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Reply to: “Reflecting the causes of variability of EEG responses elicited by cerebellar TMS”

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ABSTRACT

In their commentary on our recently published paper about electroencephalographic responses induced by cerebellar transcranial magnetic stimulation (Fong et al., 2023), Gassmann and colleagues (Gassmann et al., 2023b) try to explain the differences between our results and their own previous work on the same topic. We agree with them that many of the differences arise from our use of a different magnetic stimulation coil. However, two unresolved questions remain. (1) Which method is most likely to achieve optimal activation of cerebellar output? (2) To what extent are the evoked cerebellar responses contaminated by concomitant sensory input? We highlight the role of careful experimental design and of combining electrophysiological and behavioural data to obtain reliable TMS-EEG data.

1. Commentary

We thank Gassmann and coworkers for their interest in our recent work on electroencephalographic (EEG) responses elicited by cerebellar transcranial magnetic stimulation (TMS) (Fong et al., 2023) and for sharing their considerations on the subject (Gassmann et al., 2023b). We agree that there exist several factors that may account for the discrepancies in our respective findings.

A first key distinction lies in the approach to somatosensory sham stimulation. We opted for concurrent electrical stimulation on the masseter and trapezius muscles, aiming to closely emulate the somatosensory input from cerebellar TMS. Conversely, Gassmann and coworkers adopted a subtraction method between real TMS and a sham involving supramaximal electrical stimulation of the neck and magnetic stimulation of the shoulder. We hold the view that this solution introduces an unnecessarily large somatosensory input that, as acknowledged by the authors themselves “has increased the risk of changing the spatiotemporal patterns of the transcranially evoked EEG signature, as increased sensory inputs lead to more pronounced motor cortex modulation” (Gordon et al., 2021; Novembre et al., 2019).

Another critical technical aspect pertains to the use of distinct TMS coils. Prior literature suggests that the 50 mm flat coil employed by Gassmann and colleagues might be less effective in eliciting cerebellar-brain inhibition (CBI) compared to the double cone coil we used in our investigation (Fernandez et al., 2018; Hardwick et al., 2014; Spampinato et al., 2020). However, it is worth noting that the 50 mm flat coil may

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still induce inhibition of the contralateral primary motor cortex via cervical root stimulation (Werhahn et al., 1996). Regarding the authors' argument about their electrical field (E-field) calculations allowing definitive conclusions about effective cerebellar stimulation, it should be highlighted that the chosen site for E-field estimation (PO10, based on the international 10-10 EEG system) differs from the site used for stimulation in the main experiment (mid-point between inion and mastoid) (Gassmann et al., 2022). Furthermore, as previously underscored (Siebner et al., 2022), E-field estimation does not encompass neuronal firing and should not replace physiological measurements.

Gassmann and colleagues also raise a pertinent point concerning the possibility that our cerebellar TMS-EEG responses could be contaminated by sensory potentials, a common consideration in TMS-EEG studies. In this regard, it is crucial to note that sensory responses in the context of TMS-EEG have been thoroughly investigated and are predominantly characterized by prominent vertex N100/P200 waves (Belardinelli et al., 2019; Rocchi et al., 2021). Given this, along with the substantial differences we observed between effective TMS and sensory stimulation conditions, it is unlikely that the P80 observed in our own data is of sensory origin. Nevertheless, we acknowledge that there might be some overlap with a sensory N100 and a second component that we observed, the N110; however, there are differences in the distribution and latency of the two responses that imply that they have at least partially distinct generators (Fong et al., 2023). Interestingly, Gassman and colleagues also tacitly acknowledge the plausibility of late EEG responses by presenting convincingly asymmetric TEPs in the 70–110 ms range in a patient with dentato-thalamo-cortical damage (Gassmann et al., 2023a) and contralateral prefrontal activation in the high-beta band, up to 200 ms following cerebellar TMS in healthy subjects (Gassmann et al., 2022).

Lastly, to support the notion that the TMS-EEG responses we observed likely originate from the cerebellum, we highlight our approach that integrates electrophysiological with behavioural data. Since no established "gold standard" for TMS-EEG responses exists (Hernandez-Pavon et al., 2023), behavioural tasks are valuables methods that can help us to draw inferences about the physiological processes and cortical generators underlying TMS-EEG responses (Casula et al., 2022). In our own report we found that the P80 and N110 were modulated by a visuomotor adaptation task, and that these changes correlated with different aspects of motor learning. Our conclusion was that this evidence provides strong support that these responses have a cerebellar origin.

In conclusion, we agree that standardizing methods is pivotal for a better comprehension of cerebellar TMS-EEG responses. Nonetheless, rather than solely relying on E-field estimation, we emphasize the importance of integrating independent physiological and behavioural methodologies to inform conclusions about cerebellar activation.

Declaration of Competing Interest

All authors declare no competing interest.

Data availability

No data was used for the research described in the article.

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