TMS-EVOKED RESPONSES ARE DRIVEN BY RECURRENT LARGE-SCALE NETWORK DYNAMICS

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The brain is a complex, nonlinear, multiscale, and intricately interconnected physical system, whose laws of motion and principles of organization have proven challenging to understand with currently available measurement techniques. In such epistemic circumstances, application of systematic perturbations, and measurement of their effects, is a central tool in the scientific armoury (Deco et al., 2018). For human brains, the technological combination that best supports this non-invasive perturbation-based modus operandi is concurrent transcranial magnetic stimulation (TMS) and electroencephalography (EEG). Spatiotemporally complex and long-lasting TMS-EEG responses are believed to result from recurrent, re-entrant activity that propagates broadly across multiple cortical and subcortical regions - dispersing from, and later re-converging on, the primary stimulation site (Siebner et al., 2022). In particular, the middle and late components of trial-averaged TMS-EEG evoked potential (TEP) waveforms are often taken as key markers of recurrent large-scale network activity and excitability (Darmani et al., 2019). However, if (as seems reasonable) we loosely understand the TEP of a TMS-stimulated region as the impulse response function of a noisy underdamped harmonic oscillator, then multiple later activity components (waveform peaks) should be expected - even for an isolated network node in the complete absence of recurrent inputs. Thus emerges a critically important question for basic and clinical research on human brain dynamics: what parts of the TEP are due to purely local dynamics, what parts are due to reverberant, re-entrant network activity, and how can we distinguish between the two? In order to disentangle this, we utilize a combination of source-localized TMS-EEG analyses and whole-brain connectome-based computational modelling of meso-scale neural dynamics, including a novel and advanced methodology for single-subject TEP fitting and parameter estimation. Using this approach, we were able to identify at what point in time after the TMS pulse the outgoing and incoming connections of the stimulated site affect the TEP. Results indicate that recurrent activity begins to contribute to TEP measurements at the stimulated site from approximately 100ms post-stimulation, in line with the interpretation of these signal components as reflecting a recurrent network-level response. Further inspection and statistical analysis of estimated neurophysiological parameters additionally indicated an important role for the inhibitory population time constant in determining TEP excitability, identifying also key physiological contributors to the two principal dimensions of inter-subject variability in TEP waveforms. The novel discoveries and new software technologies introduced here should be of broad utility in basic and clinical neuroscience research.

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