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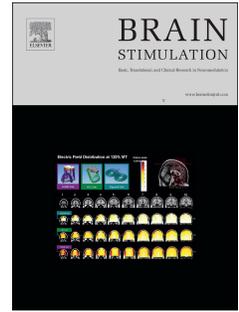
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Brain Stimulation - Letter to the editor

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High-frequency rTMS over cortical motor areas does not alleviate experimental dyspnea: a randomized sham-controlled study

Dear Editor,

Dyspnea conveys an upsetting or distressing awareness of breathing. The typical symptom of many disorders and a debilitating experience, dyspnea is associated with an ensemble of brain responses to abnormal respiratory-related messages (1). When dyspnea persists despite lung-oriented treatments, targeting its cerebral mechanisms is warranted (2). The supplementary motor area (SMA) and the primary motor cortex (M1) belong to involved respiratory-related networks, the corollary discharge mechanism being considered highly relevant to dyspnea pathogenesis (1). Because high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) over the SMA can modify the breathing pattern (3), we hypothesized that it could also modulate experimental dyspnea.

With ethical approval, we conducted a double-blind, crossover, randomized, sham-controlled study of SMA and M1 HF-rTMS conditioning on the dyspneic response to an inspiratory load consisting in a spring-loaded threshold valve that must be overcome to breathe. This procedure produces an "excessive respiratory effort" sensation. Thirty informed and consented healthy men (median age: 24.9) participated. Sham stimulation and 20Hz HF-rTMS (4-5) were applied over the SMA (12 participants) or M1 (18 participants), using appropriate 70 mm figure-of-eight coils connected to a Magstim Rapid² (Magstim, Sheffield, UK) and tracked with neuronavigation (Visor2, ANT Neuro, The Netherlands). Given neurophysiological analogies between dyspnea and pain we followed rTMS recommendations for chronic pain: we used a facilitatory protocol consisting of 1200 pulses delivered in thirty 2-second trains with an inter-train interval of 16 seconds (4). Stimulation intensity was 100% of the first digital interosseus resting motor threshold. During the experiments, breathing frequency and tidal volume were recorded using *ad hoc* instruments. Dyspnea was rated continuously and in response to one-minute interval prompting using two visual analog scales (VAS) as follows. The participants first learned to distinguish sensory and affective responses to inspiratory loading using a music analogy ("loudness" vs. "agreeableness"). They then used sliding electrical response meters (AD Instruments, Australia) for a discomfort affective rating (affective VAS, from 0 –no discomfort– to 10 –intolerable–; primary outcome) and a sensory rating (sensory VAS, from 0 –no sensation– to 10 –maximum imaginable–). At the end of each experimental epoch (see below), they were asked to complete a multidimensional questionnaire (Multidimensional Dyspnea Profile) (6). Each participant was involved in two sessions separated by a 3-day washout. Experiments started with inspiratory loading titration to obtain an affective VAS rating of 5. Experiments were then divided into four epochs followed by a 5-minute rest: (1) baseline dyspnea challenge, 5 minutes (baseline, BL); (2) SMA or M1 conditioning by active or sham rTMS, 10 minutes; (3) second dyspnea challenge, 5 min (T1); (4) third dyspnea challenge, 5 min (T2) (Electronic Supplement, ES1). Statistical analysis was performed with Prism[®] 9.4.1 (GraphPad, USA). Normality and sphericity were tested using d'Agostino & Pearson test, with sphericity violations corrected using the Greenhouse-Geisser procedure. Dyspnea and respiratory data were compared between conditions using a two-way repeated ANOVA (HF-rTMS factor, active vs. sham; time factor, BL vs. T1 vs T2). $p < 0.05$ was considered significant.

In the SMA group, one subject withdrew consent, and one subject was excluded because reporting no respiratory discomfort at baseline, leaving 10 participants for analysis. In the M1 group, all participants completed the study. All participants tolerated the stimulation procedures well. Regarding dyspnea affective VAS (primary outcome), no statistically significant effect was detected between HF-rTMS conditions, and there was no significant HF-rTMS-time interaction after SMA conditioning ($F_{(1,9)}=0.17$,

$p=0.69$; $F_{(1.42,12.8)}=1.54$, $p=0.25$ respectively), or after M1 conditioning ($F_{(1,17)}=0.27$, $p=0.61$; $F_{(1.72,29.22)}=1.85$, $p=0.18$) (Figure 1). The same was true for dyspnea sensory VAS, breathing frequency, and tidal volume. Regarding the Multidimensional Dyspnea Profile, the participants consistently chose the expression "excessive inspiratory effort" to designate their sensory response. No difference was found after HF-rTMS regarding the sensory and affective dimensions of dyspnea as explored by this questionnaire. (Electronic Supplement, ES2).

In this study, HF-rTMS, otherwise known to alleviate certain forms of chronic pain (7) and previously shown to modify breathing pattern during inspiratory loading (3), did not interfere with inspiratory loading-induced experimental dyspnea when applied over the SMA or M1. This negative result could stem from several mechanisms. Firstly, we studied the effects of HF-rTMS conditioning after up to 20 minutes, possibly too early to detect an effect (7). Secondly, the analgesic effects of HF-rTMS are often observed only after repeated sessions (7). Thirdly, contrary to a previous study on inspiratory loading (3), we used a high level of inspiratory loading for standardization purposes: this could have masked HF-rTMS effects on breathing pattern and dyspnea through a ceiling effect. Fourthly, cortical excitability is increased when respiratory-related cortical networks encompassing the SMA and M1 are activated to maintain ventilation in response to inspiratory loading (8). In this regard, our study's bout of inspiratory loading preceding HF-rTMS conditioning could have impaired the long-term potentiation-like plasticity mechanisms activated by HF-rTMS (9). In this hypothesis, in contrast to pain, an inhibitory low-frequency M1-rTMS protocol could be preferred to mitigate dyspnea. Fifthly, despite the known SMA activation in response to inspiratory loading, the SMA role in the corollary discharge mechanism and in the modulation of effort perception (10), all of which made it a logical target for dyspnea mitigation by HF-rTMS, it is possible that the conditioning protocol we used was not able to interfere with the SMA connections to limbic areas (insular cortex or cingulate gyrus) that play a determinant role in dyspnea pathogenesis (1). Finally, experimental dyspnea in healthy subjects may not be the best model to test HF-rTMS-induced neural plasticity approaches, mainly because it does not involve the anticipatory phenomena that result, in patients, from repeated exposure to dyspnea and the unavoidable ensuing brain functional reorganization. In conclusion, pursuing the exploration of rTMS as a method to alleviate persistent dyspnea seems to require other brain targets, other models, or both. Future studies could use specific coil designs to target the insular cortex. Another option would be to bypass experimental models and conduct proof of concept studies in patients with persistent dyspnea.

Competing interests

The authors have no conflict of interest to declare.

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Abbreviations

HF-rTMS: high-frequency repetitive transcranial magnetic stimulation

M1: primary motor cortex

SMA: supplementary motor area

VAS: visual analog scale

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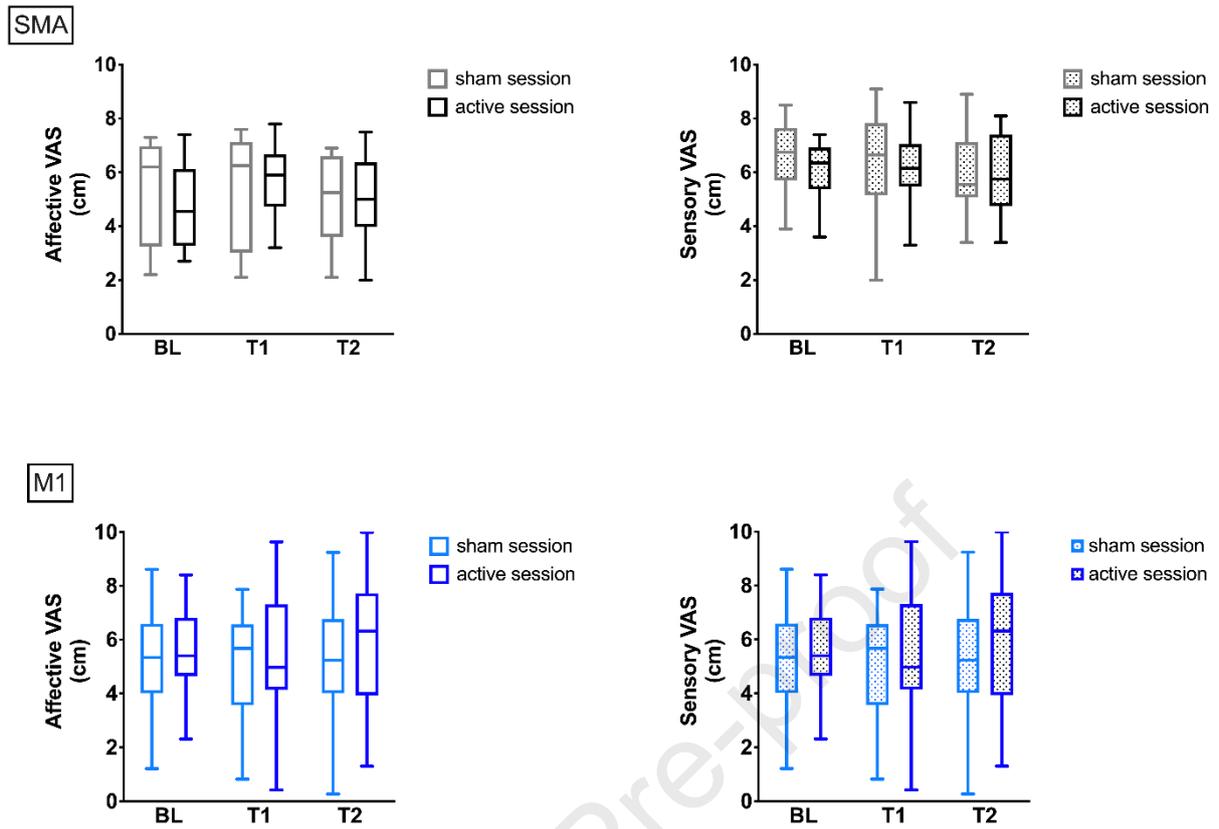


Figure 1 legend:

Effects on SMA HF-rTMS conditioning and M1 HF-rTMS conditioning on affective and sensory visual analog scale (VAS) ratings at BL, T1 and T2. All data are expressed as absolute values.

The boxes depict the interquartile range with indication of the median. Whiskers show min-max.

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Data acquisition: JH, CLF, AS, JV, NN, LS

Analysis and interpretation: JH, TS, MCN

Drafting the manuscript: JH, CLF, AS, TS, MCN.

Final approval: all the authors.

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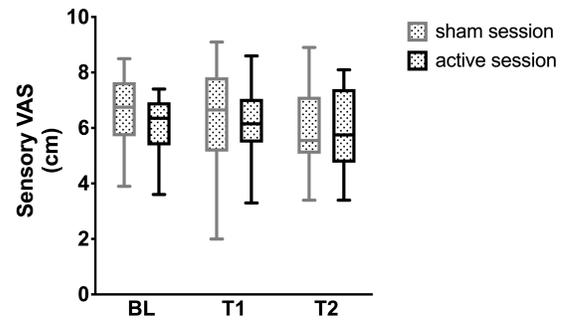
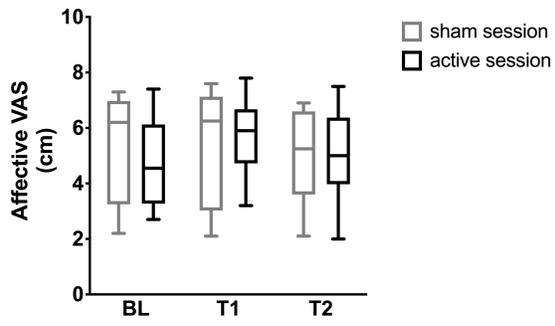
Ethics approval and consent to participate

The study was approved by the appropriate French ethics and regulatory authorities (Comité de Protection des Personnes Ouest IV RCB ID 2018-A03131-54, et Ouest I RCB ID 2021-A02240-41 and Agence Nationale de la Sécurité du Médicament). All subjects received detailed information and provided their written informed consent.

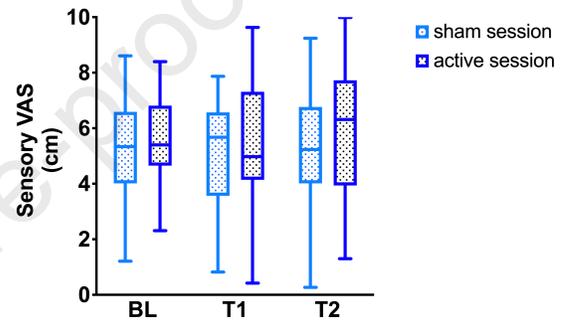
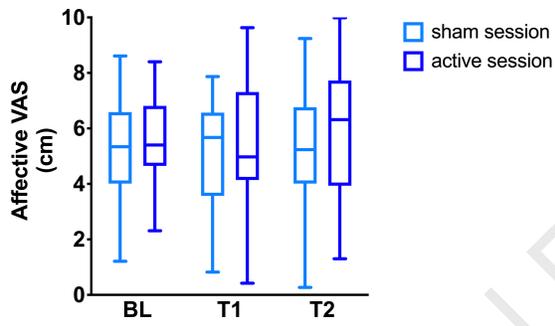
Availability of data and materials

Our data are available to ensure transparency.

SMA



M1



Declaration of interests

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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