Altered Prefrontal Theta and Gamma Activity during an Emotional Face Processing Task in Parkinson Disease

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Abstract

■ Patients with Parkinson disease (PD) often experience nonmotor 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 pFC of patients with PD and essential tremor, 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 patients with PD had less task-related theta–alpha power and greater task-related gamma power in the dorsolateral pFC, inferior frontal cortex, and lateral OFC. 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 nonmotor circuits undergo characteristic changes in PD. ■

INTRODUCTION

Parkinson disease (PD) is a movement disorder that is also characterized by nonmotor symptoms, such as cognitive deficits, depression, and anxiety (Chaudhuri, Healy, Schapira, & National Institute for Clinical Excellence, 2006). These nonmotor symptoms are an integral component of the disease itself, constituting the prodromal stage and advancing with disease progression (Schapira, Chaudhuri, & Jenner, 2017). A specific deficit in affective and cognitive functioning is the impaired ability to recognize emotional face images (Wagenbreth, Wattenberg, Heinze, & Zaehle, 2016; Enrici et al., 2015; Wieser et al., 2006). However, neural activity during emotional face recognition tasks in the dopamine-depleted state remains poorly understood.

Unlike nonmotor circuits, the physiology of motor networks in PD has been studied extensively. Human brain recording techniques with high spatio-temporal resolution have informed the "oscillatory model" of the Parkinsonian hypokinetic phenotype (de Hemptinne et al., 2013, 2015; Hammond, Bergman, & Brown, 2007). 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 recordings have been implemented acutely during deep brain stimulation (DBS) surgeries to study canonical motor regions (Panov et al., 2017). These methods have the capability of assessing low-frequency rhythms important for interregion communication (Fries, 2005, 2015) as well as broadband high-frequency activity that assays local cortical activation at very fast time scales (Manning, Jacobs, Fried, & Kahana, 2009; Mukamel et al., 2005). However, these tools have not yet been widely applied to the study of nonmotor 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. pFC is thought to be involved in cognitive and affective processes, including the appraisal of emotional stimuli (Fusar-Poli et al., 2009; Montgomery & Haxby, 2008; Rolls, 2004; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Phillips, Drevets, Rauch, & Lane, 2003; Hariri, Bookheimer, & Mazziotta, 2000). To determine whether PD is characterized by distinct prefrontal physiology during a complex task, we compared patients with PD to a cohort of essential tremor (ET) patients. Although ET is also associated with psychiatric and other nonmotor symptoms (Chandran & Pal, 2012; Lombardi, Woolston, Roberts, & Gross, 2001), they are generally milder than

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Journal of Cognitive Neuroscience 31:11, pp. 1768–1776
https://doi.org/10.1162/jocn_a_01450

in PD and are unlikely to be connected to dopamine depletion. We found that patients with PD 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.

METHODS

Participants

Participants 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 before DBS surgery using the Unified Parkinson's Disease Rating Scale (UPDRS) for patients with PD. All patients with PD had neuropsychiatric evaluations conducted by a psychiatrist or clinical psychologist as a part of routine clinical care. Inclusion criteria for patients with PD included primary rigid–akinetic motor phenotype, UPDRS Part III $\geq$ 30, and motor fluctuations on versus off dopaminergic medications. Inclusion for patients with ET 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 pFC for research purposes. All patients provided informed consent before surgery, per protocol approved by the institutional review board.

DBS and ECoG Placement

Patients with PD had DBS electrodes targeted to the subthalamic nucleus (STN) or globus pallidus internus, and patients with ET had DBS electrodes placed in the ventralis intermedius nucleus of the thalamus. DBS electrodes were placed under standard surgical protocol (Starr, 2002). A temporary, high-resolution, subdural ECoG strip (Ad-tech) was inserted through the same burr hole used for DBS implantation (Panov et al., 2017). The 28-contact ECoG strip consisted of two 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 pFC (dlPFC), 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), 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 (Desikan et al., 2006; Fischl et al., 2002; Dale, Fischl, & Sereno, 1999). 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 (Hamilton, Chang, Lee, & Chang, 2017). We implemented an electrode projection method using surface vectors (Kubanek & Schalk, 2015), which visually minimized the distortion of projected strip electrodes and improved estimates of electrode location. Code for imaging analyses can be found at github.com/MichaelLebrand/img_pype.

Emotional Face Processing Task

Participants performed Tap That Emotion (Posit Science), an emotional go/no-go task developed for the iPad (Apple; Figure 1). Six patients performed the task before DBS lead insertion; and six patients, after DBS lead insertion. An iPad was positioned 2 ft in front of the participant, and patients were presented with 50–100 images of emotional face images. Forty percent of the trials were happy faces, 40% were sad faces, and 20% were neutral faces. Trial order was randomized.

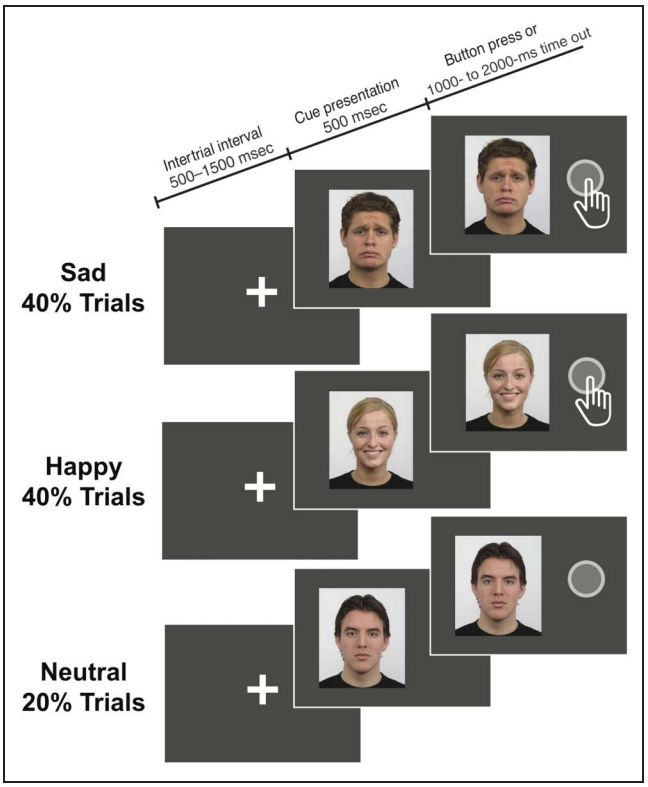

Figure 1. Emotional face processing task design. Participants were instructed to identify the emotional valence of the image and to respond with a button press for sad and happy faces, but not for neutral faces.

Participants 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 msec, with a variable intertrial interval between 500 and 1500 msec. The maximum period for response was 1000–2000 msec 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 participant with difficult or subtle distinctions.

Signal Recordings

ECoG potentials were recorded on the Neuro Omega (Alpha Omega) or TDT PZ5 (Tucker Davis Technologies) 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 (The MathWorks) 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 (Canolty et al., 2007). In a single patient, ECoG potentials for each channel were filtered with Gabor wavelets into 128 center frequencies ranging from 2.5 to 250 Hz. Epochs of data were time-locked to the image onset of each trial, and all epochs were averaged. Each frequency in the spectrogram was baseline corrected by subtracting the average power of the 500 msec preceding the cue, corresponding to the intertrial 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

Table 1. Patient Characteristics

											Number of ECoG Contacts			
	Age	*Sex*	*Disease Duration (Years)*	*UPDRS-III On/Off Meds*	*ECoG Side*	*DBS Target*	*PAS*	*BDI*	*MOCA*	*Psychiatric Medications*	*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[a]	65	M	3	21/41	L	STN	17	14	25	Citalopram, gabapentin, trazodone	10	0	14	0

UPDRS-III = UPDRS Part III; PAS = Parkinson's Anxiety Scale; BDI = Beck Depression Inventory; MOCA = Montreal Cognitive Assessment; pars tri = pars triangularis; pars orb = pars orbitalis; lOFC = lateral OFC; Vim = ventralis intermedius nucleus of the thalamus; GPi = globus pallidus internus; M = male; F = female; L = left; R = right.

[a] ECoG channels not located on pFC were excluded from these analyses.

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 msec) to the mean RT 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 ANOVAs were performed to compare task-related power between disease groups and between anatomic regions. Post hoc Bonferroni tests were conducted for pairwise comparisons. A Bonferroni-corrected p value $< .05$ was considered statistically significant for grouped data.

RESULTS

Participants

Twelve patients were enrolled in this study: seven with PD (three men and four women) and five with ET (four men and one woman; Table 1). The mean age of the patients with PD and with ET were 61.7 ± 10.0 and 69.0 ± 6.4 years, respectively. The average disease duration for patients with PD was 8.1 ± 4.6 years, and for patients with ET, it was 35.0 ± 12.8 years. Four of seven participants with PD and two of five participants with ET were prescribed medications for psychiatric symptoms (Table 1).

ECoG potentials were recorded from the right hemisphere in seven patients and from the left hemisphere in five patients. Three hundred ECoG electrodes covering the frontal lobe were analyzed (Table 1; Figure 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 four participants, 36 channels were not included in the analyses because of electrical noise or equipment failure during recording.

Patients with PD Have Reduced Prefrontal Theta–Alpha and Increased Prefrontal Gamma Activity during an Emotional Face Processing Task

Behaviorally, patients with PD and with ET performed similarly on the emotional face processing task. Mean RTs for patients with PD and with ET were and 968 ± 287 and 1139 ± 201 msec, respectively, and mean task accuracy was 72% ± 14% and 72% ± 16%, respectively.

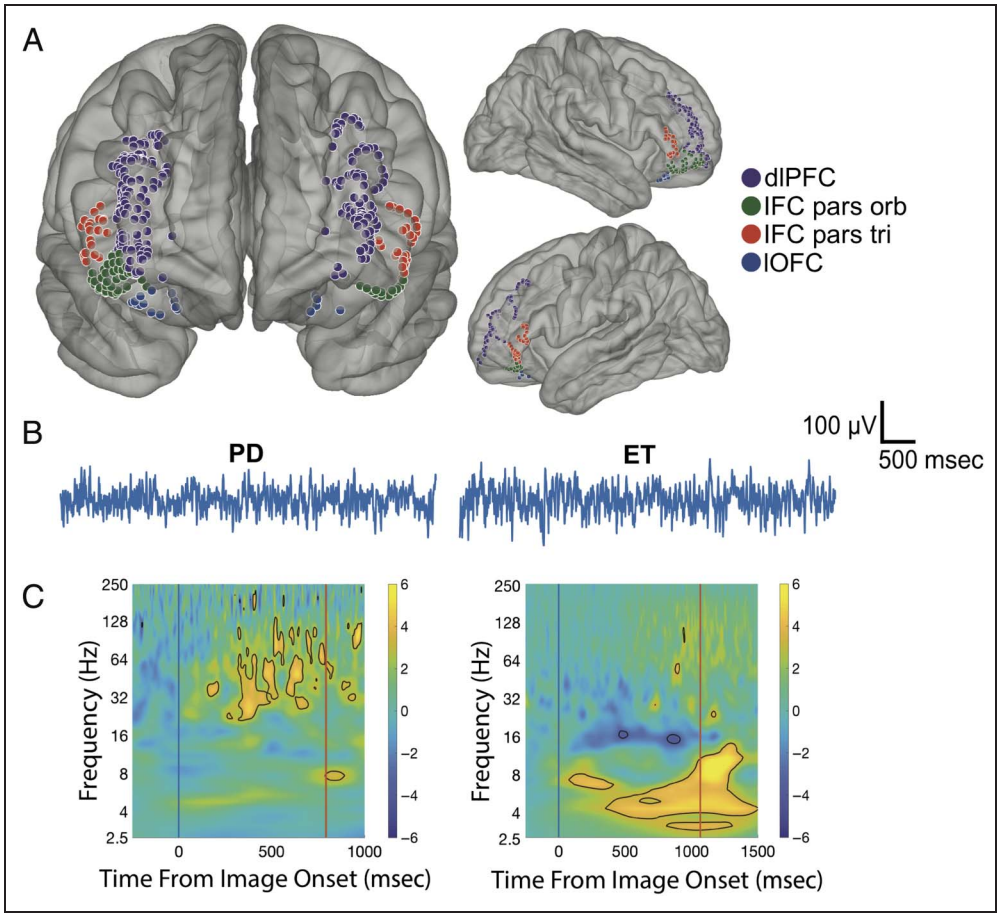

Figure 2. High-resolution ECoG in patients with PD and with ET. (A) 3-D reconstruction of prefrontal ECoG contact locations for all patients, projected onto an atlas brain. (B) Sample resting ECoG potentials in a single ECoG channel for a patient with PD (left) and a patient with ET (right). (C) Sample task-related spectrograms for a single ECoG channel in a patient with PD (left) and a patient with ET (right) during an emotional face processing task. Activity is time-locked to image onset at 0 msec, and the red line marks each patient's average RT. All trials are averaged. Color axis indicates z-score-normalized power values. Outlined areas highlight regions of significant task-related activity corresponding to $p < .01$, false discovery rate corrected.

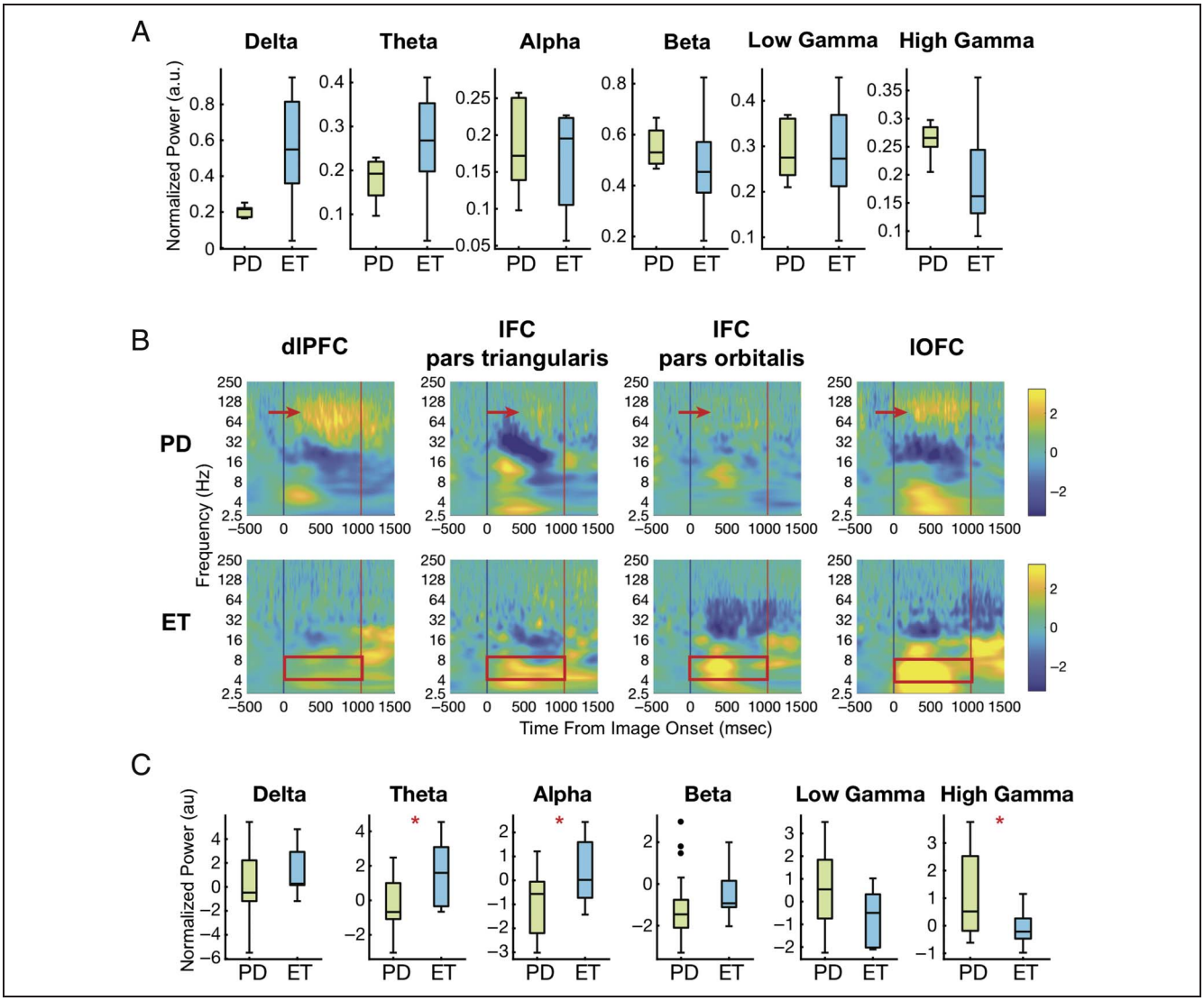

Figure 3. Disease-specific alterations in task-related theta/alpha and high-gamma activity. (A) Quantification of spectral power during baseline at rest. Spectral power for 1 min of resting data was calculated per patient, and all ECoG contacts were averaged within a patient. Power per frequency range was normalized to total power between 5 and 55 Hz (delta, theta, alpha, beta) or 65 and 100 Hz (low gamma, high gamma). (B) Grand-averaged spectrograms of task-related activity during an emotional face processing task in patients with PD (top row) versus patients with ET (bottom row), per anatomic region. Spectrograms are aligned to image onset at 0 msec. Red line at 1039 msec indicates the average RT for all patients. (C) Quantification of spectral power during the emotional face processing task. The average power per frequency range was calculated from 0 to 1039 msec. Patients with PD had lower task-related theta (p = .0246) and alpha (p = .0409) as well as greater high gamma (p = .0412).

There were no statistical differences in RT (Wilcoxon rank sum, p = .27) or task accuracy (Wilcoxon rank sum, p = .96) between the two groups. We compared ECoG potentials between patients with PD and with ET at rest and during the emotional face processing task (Figure 2B and C). At baseline during rest, there were no differences in prefrontal spectral power in any frequency range (Wilcoxon rank sum; Figure 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 RT, 1039 msec. Patients with PD have lower task-related low-frequency activity in the theta band, $F(1, 21) = 5.87$, p = .0246 (Figure 3B and C), and alpha band, $F(1, 21) = 4.75$, p = .0409 (Figure 3B and C). Patients with PD also had greater task-related prefrontal high gamma than patients with ET, $F(1, 21) = 4.73$, p = .0412 (Figure 3B and 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 pFC. 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 (Figure 4A and B).

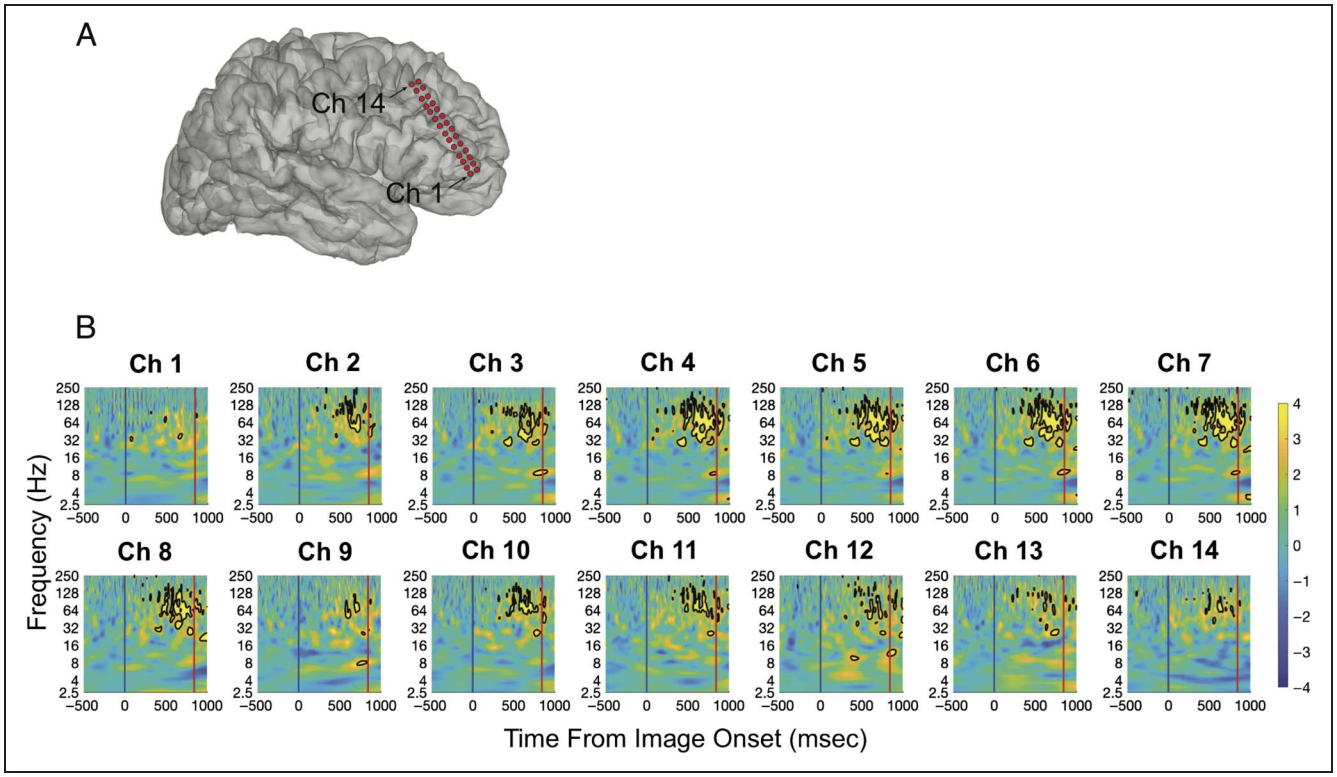

Figure 4. No topographic focality in task-related high-gamma activity during emotional face processing. (A) 3-D reconstruction of ECoG strip location for a single patient with PD. (B) Task-related spectrograms for one row of ECoG channels, with all trials averaged. Outlined areas highlight regions of significant task-related activity corresponding to $p < .01$, false discovery rate corrected.

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 participant and then averaged participants 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 participant. 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 patients with PD and with ET. We targeted the dlPFC, IFC, and OFC because functional imaging studies have implicated these regions of pFC in emotional and cognitive processing (Fusar-Poli et al., 2009; Montgomery & Haxby, 2008; Rolls, 2004; Carr et al., 2003; Phillips et al., 2003; Hariri et al., 2000). In all regions studied, we found that patients with PD have lower theta–alpha and greater high gamma during an emotional face processing task compared with patients with ET. 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 PD.

Deficit in Theta Reactivity May Affect Circuit Integration in Nonmotor 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 (Fries, 2005, 2015). Functional connectivity between pFC and other brain structures, such as the amygdala, is required for emotional processing and regulation (Wang et al., 2017; Gold, Morey, & McCarthy, 2015). pFC exerts top–down control of stimulus processing (Gold et al., 2015), and these top–down control mechanisms may be mediated by interregion theta coherence (Herz et al., 2017; Zavala

et al., 2014). In cognitive networks, theta oscillations have been shown to orchestrate prefrontal cortical and subcortical structures during learning, memory, and attentional processes (Cavanagh & Frank, 2014; Benchenane, Tiesinga, & Battaglia, 2011; Cavanagh et al., 2011). In PD, theta is similarly involved in complex cognitive functions including conflict and error monitoring, particularly between the medial pFC and STN (Kelley et al., 2018; Zavala et al., 2016). Furthermore, scalp EEG recording in humans with PD (Singh, Richardson, Narayanan, & Cavanagh, 2018) and optogenetic studies in rodent models (Kim et al., 2017; Parker, Chen, Kingyon, Cavanagh, & Narayanan, 2015) show that midfrontal 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 nonmotor 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 patients with PD compared with patients with ET, and this attenuated prefrontal theta reactivity in PD may reflect a disease-specific deficit arising from dopamine depletion. Given the diverse roles of pFC, 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 tasks. The involvement of theta oscillations in Parkinsonian nonmotor functioning suggests new therapeutic strategies aimed at restoring task-related theta increases. In non-Parkinsonian patients with depression, for example, DBS in the limbic striatum boosts theta activity during a cognitive task performed in the presence of emotional distractors and improves task performance (Widge et al., 2019).

Patients with PD May Compensate for Oscillatory Deficits by Excessive Activation of pFC

In healthy participants, functional imaging studies suggest that various prefrontal regions are engaged during emotional processing tasks, but there is no consensus on topography (Phan, Wager, Taylor, & Liberzon, 2002). Behaviorally, patients with PD have deficits in the ability to assess the valence of emotional face images (Wagenbreth et al., 2016; Enrici et al., 2015; Wieser et al., 2006). Assessments of gray matter volume in patients with PD suggest that bilateral OFC gray matter volume is positively correlated with facial emotion recognition performance (Ibarretxe-Bilbao et al., 2009). 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 (Anders et al., 2012), and patients with symptomatic PD have a hyperactive medial pFC while processing arousing emotional images (Moonen et al., 2017). 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 (Manning et al., 2009; Mukamel et al., 2005; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). We found greater task-related gamma in patients with PD compared with patients with ET in the IFC pars triangularis, IFC pars orbitalis, dlPFC, and lateral OFC, suggesting a hyperactive pFC. The area of pFC over which this disease-specific gamma band activation occurred serves diverse cognitive functions (Duncan & Owen, 2000). These power spectral changes may reflect a change in the balance between cortical excitation and inhibition (Gao, Peterson, & Voytek, 2017).

Prefrontal theta–gamma coupling in rodent models has been shown to be modulated by dopaminergic input to pFC (Lohani, Martig, Deisseroth, Witten, & Moghaddam, 2019). 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 (Aron, Herz, Brown, Forstmann, & Zaghloul, 2016), 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 participants who performed a nonemotional go/no-go task with a similar cortical recording paradigm (data not shown).

Limitations

Because of the invasive nature of our study, patients with PD were compared with patients with ET instead of healthy controls. Although nonmotor 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 patients with ET. 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 because of ceiling effects. Our findings suggest that prefrontal physiology in patients with PD and with ET is 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 prelead and postlead 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 patients with PD and with ET 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 pFC (data not shown).

Conclusions

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

Acknowledgments

This work was supported by the Defense Advanced Research Projects Agency under Cooperative Agreement Number W911NF-14-2-0043, issued by the Army Research Office, contracting office in support of DARPA's SUBNETS program.

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REFERENCES

Anders, S., Sack, B., Pohl, A., Münte, T., Pramstaller, P., Klein, C., et al. (2012). Compensatory premotor activity during affective face processing in subclinical carriers of a single mutant Parkin allele. *Brain*, *135*, 1128–1140.

Aron, A. R., Herz, D. M., Brown, P., Forstmann, B. U., & Zaghloul, K. (2016). Frontosubthalamic circuits for control of action and cognition. *Journal of Neuroscience*, *36*, 11489–11495.

Benchenane, K., Tiesinga, P. H., & Battaglia, F. P. (2011). Oscillations in the prefrontal cortex: A gateway to memory and attention. *Current Opinion in Neurobiology*, *21*, 475–485.

Canolty, R. T., Soltani, M., Dalal, S. S., Edwards, E., Dronkers, N. F., Nagarajan, S. S., et al. (2007). Spatiotemporal dynamics of word processing in the human brain. *Frontiers in Neuroscience*, *1*, 185–196.

Carr, L., Iacoboni, M., Dubeau, M.-C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences, U.S.A.*, *100*, 5497–5502.

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Sciences*, *18*, 414–421.

Cavanagh, J. F., Wiecki, T. V., Cohen, M. X., Figueroa, C. M., Samanta, J., Sherman, S. J., et al. (2011). Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold. *Nature Neuroscience*, *14*, 1462–1467.

Chandran, V., & Pal, P. K. (2012). Essential tremor: Beyond the motor features. *Parkinsonism & Related Disorders*, *18*, 407–413.

Chaudhuri, K. R., Healy, D. G., Schapira, A. H., & National Institute for Clinical Excellence. (2006). Non-motor symptoms of Parkinson's disease: Diagnosis and management. *The Lancet. Neurology*, *5*, 235–245.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*, *9*, 179–194.

de Hemptinne, C., Ryapolova-Webb, E. S., Air, E. L., Garcia, P. A., Miller, K. J., Ojemann, J. G., et al. (2013). Exaggerated phase–amplitude coupling in the primary motor cortex in Parkinson disease. *Proceedings of the National Academy of Sciences, U.S.A.*, *110*, 4780–4785.

de Hemptinne, C., Swann, N. C., Ostrem, J. L., Ryapolova-Webb, E. S., San Luciano, M., Galifianakis, N. B., et al. (2015). Therapeutic deep brain stimulation reduces cortical phase–amplitude coupling in Parkinson's disease. *Nature Neuroscience*, *18*, 779–786.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, *31*, 968–980.

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences*, *23*, 475–483.

Enrici, I., Adenzato, M., Ardito, R. B., Mitkova, A., Cavallo, M., Zibetti, M., et al. (2015). Emotion processing in Parkinson's disease: A three-level study on recognition, representation, and regulation. *PLoS One*, *10*, e0131470.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., et al. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*, 341–355.

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, *9*, 474–480.

Fries, P. (2015). Rhythms for cognition: Communication through coherence. *Neuron*, *88*, 220–235.

Fusar-Poli, P., Placentino, A., Carletti, F., Allen, P., Landi, P., Abbamonte, M., et al. (2009). Laterality effect on emotional faces processing: ALE meta-analysis of evidence. *Neuroscience Letters*, *452*, 262–267.

Gao, R., Peterson, E. J., & Voytek, B. (2017). Inferring synaptic excitation/inhibition balance from field potentials. *Neuroimage*, *158*, 70–78.

Gold, A. L., Morey, R. A., & McCarthy, G. (2015). Amygdala–prefrontal cortex functional connectivity during threat-induced anxiety and goal distraction. *Biological Psychiatry*, *77*, 394–403.

Hamilton, L. S., Chang, D. L., Lee, M. B., & Chang, E. F. (2017). Semi-automated anatomical labeling and inter-subject warping of high-density intracranial recording electrodes in electrocorticography. *Frontiers in Neuroinformatics*, *11*, 62.

Hammond, C., Bergman, H., & Brown, P. (2007). Pathological synchronization in Parkinson's disease: Networks, models and treatments. *Trends in Neurosciences*, *30*, 357–364.

Hariri, A. R., Bookheimer, S. Y., & Mazziotta, J. C. (2000). Modulating emotional responses: Effects of a neocortical network on the limbic system. *NeuroReport*, *11*, 43–48.
Herz, D. M., Tan, H., Brittain, J.-S., Fischer, P., Cheeran, B., Green, A. L., et al. (2017). Distinct mechanisms mediate speed-accuracy adjustments in cortico-subthalamic networks. *elife*, *6*, e21481.
Ibarretxe-Bilbao, N., Junque, C., Tolosa, E., Marti, M. J., Valldeoriola, F., Bargallo, N., et al. (2009). Neuroanatomical correlates of impaired decision-making and facial emotion recognition in early Parkinson's disease. *European Journal of Neuroscience*, *30*, 1162–1171.
Kelley, R., Flouty, O., Emmons, E. B., Kim, Y., Kingyon, J., Wessel, J. R., et al. (2018). A human prefrontal–subthalamic circuit for cognitive control. *Brain*, *141*, 205–216.
Kim, Y. C., Han, S. W., Alberico, S. L., Ruggiero, R. N., De Corte, B., Chen, K. H., et al. (2017). Optogenetic stimulation of frontal D1 neurons compensates for impaired temporal control of action in dopamine-depleted mice. *Current Biology*, *27*, 39–47.
Kubanek, J., & Schalk, G. (2015). NeuralAct: A tool to visualize electrocortical (ECoG) activity on a three-dimensional model of the cortex. *Neuroinformatics*, *13*, 167–174.
Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*, 150–157.
Lohani, S., Martig, A. K., Deisseroth, K., Witten, I. B., & Moghaddam, B. (2019). Dopamine modulation of prefrontal cortex activity is manifold and operates at multiple temporal and spatial scales. *Cell Reports*, *27*, 99–114.
Lombardi, W. J., Woolston, D. J., Roberts, J. W., & Gross, R. E. (2001). Cognitive deficits in patients with essential tremor. *Neurology*, *57*, 785–790.
Manning, J. R., Jacobs, J., Fried, I., & Kahana, M. J. (2009). Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *Journal of Neuroscience*, *29*, 13613–13620.
Montgomery, K. J., & Haxby, J. V. (2008). Mirror neuron system differentially activated by facial expressions and social hand gestures: A functional magnetic resonance imaging study. *Journal of Cognitive Neuroscience*, *20*, 1866–1877.
Moonen, A. J. H., Weiss, P. H., Wiesing, M., Weidner, R., Fink, G. R., Reijnders, J., et al. (2017). An fMRI study into emotional processing in Parkinson's disease: Does increased medial prefrontal activation compensate for striatal dysfunction? *PLoS One*, *12*, e0177085.
Mukamel, R., Gelbard, H., Arieli, A., Hasson, U., Fried, I., & Malach, R. (2005). Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science*, *309*, 951–954.
Panov, F., Levin, E., de Hemptinne, C., Swann, N. C., Qasim, S., Miocinovic, S., et al. (2017). Intraoperative electrocorticography for physiological research in movement disorders: Principles and experience in 200 cases. *Journal of Neurosurgery*, *126*, 122–131.
Parker, K. L., Chen, K. H., Kingyon, J. R., Cavanagh, J. F., & Narayanan, N. S. (2015). Medial frontal approximately ~4-Hz activity in humans and rodents is attenuated in PD patients and in rodents with cortical dopamine depletion. *Journal of Neurophysiology*, *114*, 1310–1320.
Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*, *16*, 331–348.
Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*, *54*, 504–514.
Rolls, E. T. (2004). The functions of the orbitofrontal cortex. *Brain and Cognition*, *55*, 11–29.
Schapira, A. H. V., Chaudhuri, K. R., & Jenner, P. (2017). Non-motor features of Parkinson disease. *Nature Reviews Neuroscience*, *18*, 435–450.
Singh, A., Richardson, S. P., Narayanan, N., & Cavanagh, J. F. (2018). Mid-frontal theta activity is diminished during cognitive control in Parkinson's disease. *Neuropsychologia*, *117*, 113–122.
Starr, P. A. (2002). Placement of deep brain stimulators into the subthalamic nucleus or globus pallidus internus: Technical approach. *Stereotactic Functional Neurosurgery*, *79*, 118–145.
Wagenbreth, C., Wattenberg, L., Heinze, H. J., & Zaehle, T. (2016). Implicit and explicit processing of emotional facial expressions in Parkinson's disease. *Behavioural Brain Research*, *303*, 182–190.
Wang, S., Yu, R., Tyszka, J. M., Zhen, S., Kovach, C., Sun, S., et al. (2017). The human amygdala parametrically encodes the intensity of specific facial emotions and their categorical ambiguity. *Nature Communications*, *8*, 14821.
Widge, A. S., Zorowitz, S., Basu, I., Paulk, A. C., Cash, S. S., Eskandar, E. N., et al. (2019). Deep brain stimulation of the internal capsule enhances human cognitive control and prefrontal cortex function. *Nature Communications*, *10*, 1536.
Wieser, M. J., Mühlberger, A., Alpers, G. W., Macht, M., Ellgring, H., & Pauli, P. (2006). Emotion processing in Parkinson's disease: Dissociation between early neuronal processing and explicit ratings. *Clinical Neurophysiology*, *117*, 94–102.
Zavala, B., Tan, H., Ashkan, K., Foltynie, T., Limousin, P., Zrinzo, L., et al. (2016). Human subthalamic nucleus–medial frontal cortex theta phase coherence is involved in conflict and error related cortical monitoring. *Neuroimage*, *137*, 178–187.
Zavala, B. A., Tan, H., Little, S., Ashkan, K., Hariz, M., Foltynie, T., et al. (2014). Midline frontal cortex low-frequency activity drives subthalamic nucleus oscillations during conflict. *Journal of Neurosciences*, *34*, 7322–7333.