

Transcranial magnetic stimulation as a biomarker of treatment response in epilepsy

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Epilepsy treatment remains a major challenge with nearly 30% of people continuing to experience seizures despite the availability of over 20 antiepileptic drugs. One of the major difficulties to improve epilepsy treatment is the heterogeneity of epilepsy pathophysiology. Antiepileptogenic (i.e., drugs used to prevent the development of epilepsy) and antiseizure (i.e., drugs used to stop epileptic seizures) treatments need to be developed and chosen on an individualised basis, according to a precision medicine paradigm. So, it becomes vital to identify biomarkers that can help to guide epilepsy treatments.

Epilepsy pathophysiology reflects altered cortical network excitability. Transcranial Magnetic Stimulation (TMS) is a non-invasive tool which is applied extra-cranially with time-varying magnetic fields to measure cortical physiology. TMS has high temporal resolution, capable to expose causal relations following stimulation due to the temporal sequence of evoked activity. TMS was used to probe cortical excitability in genetic epileptic encephalopathies: e.g. in Dravet Syndrome, a distinct neurophysiological phenotype has been identified, suggesting the role of TMS as a putative biomarker of mutation-driven cortical pathophysiology and a rapid readout predictor of drug effect.¹ TMS has also shown how cortical excitability correlates with seizure control and epilepsy duration in chronic epilepsy.² TMS represent a great tool to understand disease biology *in vivo*, and subsequently guide and monitor individualised treatments. The study of Andreasson *et al.*,³ in this issue, is a great example of such applications of TMS in epilepsy. Their findings further support the potential role of TMS as a biomarker of drug response. There are, however, some controversial issues, which need to be addressed for future applications. TMS combined with electromyography (TMS-EMG) only measures excitability from the motor cortex, and its responses are also affected by the excitability of corticospinal and spinal neurons. Currently, the correlation of resting motor threshold (RMT) with epilepsy type remains uncertain, with some evidence of lower RMT values in generalised epilepsies, and no significant evidence in focal epilepsies.⁴ Methods for RMT determination vary across previous studies, with subsequent issues in the reproducibility of outcome.⁴ Similarly, methodological differences and reproducibility issues have emerged in studies using long-interval intracortical inhibition (LICI) measures as a biomarker in epilepsy, emphasising the need for prospective multi-centre studies to test and validate the reproducibility of TMS protocols and measures.⁵ Furthermore, to interpret variation in RMT and other single and paired pulse TMS measures, there are a number of potential confounding factors that should be taken into account. These include age, hemispheric dominance, presence of brain lesions, circadian differences, cognitive function, hormonal fluctuations, and possibly others. The role of these factors should be clearly established, so to minimise interindividual variability and enhance the use of TMS as a biomarker for epilepsy management. Once the reliability and reproducibility of TMS protocols are consolidated, the potential of this technique to investigate epilepsy pathophysiology and treatment is high. Combining

TMS with EEG (TMS-EEG) is likely to increase its spatial resolution, by allowing direct probing of cortical excitability even in non-motor areas, bypassing sensorimotor pathways and subcortical structures. Furthermore, the direct measurement of cortical potentials in response to stimulation may allow the investigation of small populations of neurons, which in comparison to other neuroimaging methodologies like MRI, could show subtle functional disturbances in very focal brain regions, which is beneficial given the inter-individual phenotypic variability in epilepsy. Further studies are warranted, but pharmaco-TMS may soon become a reliable tool to monitor and predict clinical treatment outcome and to develop new antiepileptogenic therapies, on an individualised basis.

References

1. Stern WM, Sander JW, Rothwell JC, et al. Impaired intracortical inhibition demonstrated in vivo in people with Dravet syndrome. *Neurology* 2017; **88**:1659-65.
2. Pawley AD, Chowdhury FA, Tangwiriyasakul C, et al. Cortical excitability correlates with seizure control and epilepsy duration in chronic epilepsy. *Ann Clin Transl Neurol.* 2017; **4**:87-97.
3. Andreasson AC, Sigurdsson GV, Pegenius G, Thordstein M, Hallböök T. Cortical excitability measured with transcranial magnetic stimulation in children with epilepsy before and after introduction of antiepileptic drugs. *Developmental Medicine & Child Neurology* 2020.
4. de Goede AA, Ter Braack EM, van Putten MJ. Single and paired pulse transcranial magnetic stimulation in drug naïve epilepsy. *Clin Neurophysiol.* 2016; **127**:3140-55.
5. Bauer PR, de Goede AA, Stern WM, et al. Long-interval intracortical inhibition as biomarker for epilepsy: a transcranial magnetic stimulation study. *Brain* 2018; **141**:409–21.