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Letter to the editor: Chronic theta burst stimulation does not significantly modulate glial activity in the healthy non-human primate brain

Repetitive Transcranial Magnetic stimulation (rTMS) is a non-invasive therapeutic tool currently approved by the FDA and Health Canada as an intervention for treatment-resistant depression and is being investigated as an intervention for other neuropsychiatric and neurophysiological disorders [1]. As the clinical applicability of rTMS increases and new protocols are developed, the study of chronic stimulation safety is imperative.

While rTMS is considered a relatively safe intervention, it is important to note that most studies report the immediate side effects of acute delivery, such as seizure, headache, and other measurements related to patient discomfort. Only a limited number of studies have evaluated cellular and molecular markers to investigate the safety of chronic stimulation.

Glial cells are an important component of the central nervous system and have a major role in the neuroinflammatory response. In the study of rTMS, the assessment of glial cells is relevant given that they respond to electrical activity involved in neuronal signaling [2] and are possible mediators of rTMS effects. The evaluation of glial activity could provide insight into the effects of chronic stimulation, specifically in the study of neuroinflammatory effects and interventional safety, as sustained low-grade neuroinflammation can have long-term detrimental effects [3].

We investigated the impact of a clinical course of theta burst stimulation (TBS), a patterned form of rTMS, in glial activation. Positron emission tomography (PET) was used to evaluate the expression of translocator protein (TSPO), a biomarker for neuroinflammation as it is overexpressed in activated microglia [4].

Non-human primates were randomly assigned to receive intermittent TBS (iTBS), continuous TBS (cTBS), or sham stimulation. TBS was delivered over the left motor cortex in awake rhesus monkeys (n = 11, 4 females, age 9.3 ± 4 years) Monday to Friday for 3–4 weeks following typical stimulation parameters: three pulses delivered at 50 Hz and repeated at 5 Hz (cTBS: 40s-train of uninterrupted TBS; iTBS: 2s-train of TBS, repeated every 10s), 600 pulses total at 90% resting motor threshold (RMT). Sham stimulation was delivered using the same parameters as cTBS, but at 15% RMT and with stimulation coil placed "upside down". [^{11}C]PBR28 images were acquired with a High-Resolution Research Tomograph PET scanner before and 24 hrs after the last TBS session. Some subjects underwent more than one stimulation/sham protocol; each protocol was separated by an average of 11 months (range: 4 months (N = 2) to 22 months (N = 1)). The number of sessions was based on PET scanner and tracer availability (average iTBS = 17 ± 3; average cTBS sessions = 16 ± 3; average sham sessions = 16 ± 2). In total, 7 animals received cTBS, 8 received iTBS, and 7 received sham stimulation.

The total volume of distribution (V_T) was calculated using a population-based input function as previously described [5]. We also calculated the distribution volume ratio (DVR) using the cerebellum as a reference region [6]. V_T and DVR estimates were computed from the left and right motor cortex (Fig. 1). We reported both measurements (V_T and DVR) aiming to show the robustness of our results, regardless of the type of analysis performed. Both analyses represent an estimate of the amount of tracer binding (i.e., the level of microglial activation) in a given region compared to either a volume of plasma (V_T) or a region with negligible amount of receptor sites (DVR). While there is no true region with negligible concentration of microglia in the brain, the cerebellum is often used as reference in human TSPO studies. In our case the cerebellum was used as we did not expected it to be significantly affected by stimulation of frontal cortical areas.

Bayesian paired *t*-test of V_T indicated anecdotal evidence for an absence of intervention effect in the bilateral motor cortex after cTBS (left $BF_{10} = 0.87$; right $BF_{10} = 0.64$), iTBS (left $BF_{10} = 0.64$; right $BF_{10} = 0.38$) and sham (left $BF_{10} = 0.70$; right $BF_{10} = 0.80$). Similarly, Bayesian paired *t*-test of DVR estimates indicated anecdotal evidence for an absence of intervention effect after cTBS (left $BF_{10} = 0.36$; right $BF_{10} = 0.35$), iTBS (left $BF_{10} = 0.38$; right $BF_{10} = 0.53$), and sham (left $BF_{10} = 0.39$; right $BF_{10} = 0.38$).

Our results showed no evident effects of stimulation on TSPO expression after chronic delivery of TBS. This suggests the absence of a sustained inflammatory response following a clinical course of TBS in healthy brains.

Our findings align with reports from rodent studies, where no microglia or astrocyte reactivity changes were found after 3 and 5 sessions of high or low rTMS stimulation delivered in healthy brains [7,8]. Conversely, in a rodent model of spinal cord injury and depression, daily rTMS for 8 to 4 weeks decreased the activation of microglia and other inflammatory markers [9,10]. These findings suggest that rTMS delivery modulates glial markers of reactivity in cells already in a reactive state from disease or injury. However, further studies should evaluate these statements as the comparability between the current work and past rodent studies is limited by the differences in species and rTMS protocols used.

Some of the limitations of this study are related to the sensitivity and specificity of TSPO as a biomarker for microglial activation, which can vary depending on the specific context (e.g., neuroinflammation progression, tracer used, subject population). Thus, some levels of glial activation may not result in a measurable change in PET-TSPO. Furthermore, the Bayesian factors reported (ranging from 0.35 to 0.87) also indicated that the evidence against effect of stimulation is modest. These limitations warrant further research on the effects of rTMS on the neuroinflammatory response.

Ultimately, our findings provide novel insight into the safety of TBS

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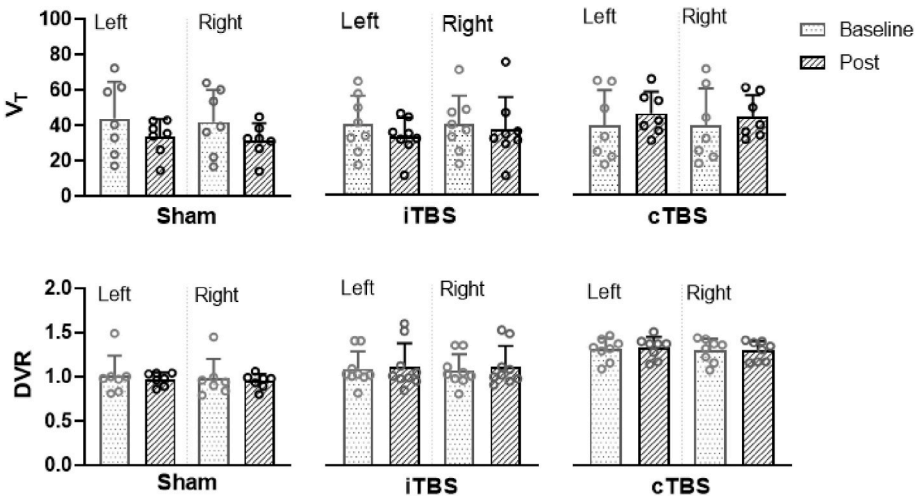

Fig. 1. Volume of distribution (V_T) and distribution volume ratio (DVR) estimates from the left and motor cortex before and after sham stimulation, iTBS, and cTBS.

specifically and rTMS generally and prompt further research of neuroinflammatory effects following multiple TBS stimulation sessions. This work also highlights the relevance and feasibility of molecular and cellular studies regarding the safety of non-invasive brain stimulation.

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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