Dopamine and stimulation distinctly modulate cortico-subthalamic communication in Parkinson's disease

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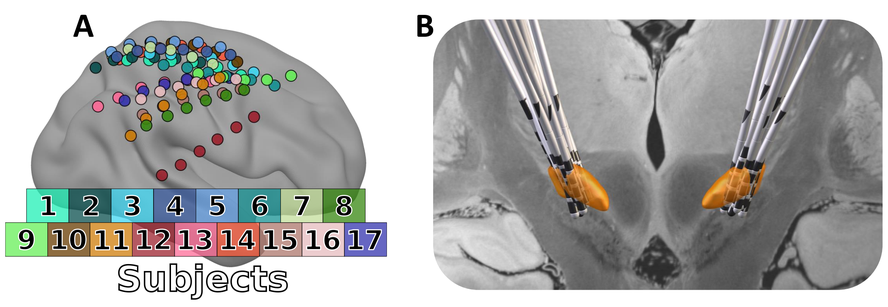
INTRODUCTION

- Excessive beta band (13-35 Hz) activity in the subthalamic nucleus (STN) of the dopamine-depleted basal ganglia is a hallmark of Parkinson's disease.
- Evidence suggests cortical beta synchrony is not elevated in the hypodopaminergic state but may drive pathological basal ganglia activity [1].
- Results from previous studies addressing this paradox with non-invasive cortical recordings have been inconclusive [2].
- Using a fully invasive, within-patient approach, we provide authoritative evidence on pathological brain circuit communication in Parkinson's disease.

Figure 1: Cortex and STN recording locations



METHODS

- Electrocorticography (Fig. 1A) and subthalamic local field potential (Fig. 1B) signals were recorded in 17 Parkinson's disease patients at rest following withdrawal and administration of dopaminergic medication.
- Further recordings were taken from a subset of 8 patients with deep brain stimulation, without medication, from which stimulation artefacts were removed using period-based rejection [3].
- Multivariate components of power were extracted using spatio-spectral decomposition [4], and univariate periodic components of power were extracted using Gaussian-based parameterisation [5].
- Undirected oscillatory connectivity was quantified with a multivariate form of the imaginary part of coherency [6], and its directionality was quantified with multivariate time-reversed Granger causality [7, 8].
- Cortico-subthalamic structural connectivity profiles were determined using hyperdirect fibres of the holographic atlas [9], and whole-brain functional connectivity maps were generated from a Parkinson's disease fMRI group connectome [10].

Figure 2: Subthalamic power

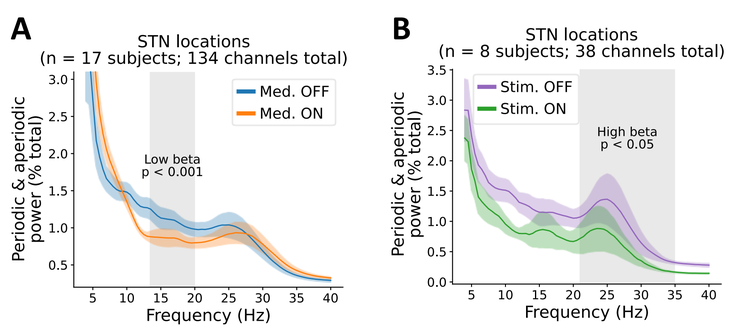


Figure 3: Spatio-spectral decomposition of cortical power

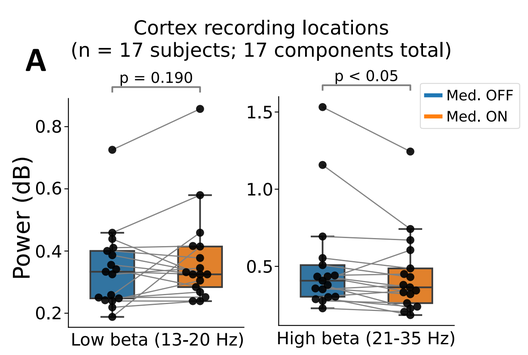


Figure 4: Sensorimotor cortex power

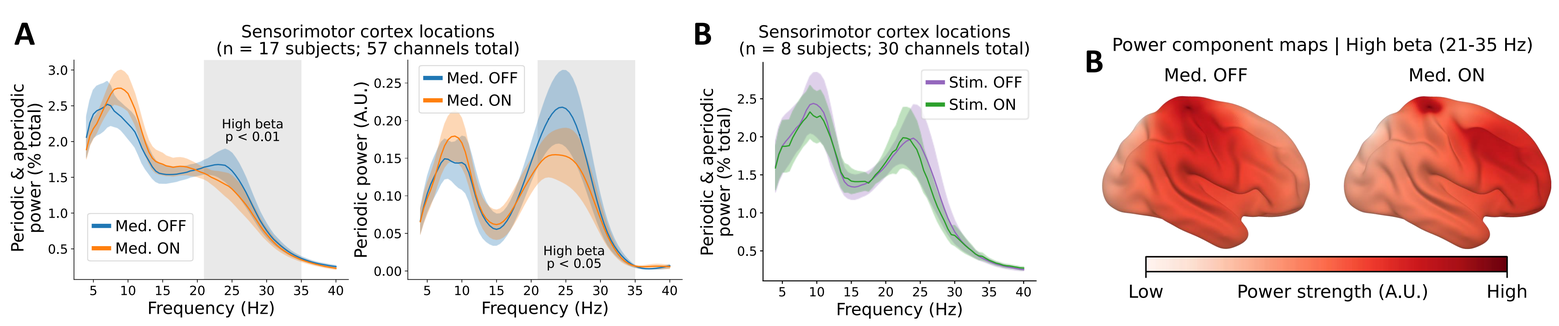


Figure 5: Cortico-subthalamic oscillatory connectivity maps

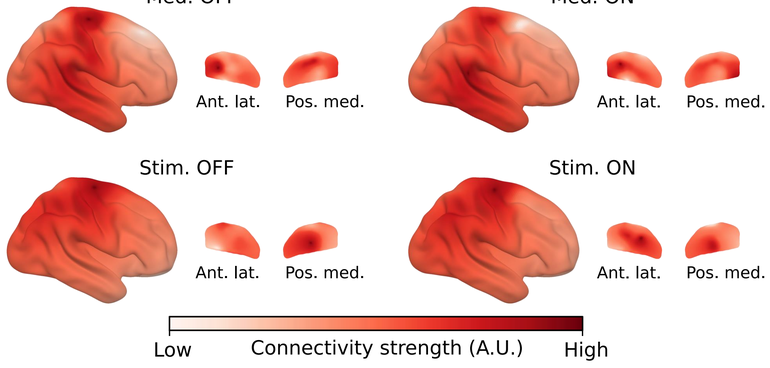


Figure 6: Cortico-subthalamic oscillatory connectivity spectra

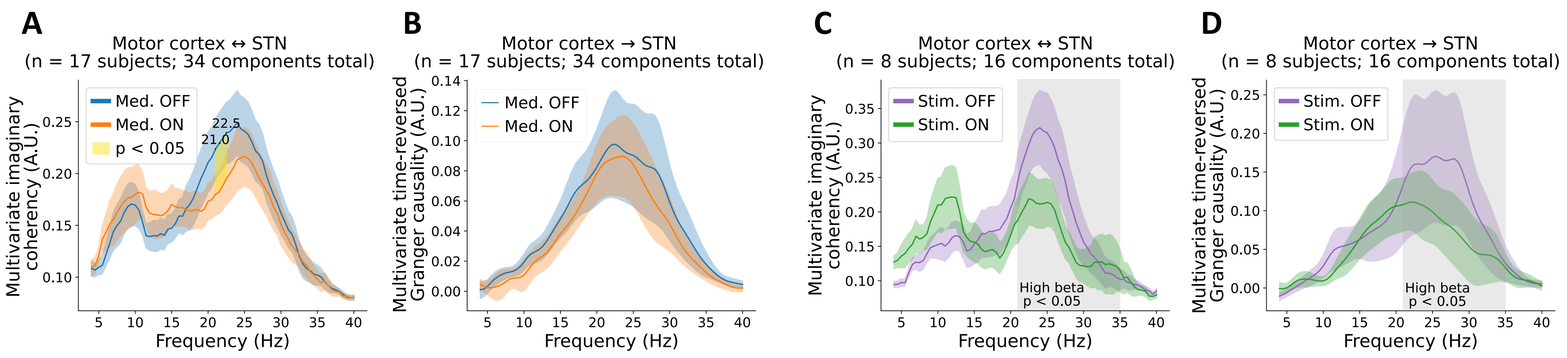
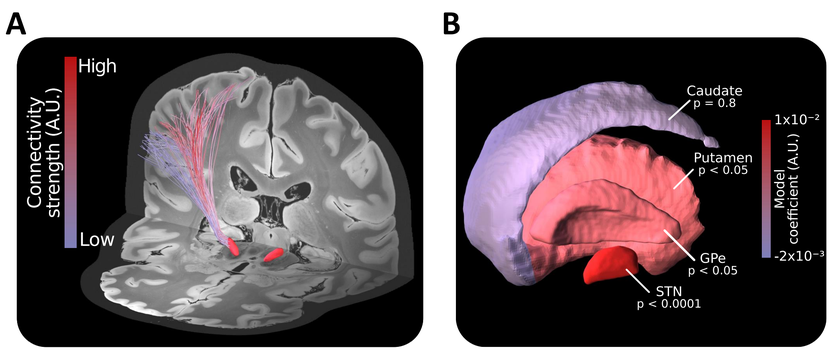


Figure 7: Hyperdirect and indirect pathway connectivity



RESULTS

- Dopamine and stimulation suppressed STN low and high beta power, respectively (Fig. 2A-B).
- High beta (21-35 Hz) power was focal over sensorimotor regions (Fig. 3B) and suppressed with dopamine (Fig. 3A), which was captured in periodic activity alone (Fig. 4A). Stimulation did not significantly alter sensorimotor cortex power (Fig. 4B).
- Oscillatory beta connectivity was focal between motor cortex and sensorimotor STN (Fig. 5), with medication and stimulation both reducing high beta connectivity (Fig. 6A, C).
- Motor cortex drove 5-40 Hz oscillatory connectivity with STN across medication and stimulation states, with stimulation (Fig. 6D) but not medication (Fig. 6B) reducing high beta drive.
- Cortico-subthalamic hyperdirect pathway connectivity (Fig. 7A) correlated with the contributions of cortex and STN to oscillatory high beta connectivity (coeff.=0.749, $p < 0.0001$).
- Cortex-basal ganglia indirect pathway nuclei functional connectivity correlated with the contribution of cortex to oscillatory low beta connectivity (Fig. 7B; coeff.=0.007, $p < 0.01$).

DISCUSSION

- Sensorimotor cortex drives information flow in cortico-subthalamic connectivity.
- Dopamine and stimulation diminish distinct aspects of connectivity with unique spectral profiles.
- There is a novel observation of a reduction in cortical beta power with dopamine, in contrast to earlier paradoxical results.
- These findings further support a role for excessive cortico-subthalamic communication in the origin of pathological beta synchrony in Parkinson's disease, and highlight the unique effects of therapies on this communication.

References: [1] Oswal *et al.* (2021). Neural signatures of hyperdirect pathway activity in Parkinson's disease. *Nat. Commun.*; [2] Litvak *et al.* (2011). Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. *Brain*; [3] Dastin van-Rijn *et al.* (2021). Uncovering biomarkers during therapeutic neuromodulation with PARRM. *Cell Rep. Methods*; [4] Nikulin *et al.* (2011). A novel method for reliable and fast extraction of neuronal EEG/MEG oscillations on the basis of spatio-spectral decomposition. *NeuroImage*; [5] Donoghue *et al.* (2020). Parameterizing neural power spectra into periodic and aperiodic components. *Nat. Neurosci.*; [6] Ewald *et al.* (2012). Estimating true brain connectivity from EEG/MEG data invariant to linear and static transformations in sensor space. *NeuroImage*; [7] Seth & Barnett (2015). Granger causality for state-space models. *Phys. Rev. E*; [8] Winkler *et al.* (2016). Validity of time reversal for testing Granger causality. *IEEE Trans. Signal Process.*; [9] Petersen *et al.* (2019). Holographic Reconstruction of Axonal Pathways in the Human Brain. *Neuron*; [10] as in Horn *et al.* (2017). Connectivity predicts deep brain stimulation outcome in Parkinson disease. *Ann. Neurol.*

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