

Rethinking the endpoints for non-invasive neuromodulation interventions: from behavioural proxies to biomarkers of adaptive plasticity

Theo F Marins¹, Lorena Melo², Guilherme Wood^{1,3}.

¹Institute of Psychology, University of Graz, Graz, Austria

²SensoriMotor Laboratory, Jules-Gonin Eye Hospital, Fondation Asile des Aveugles, Department of Ophthalmology, University of Lausanne, Lausanne, Switzerland (lorena.melo@fa2.ch)

³BioTechMed-Graz, Graz, Austria

Non-invasive neuromodulation, including transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), and neurofeedback (NF), faces challenges that undermine the reliability of its findings and ultimately limiting its clinical translation. Converging evidence suggests that a fundamental and underexplored source of these challenges might be the limited emphasis on establishing whether interventions engage mechanisms of **adaptive plasticity**, i.e., brain changes that lead to adaptive behaviour, such as learning and recovery. Anchoring observed effects in established mechanisms of adaptive plasticity reduces the risk of conflating improvements to non-specific influences, compensatory strategies, or transient contextual factors⁴², improving the interpretability and replicability of findings. In practice, however, several studies have prioritized neurophysiological proxies of brain plasticity, such as motor-evoked potentials (MEPs), which link with adaptive behaviour remains controversial.

Here, we introduce the Plasticity-Informed (PIN) framework, a set of experimental principles that supports the adoption of surrogate endpoints based on known biomarkers of adaptive plasticity. The implementation of this framework predicts three steps: (1) Target Plasticity-Driven Endpoints, (2) Track Plasticity Across Timescales, and (3) Account for Biological Moderators. These steps are designed to increase the likelihood that the mechanisms of action of non-invasive neuromodulation tools engage the neural machinery required for higher-level improvements. A wider adoption of mechanistically verified interventions may enable non-invasive neuromodulation to realize its transformative potential in fundamental and clinical neuroscience.