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TRR 295 ReTune

Vestibular nucleus stimulation for ameliorating locomotor dynamics in a Parkinsonian mouse model.

Hartig J*, Friedrich MU*, Signoret-Genest J*, Gruber M, Tabuchi S, Alimohammadi H, Leuschner M, Schöneberg N, Peach R, Doll D, Petschner T, Neumann A, Knorr S, Volkmann J, Tovote P#, Ip CW#.

*/#equal contribution

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Postural instability and gait dysfunction are among the most disabling axial features of Parkinson's disease (PD), yet they often respond incompletely to dopaminergic medication and conventional deep brain stimulation. In our study within the framework of ReTune, we therefore asked whether the vestibular system could provide an alternative entry point for retuning dysfunctional motor networks. We focused on excitatory, Vglut2-expressing neurons in the vestibular nucleus complex (VNC), a brainstem hub that transforms sensory information about head and body motion into postural and locomotor commands. Using brain-wide viral tracing in mice, we found that these neurons are embedded in a much broader motor network than classical vestibular reflex pathways alone would suggest.

Perithreshold optogenetic stimulation—individually calibrated just below the intensity producing overt vestibular symptoms—recruited several of these downstream nodes, including the parafascicular thalamus and gigantocellular reticular nucleus. We next tested the functional consequences in control mice and in an α-synuclein-based A53T mouse model of PD. Increasing stimulation intensity produced a continuous spectrum of reversible postural and locomotor effects, ranging from head tilting to turning, circling, and retropulsion. This demonstrated that stimulation strength is decisive: suprathreshold activation disrupted locomotion and gait, whereas carefully titrated perithreshold stimulation increased overall movement in both healthy and parkinsonian mice. Unsupervised analysis of pose dynamics further showed that stimulation reorganized transitions between elementary behavioural modules, indicating a broader retuning of behavioural structure rather than a simple increase in activity. The most disease-specific benefit emerged in detailed treadmill analyses. Parkinsonian mice developed reduced power at the principal gait frequency, impaired temporal coordination between limbs, and a disrupted relationship between stride frequency and oscillation amplitude. Perithreshold VNC activation shifted these measures back towards baseline and control-like patterns, effectively stabilizing gait dynamics, although it did not restore maximal running velocity or broadly normalize every motor deficit.

Together, our findings identify excitatory vestibular circuits as a potential target for axial motor symptoms in PD. In the spirit of ReTune, the study highlights that successful neuromodulation depends not only on where we stimulate, but also on precisely how strongly and in which functional state we engage a distributed motor network. It provides a circuit-level framework for refining non-invasive vestibular stimulation and developing more individualized, symptom-specific interventions.

Dr. Johannes Hartig

He is a clinician-scientist and a postdoctoral associate in the labs of Chi Wang Ip and Philip Tovote. He primarily works on translational systems neuroscience in neurological disorders, currently using both human and rodent approaches.

Dr. Maximilian Friedrich

He is a physician scientist in neurology currently working as a postdoc associate with Michael Fox at the Center for Brain Circuit Therapeutics, Boston. His experience spans experimental and clinical neurosciences, including optogenetic and electrical brain stimulation, circuit mapping, and movement analysis.

Dr. Jérémy Signoret-Genest

He is a postdoc research fellow in the Tovote lab. His research is based on the computational analysis of multi-dimensional read-outs displayed during fear and anxiety in order to identify integrated defensive states.

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