

Neurophysiological effects of rTMS

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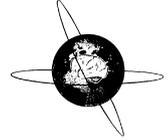
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Editorial

Neurophysiological effects of rTMS: Revisiting the role of the N100 as a clinically useful marker in depression



See Article, pages 2306–2316

Transcranial Magnetic Stimulation (TMS) as a treatment for drug-resistant major depressive disorder (MDD) has been around since the first pioneering reports by Mark George (George et al., 1995) and Alvaro Pascual-Leone (Pascual-Leone et al., 1996) in the mid 1990s. However, the exact working mechanism of rTMS remains elusive as of this day. The initial conceptualizations revolved around the earlier idea of 'left prefrontal dysfunction'. Our current understanding of brain function in MDD has moved away from a locationistic view to a distributed network function view, attributing important roles to the Default Mode and Central Executive networks for a role in MDD, with rTMS thought to modulate functional connectivity within and between these networks with a key role for the subgenual anterior cingulate cortex (ACC) (Liston et al., 2014).

TMS as a technique has not only brought us an innovative treatment modality, but also a valuable technique that can 'ping the brain' to better understand brain function, and possibly a biomarker, also referred to as TMS Evoked Potentials or TEP. TEPs are thought to index propagation of the TMS pulse as well as transsynaptic cortical effects. However, due to the nature of the relatively loud TMS pulses and somatosensory effects (potentially eliciting evoked potentials with auditory and somatosensory origin), caution has been warranted in attributing all TEP components to be related to the TMS pulse alone, since temporal and spatial features of a realistic sham stimulation closely matched real-TMS TEPs (Conde et al., 2019). On the other hand, as Poorganji and colleagues (Poorganji et al., 2021) recently reported in this journal, while the morphology and topography of activation appears similar, real-TEPs had considerable larger amplitudes compared to sham-TEPs.

In this issue of *Clinical Neurophysiology*, Voineskos and colleagues (Voineskos et al., 2021) assessed TEPs before and after real and sham-rTMS. In their study, they nicely demonstrate rTMS treatment effects on two negative components of the TEP (N45 and N100), whereas no such effects were found for the sham rTMS group. More specifically, from pre- to post-treatment they reported that active rTMS resulted in a globally decreased N45 and N100 amplitude, that are thought to reflect GABA_A and GABA_B receptor mediated inhibition, respectively. The change from pre- to post-treatment in N100 amplitude was strongly associated with clinical

response as measured using the Hamilton depression scale (HAMD) with an explained variance of 63%. More focal TEP analyses restricted to the left DLPFC further demonstrated an overall effect of TEP amplitude, not associated with HAMD symptom change, but with baseline TEP amplitude being highly predictive of post-treatment resolution of suicidality with sensitivity and specificity of 87.5% and 77.8%, respectively.

The N100 has often been implicated in studies on MDD and antidepressant response, for instance when recorded in an auditory oddball paradigm where larger N100 amplitudes (more negative) were found to be associated with better clinical response to several antidepressants (Spronk et al., 2011), and worse response to venlafaxine for males in the large iSPOT-D trial (van Dinteren et al., 2015). Furthermore, N100 is also an important component of the Loudness Dependent Auditory Evoked Potential (LDAEP) that has been shown to index serotonergic and possibly glutamatergic innervation (Kenemans and Kähkönen, 2010), and has received interest as a diagnostic and predictive biomarker in MDD. Using an auditory oddball paradigm instead of TMS-EEG, we also reported a decreased N100 amplitude from pre- to post-rTMS in MDD, that was specifically confined to the left pre-frontal cortex (Spronk et al., 2008), conceptually in line with the TEP-N100 results as reported by Voineskos and colleagues (Voineskos et al., 2021). This raises the question, how specific the N100 TEP as reported by Voineskos and colleagues (Voineskos et al., 2021) is to transcranial stimulation, auditory stimulation, a combination thereof, or simply an overlap in neural underpinnings. This will require further elucidation, since, if similar associations could be obtained using an auditory oddball paradigm, this might be preferred over TMS-EEG, for ease of use and higher yield of good quality signal which is crucial for clinical applications (e.g., only for 30/66 people TEPs could be determined due to excessive artifacts, inadequately low trial numbers with TMS pulses and incomplete recordings). Future studies might collect both TEP as well as auditory oddball ERP data within the same MDD patients to shed further light on similarities and differences and unique signal between both approaches to further uncover the added value of both techniques. Nonetheless, the results from Voineskos and colleagues (Voineskos et al., 2021) add to an existing literature that

posits an important role for the N100 ERP/TEP component in tracking and predicting antidepressant response. This suggests that the N100 might be more relevant than other commonly investigated ERP components such as the P300 that yielded relatively little success and inconsistent findings (van Dinteren et al., 2015).

The finding from Voineskos and colleagues (Voineskos et al., 2021) regarding the more focal left DLPFC TEP amplitude so strongly predicting suicidality response to rTMS treatment are novel and intriguing. Clinical implications for such a predictive marker would be immense (and literally life-saving), since it could help prioritize rTMS treatment for specific high-risk patient groups that present with that specific marker. However, that finding calls for replication in an independent sample and extension to other antidepressant treatments to ensure its potential as a clinically actionable biomarker, something we've recently been unsuccessful with for a suicidality EEG-risk marker (Krepel et al., 2021). If replicated, this finding would bring back old memories of the original more focal 'left prefrontal dysfunction' hypothesis, however, now more specifically as a target for remission of suicidality after rTMS, potentially in line with suicidality fulfilling a more transdiagnostic role in psychiatry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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