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Washout of chronic therapeutic deep brain stimulation increases cortical phase-amplitude coupling

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ABSTRACT

Invasive human brain recordings have shown that acute therapeutic deep brain stimulation (DBS) reduces cortical synchronization, measured by coupling of beta phase to gamma amplitude. Here we show by non-invasive scalp electroencephalography that withdrawal of chronic DBS elevates phase-amplitude coupling, in proportion to the worsening of contralateral rigidity.

High levels of neuronal synchronization in the basal ganglia-thalamo-cortical network are thought to underlie the hypokinetic motor signs of Parkinson's disease (PD). One putative electrophysiological biomarker of this excessive synchronization is exaggerated coupling of broadband gamma (50–200 Hz) amplitude to beta phase in motor cortex (phase-amplitude coupling, PAC) [1]. In the normal state, PAC is thought to integrate functionally related cortical areas that are important for voluntary movement [2]. Invasive electrocorticography studies have indicated that PAC is reduced by therapeutic deep brain stimulation (DBS) of the subthalamic nucleus or globus pallidus internus and that this change is correlated with symptom improvement [3,4]. Recent work has suggested that PAC can be detected in PD patients using scalp electroencephalography (EEG) [5]. In the current study, using scalp EEG, we show elevation of phase amplitude coupling following withdrawal of DBS therapy that correlated with worsening of hypokinetic motor signs.

We recorded scalp EEG activity from 11 patients with rigid-akinetic Parkinson's disease (mean age = 66.4 years, mean duration of disease = 16.5 years). Informed written consent was obtained prior to initiation of study procedures under a protocol approved by the UCSF Institutional Review Board. All patients had undergone deep brain stimulator placement at least 6 months prior to ensure optimization of therapy, with a mean stimulation duration of 4.3 years. Six patients had leads placed bilaterally in the subthalamic nucleus (STN), one patient had left STN, two patients had right STN, one patient had lead placement in left Globus Pallidus Internus (GPi), and one had right GPi placement. Patients withheld use of dopaminergic medication for 12 hours prior to recording. PD patients with tremor (UPDRS part III resting tremor score greater than 1 on either side in the Off stimulation state) were excluded, as tremor may introduce significant movement artifacts in the EEG signal. Patients had a mean UPDRS III score of 33.5 Off stimulation and 26.9 On stimulation. Resting-state EEG was first recorded with DBS on, and then again 20 minutes after DBS was turned off.

Data from the sensorimotor electrode contralateral to each patient's more symptomatic side were analyzed (C3 or C4). PAC was calculated using previously described methods [1,5]. To evaluate the significance of observed PAC for each patient, an established surrogate analysis method [2] was used to generate z-scored values for each raw PAC value. All PAC analyses were conducted on these z-scored values. Statistics were corrected for multiple comparisons using the Benjamini-Hochberg method. Mean PAC for each patient was computed by averaging modulation index values in the 13–30 Hz phase frequency range and 50–150 Hz amplitude frequency range.

Changes in PAC following DBS withdrawal were associated with changes in contralateral rigidity measured by the UPDRS, such that increased PAC values off stimulation were associated with worsening in contralateral hemibody rigidity (Fig. 1A) (Spearman's Rho = 0.78, $p = 0.044$). Change in PAC was not associated with change in total UPDRS (Rho = .46, $p = 0.17$) or with bradykinesia (Rho = .45, $p = 0.17$). Of note, one patient did not have worsening rigidity after DBS withdrawal, and two patients had paradoxical symptomatic *improvement* after withdrawal of stimulation, both associated with PAC *decrease*.

At rest, among the eight patients whose rigidity worsened with withdrawal of stimulation, mean PAC was elevated in patients Off stimulation compared to On stimulation ($p = 0.039$, two-tailed, paired, Wilcoxon signed-rank test), with 6 of 8 patients showing this effect. (Fig. 1B). Without surrogate correction, the difference was not significant. Surrogate-corrected beta-gamma PAC values (Z-scores) are shown in Fig. 1C.

Because muscle activity can artifactually contribute to high PAC values [5], we also compared change in PAC across all channels within single patients in the On and Off stimulation states to characterize their spatial distribution (plotted on a scalp map in Fig. 1D). Significant differences were observed over frontocentral contacts, suggesting that artifactual PAC from temporalis or frontalis muscle activity is unlikely to be driving PAC changes we observed over sensorimotor areas.

Our findings provide support for cortical phase-amplitude coupling as a marker of pathological synchronization in Parkinson's disease that responds to deep brain stimulation therapy, and is correlated with symptomatic improvement. In a prior study, levodopa-induced PAC reduction was more closely related to bradykinesia than rigidity [6], which may reflect differences in severity of specific motor signs be-

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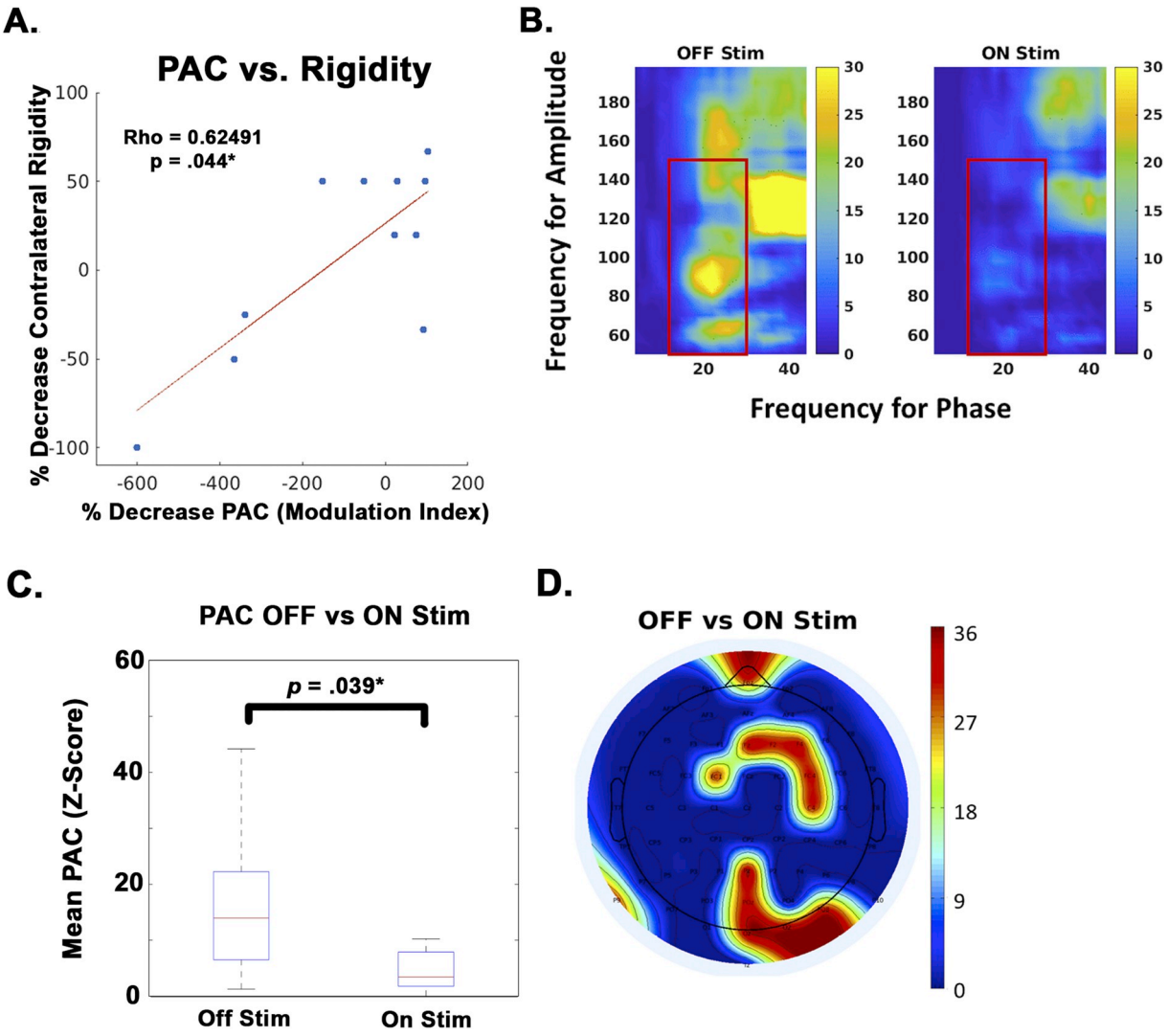

Fig. 1. Increases in Rigidity and Phase-Amplitude Coupling Following DBS Withdrawal. A) Correlations between PAC and rigidity. Change in hemibody rigidity subscale of UPDRS scores on patients more symptomatic side was correlated with change in PAC over contralateral sensorimotor area (Spearman's Rho = 0.78, p = 0.044, FDR corrected). **B).** Median comodulograms showing surrogate-corrected PAC differences among patients who had worsening of rigidity following stimulation withdrawal. PAC was elevated in patients Off stimulation compared to On stimulation (p = 0.039, two-tailed, paired, Wilcoxon signed-rank test). **C)** Boxplots showing distribution of mean surrogate-corrected beta-broadband gamma PAC values (Z-scores) among these patients Off and On stimulation **D)** Whole-scalp topography of PAC comparisons. We computed, for all 64 scalp electrodes, statistical differences in PAC values between all patients Off and On stimulation. The normalized test statistic for each comparison is plotted for each electrode that showed a significant difference in PAC ($p < .05$; Wilcoxon sign-rank).

tween the two groups. We also provide evidence for the first time that DBS-induced changes in cortical synchronization in Parkinson's disease may be detected using scalp EEG, offering implications for the use of noninvasive recording techniques in the development of control signals for closed-loop DBS paradigms.

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References

[1] C. de Hemptinne, E.S. Ryapolova-Webb, E.L. Air, P.A. Garcia, K.J. Miller, J.G. Ojemann, J.L. Ostrem, N.B. Galifianakis, P.A. Starr, Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease, Proc. Natl. Acad. Sci. 110 (12) (2013) 4780–4785.

[2] R.T. Canolty, R.T. Knight, The functional role of cross-frequency coupling, Trends Cogn. Sci. 14 (11) (2010) 506–515.

[3] C. de Hemptinne, N.C. Swann, J.L. Ostrem, E.S. Ryapolova-Webb, M. San Luciano, N.B. Galifianakis, P.A. Starr, Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease, Nat. Neurosci. 18 (5) (2015) 779–786.

[4] M. Malekmohammadi, N. AuYong, J. Ricks-Oddie, Y. Bordelon, N. Pouratian, Pallidal deep brain stimulation modulates excessive cortical high beta phase amplitude coupling in Parkinson disease, Brain Stimul. 11 (3) (2018) 607–617.

[5] N.C. Swann, C. de Hemptinne, A.R. Aron, J.L. Ostrem, R.T. Knight, P.A. Starr, Elevated synchrony in Parkinson disease detected with electroencephalography, Ann. Neurol. 78 (5) (2015) 742–750.

[6] A.M. Miller, S. Miocinovic, N.C. Swann, S.S. Rajagopalan, D.M. Darevsky, R. Gilron, C. de Hemptinne, J.L. Ostrem, P.A. Starr, Effect of levodopa on electroencephalographic biomarkers of the parkinsonian state, J. Neurophysiol. 122 (1) (2019) 290–299.

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