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Editorial

Seizures with TMS: Much ado about (almost) nothing?

See Article, pages 1409–1416

Since the demonstration that Transcranial Magnetic Stimulation (TMS) could be applied to noninvasively stimulate human motor cortex by Barker et al. (1985), TMS has become a widely used neuroscientific research and clinical tool for measuring and modifying the electrophysiological properties of the human brain *in vivo* for both research and clinical/therapeutic purposes. Although generally quite safe, the most serious acute complication of TMS is the possibility of inducing an epileptic seizure. Soon after its development, TMS in a patient with a prior medial cerebral artery stroke but without any prior history of epilepsy resulted in a first seizure (Hömberg and Netz, 1989). A few years later, the first seizure in a healthy volunteer without any prior risk factors (prior neurologic or psychiatric disease, or use of seizure threshold lowering medications) occurred during high-frequency rTMS of the primary motor cortex (Pascual-Leone et al., 1993). Following these and other such events, safety guidelines for TMS stimulation parameters were developed (Chen et al., 1997; Wassermann, 1998), and updated 10 years later in a paper that reviewed all 16 seizures that had been elicited to date with TMS (Rossi et al., 2009). In addition, Rossi et al. (2009) also listed a number of conditions and medications that might increase seizure risk, and should be taken into consideration when deciding whether to apply TMS. However, the conditions and medications that indicated elevated subject risk were typically extrapolated from various studies which evaluated *spontaneous* seizure risk; these risk factors were presumed to extend to seizures provoked by TMS. In all of this prior work, as the number of TMS sessions conducted without seizures was unknown, the true risk of TMS in terms of seizure induction could not be established.

In this issue of *Clinical Neurophysiology*, Lerner et al. (2019) approach this fundamental knowledge gap by conducting a systematic survey of seizure incidence amongst TMS practitioners. Importantly, respondents were also asked the number of TMS sessions they had conducted in total, to help determine per-session seizure rates. The key takeaway from the study of Lerner et al. is that seizures with TMS are quite uncommon; there were a total of 24 TMS-provoked seizures in 318,560 TMS sessions, for a seizure rate of 0.08 seizures per 1000 sessions. Notably, only 4 seizures occurred in the 242,067 sessions (<0.02 seizures/1000 sessions) conducted without elevated subject- or protocol-risk (as defined in Rossi et al. (2009)). By way of comparison, the annual incidence of epilepsy in the United States is approximately 0.48/1000 people (Hirtz et al., 2007), and the annual incidence of a first seizure may be even higher (e.g. 0.57/1000 people in Iceland; (Olafsson et al., 2005). Importantly, there was no increased risk with conventional rTMS/TBS protocols using conventional (figure-8 or round) coils in these subjects, with no seizures reported in >130,000 sessions. Taken together, these findings suggest that the seizure risk of TMS (including specifically high-frequency rTMS) in subjects without elevated subject-risk when following safety guidelines is actually very low, and TMS should be considered safe (at least from a seizure-induction perspective) in these subjects. Notably, no seizures were reported in these subjects even in sessions with an "elevated protocol risk", where the stimulation parameters may have exceeded the guidelines specified in Rossi et al. (2009). As such, an avenue for future research suggested by this report would be a careful expansion of the safety parameters, perhaps using EEG measures (such as TMS-evoked epileptic after discharges) as an intermediate measure of seizure risk.

The risk of seizure is also low even in sessions with elevated subject-risk (e.g. due to prior structural brain lesions, epilepsy, substance abuse, or use of medications that lower seizure threshold). A total of 19 seizures occurred in 57,185 sessions in these subjects, for a seizure risk of 0.33/1000 sessions. Even this risk is likely being driven by seizures in subjects with known epilepsy; at least 8 of these 19 seizures (42%) occurred in subjects with a prior seizure history, whereas it is highly unlikely that these subjects comprised anywhere close to 40% of the sessions. Of relevance, recent systematic reviews have estimated that the per-subject (as opposed to per-session) seizure risk with TMS in patients with epilepsy is between 1.4 and 2.9% (Bae et al., 2007; Pereira et al., 2016), much higher than the seizure rate noted here in sessions with "elevated subject risk". Another interesting and useful finding is that the majority of seizures occurred in subjects undergoing their first few TMS sessions (62% of seizures occurred in the first TMS session), suggesting that subjects who have safely undergone TMS before are even less likely to suffer seizures in subsequent sessions. One potential point of concern raised by this report is that the seizure rate in sessions with high-frequency rTMS using the H-coil (0.43/1000) is substantially higher than that observed with high-frequency rTMS using other coils (0.05/1000). Relevant to this, a recent review of all reported seizures with the H-coil (including post-marketing reports) by authors associated with the manufacturer estimated an overall seizure rate of 0.87/1000 (Tendler et al., 2018), consistent with the elevated seizure rate noted in this study.

The study by Lerner et al. does have several limitations. First and foremost is that the study is a self-reported survey with relatively low response rates (~6–7%), and drawing primarily from the research population rather than from the clinical practitioners who

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likely are responsible for the bulk of rTMS sessions, particularly in subjects with "elevated subject risk". As such, this population may not be representative, and survey responders may have had lower seizure rates than those who did not respond. Another potential limitation is that practitioners may avoid high-frequency stimulation in subjects with particularly high subject-risk (e.g. in subjects with epilepsy), and thus the relatively low reported seizure risk with high-frequency stimulation in these subjects may reflect a selection bias. Finally, participants were allowed to estimate the number of sessions if they did not have formal documentation, which could also lead to inaccuracies. Systematic approaches to collect and gather this information prospectively are clearly required.

Despite these limitations, this is an important and badly needed study that provides essential new information about seizure risk for the rapidly growing field of TMS practitioners, and that will guide the development of the next version of the TMS safety guidelines. Above all, this study reinforces the notion that when safety parameters are adhered to, TMS (including specifically high-frequency rTMS) is a fundamentally low-risk intervention. One important consequence of this is that while subject medications and neuropsychiatric diagnoses should continue to be documented to assess potential risks in future studies, at this time no medication or disease condition (with the possible exception of epilepsy) should be considered a strong contraindication to TMS. Another implication is that while basic training in management of seizures is still advisable (as is training in diagnosis and management of syncope, which is significantly more common), TMS done following safety guidelines, particularly in subjects without elevated risk, can likely be done without pre-arranged clinical support for management of possible seizures. Hopefully this report will promote further adoption of this useful and unique tool into the research and clinical armamentarium.

Declaration of Competing Interest

I have no conflict of interest related to the present work.

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