and symptomatic PD patients have a hyperactive medial prefrontal cortex while processing arousing emotional images . Although functional imaging studies have comprehensive spatial coverage of the brain, they lack temporal resolution.

Utilizing electrophysiological tools that can assess neural activity at fast time scales, our findings support imaging evidence of PD prefrontal hyperactivity during an emotional face processing task. We used cortical high gamma power as a surrogate metric for local neuronal activity, as it has been shown to correlate with fMRI BOLD and also with population spiking . We found greater task-related gamma in PD patients compared to ET patients in the IFC pars triangularis, IFC pars orbitalis, dlPFC, and lateral OFC, suggesting a hyperactive prefrontal cortex. ~~Prefrontal theta-gamma coupling in rodent models have been shown to be modulated by dopaminergic input to the prefrontal cortex . In the dopamine-depleted state, we propose that prefrontal hyperactivity stems from compensatory mechanisms to overcome the deficit in low frequency network oscillations involved in cognitive and affective processing.~~ These power spectral changes may reflect a change in the balance between cortical excitation and inhibition . The area of prefrontal cortex over which this disease-specific gamma band activation occurred serves diverse cognitive functions .

Prefrontal theta-gamma coupling in rodent models have been shown to be modulated by dopaminergic input to the prefrontal cortex . In the dopamine-depleted state, we propose that prefrontal hyperactivity stems from compensatory mechanisms to overcome the deficit in low frequency network oscillations involved in cognitive and affective processing. Given the demonstrated role of prefrontal control in movement inhibition , an alternative hypothesis is that the PD-specific pattern of gamma activation in our study is related to the movement inhibition/activation element of the task, rather than emotional face processing. However, we do not see similar task-evoked gamma activity in two subjects who performed a non-emotional go/no-go task with a similar cortical recording paradigm (data not shown).

~~These PD-specific alterations in task-evoked high gamma had a broad spatial distribution across all prefrontal regions studied. Our results highlight the task-related recruitment of dispersed frontal lobe activity, which is common to diverse cognitive functions . The cognitive and affective processes recruited during the emotional face processing task may overlap with those underlying the non-motor~~

~~features of PD, expanding current oscillatory models of PD beyond motor symptoms.~~

Limitations

Due to the invasive nature of our study, PD patients were compared to ET patients instead of healthy controls. Although non-motor symptoms may occur in both disease groups, comorbid psychiatric states are more common in PD, and dopamine depletion is specific to PD. In our cohort, comprehensive neuropsychiatric evaluations are not a part of routine clinical care for ET patients. Limited intraoperative research time restricted our tasks to simple designs and low trial numbers, which did not allow us to establish differences in task performance potentially due to ceiling effects. Our findings suggest that prefrontal physiology in PD and ET patients are distinct despite employing a task that was simple enough to evoke similar task performance. In some patients, recordings were performed after DBS lead insertion, which may produce "microlesional" effects. However, similar task-related activity was seen in pre-lead and post-lead patients (data not shown). The relatively low number of trials that can be done in the intraoperative environment precluded subgroup analyses of cortical responses to stimuli of different emotional valences. Therefore, we cannot attribute task-related activity specifically to emotional face processing, as the neurophysiological modulations may reflect a variety of cognitive and affective processes. We grouped PD and ET patients who had ECoG recorded in both left and right hemispheres, as we did not have sufficient patients to statistically analyze laterality within disease groups. However, we found similar activity in both the left and right prefrontal cortex (data not shown).

Conclusions

~~Prefrontal neurophysiology in~~The effect of the parkinsonian state on the neurophysiology of the prefrontal cortex ~~PD~~ during complex cognitive and affective tasks has been underexplored. ~~We utilized intracranial recordings during an emotional face processing task, and~~Utilizing intracranial recordings during an emotional face processing task in PD and ET, we demonstrate PD-specific changes in low frequency oscillatory activity as well as~~and~~ high gamma ~~network~~ broadband activity. This work ~~extends the~~suggests that the "oscillation model" of the motor system in PD, widely used to explain ~~of PD~~ specific motor deficits, may also extend to prefrontal cortical areas ~~to non-motor~~that contribute to nonmotor deficits. ~~functioning.~~

AUTHOR CONTRIBUTIONS

C.d.H. and P.S. conceived the research. W.C., C.d.H., A.M., and P.S. performed experiments and collected data. W.C. conducted data analyses. M.L. implemented technical tools to assist with imaging analyses. P.L. and P.S. performed surgical procedures. W.C. wrote the original draft. All authors reviewed the manuscript.

DECLARATION OF INTERESTS

P.L. receives honoraria from Medtronic. The remaining authors declare no conflicts.

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Table 1. Patient characteristics.

	Age	Sex	Disease Duration (years)	UPDRS-III ON/OFF Meds	ECoG Side	DBS Target	PAS	BDI	MOCA	Psychiatric Medications	Number of ECoG Contacts			
											IFC pars tri	IFC pars orb	dlPFC	lOFC
ET 039	68	M	40	--	R	Vim	--	--	--	--	0	11	0	17
ET 040	70	M	54	--	L	Vim	--	--	25	Buspirone, Citalopram, Quetiapine	9	13	1	5
ET 047	60	F	31	--	R	Vim	--	--	--	Clonazepam	0	0	27	0
ET 048	69	M	40	--	R	Vim	--	--	--	--	1	2	22	0
ET 049	78	M	20	--	L	Vim	--	--	--	None	0	0	28	0
PD 100	72	M	6	16/28	R	STN	--	9	29	Clonazepam	0	5	23	0
PD 119	52	F	14	29/60	L	STN	7	--	26	None	0	1	27	0
PD 121	56	F	6	5/31	L	STN	10	12	24	Buproprion, Alprazolam	0	0	11	1
PD 123	47	M	5	21/39	R	GPi	19	18	23	Escitalopram	0	4	12	0
PD 153	71	F	8	9/33	R	STN	8	10	21	None	11	10	1	6
PD 155	69	F	15	7/16	R	STN	3	--	24	None	10	10	1	7
PD 162*	65	M	3	21/41	L	STN	17	14	25	Citalopram, Gabapentin, Trazodone	10	0	14	0

UPDRS-III = Unified Parkinson's Disease Rating Scale Part III; PAS = Parkinson's Anxiety Scale; BDI = Beck Depression Inventory; MOCA = Montreal Cognitive Assessment; IFC pars tri = inferior frontal cortex pars triangularis; IFC pars orb = inferior frontal cortex pars orbitalis; dlPFC = dorsolateral prefrontal cortex; lOFC = lateral orbitofrontal cortex. *ECoG channels not located on the prefrontal cortex were excluded from these analyses.

FIGURE LEGENDS

Figure 1. Emotional face processing task design.
Subjects were instructed to identify the emotional valence of the image and to respond with a button press for sad and happy faces, but not for neutral faces.

Figure 2. High-resolution ECoG in PD and ET patients.
a) 3D reconstruction of prefrontal ECoG contact locations for all patients, projected onto an atlas brain. b) Sample resting ECoG potentials in a single ECoG channel for a PD (left) and ET (right) patient. c) Sample task-related spectrograms for a single ECoG channel in a PD (left) and ET (right) patient during emotional face processing ask. Activity is time-locked to image onset at 0 ms, and the red line indicates each patient's average reaction time. All trials are averaged. Color axis indicates z-score normalized power values. Outlines indicate regions of significant task-related activity corresponding to an FDR-corrected $p<0.01$.

Figure 3. Disease-specific alterations in task-related theta/alpha and high gamma activity.
a) Quantification of spectral power during baseline at rest. Spectral power for 1 minute of resting data was calculated per patient, and all ECoG contacts were averaged within a patient. Power per frequency range was normalized to total power between 5-55 Hz (delta, theta, alpha, beta) or 65-100 Hz (low gamma, high gamma). b) Grand averaged spectrograms of task-related activity during emotional face processing task in PD (top row) vs. ET (bottom row) patients, per anatomic region. Spectrograms are aligned to image onset at 0 ms. Red line at 1039 ms indicates the average reaction time for all patients. c) Quantification of spectral power during the emotional face processing task. The average power per frequency range was calculated from 0-1039 ms. PD patients had lower task-related theta ($p=0.0246$) and alpha ($p=0.0409$), as well as greater high gamma ($p=0.0412$).

Figure 4. No topographic focality in task-related high gamma activity during emotional face processing. 3D reconstruction of ECoG strip location for a single PD patient (top). Task-related spectrograms for one row of ECoG channels, all trials averaged. Outlines indicate regions of significant task-related activity corresponding to an FDR-corrected $p<0.01$.

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