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Low β predicts motor output and cell degeneration in the A53T Parkinson's disease rat model.

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Parkinson's disease is characterized not only by its hallmark motor symptoms but also by distinct changes in brain activity, particularly in the β (13–30 Hz) frequency range. These oscillatory patterns have emerged as both diagnostic biomarkers and promising therapeutic targets for advanced treatments like adaptive deep brain stimulation. However, critical gaps remain in understanding how these oscillations evolve and their precise relationship to neurodegeneration—questions that traditional animal models fail to address due to their inability to closely replicate human disease progression and Lewy body-like pathology.

Our study provides transformative insights by utilizing the AAV-A53T α-synuclein rat model, which recapitulates human pathology including α-synuclein aggregation, dopaminergic neuron loss, and motor deficits. Using a viral vector-mediated approach, we established dose-dependent pathology in rats, in which motor dysfunction became detectable only after progressive neurodegeneration exceeded compensatory capacity. Through longitudinal electrophysiological recordings, we observed that pathological β activity develops progressively in both the motor cortex and subthalamic nucleus, manifesting as three distinct phenomena: (1) elevated β power, driven primarily by an increase in high β (21–30 Hz) oscillations, (2) increased high β burst parameters (amplitude, rate and percentage of long bursts), and (3) intensified cortico-subcortical synchronization over time. These abnormal oscillatory patterns emerge in parallel with developing motor deficits and ongoing degeneration of the nigrostriatal system over an 8-week period, establishing a clear temporal relationship between neural circuit dysfunction and motor impairment manifestation. Notably, pathological high β activity specifically in the subthalamic nucleus - particularly increased power, burst amplitude, and prolonged bursts - showed strong correlations with both motor impairment and dopaminergic neuron loss, while motor cortex activity remained unrelated to these disease manifestations. Multivariate analyses reveal three groundbreaking findings by using β parameters: First, high-β activity specifically predicts motor impairment but not neuronal loss, implicating it in motor impairment generation. Second, low-β power (13–20 Hz) combined with striatal dopamine depletion forecasts both motor deficits and neurodegeneration, revealing distinct roles for β sub-bands. Third, these relationships are preserved in human Parkinson's disease patients, with identical patterns predicting clinical scores and dopaminergic uptake deficiency in cross-species validation.

A further approach emerging from our findings suggests two distinct therapeutic strategies with potential clinical implications: (1) targeting high-β oscillations via neuromodulation to alleviate motor impairment and (2) monitoring low-β activity as a biomarker of disease progression—while not inherently pathological, its predictive value becomes evident when combined with dopamine depletion. This dual strategy leverages the A53T model's unique ability to replicate human pathophysiology, bridging critical gaps between preclinical research and clinical translation.

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Katarina Hofman is a postdoctoral researcher in the Neurology Department at Würzburg in the lab of Chi Wang Ip. Her work focuses on characterizing pathological brain activity in Parkinson's disease, studying how dysfunctional neural circuits contribute to symptoms and respond to treatment.

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