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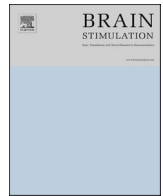
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No place in France for repetitive transcranial magnetic stimulation in the therapeutic armamentarium of treatment-resistant depression?

Dear editor

Hereby, an international group of TMS experts responds to a recent report* from French Health authority “La Haute Autorité de Santé” (HAS) that released on July 2022 a negative statement on repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant depression (TRD). The overarching goal of this report was to determine 1/the level of evidence of active versus sham high frequency rTMS in the indication of TRD (as defined by failure of two antidepressant (AD) trials) in acute depressive phase and 2/the level of evidence of maintenance therapy in the same indication, 3/the place of this technique in the therapeutic armamentarium for TRD specifically against electroconvulsive therapy (ECT). The HAS panel conducted a meta-analysis that was supposed to synthesize the available data – published between 01/2017 and 11/2021 – that used high frequency conventional TMS over the left dorsolateral prefrontal cortex (DLPFC) in patients suffering from TRD. Eight studies have been included in this work with total of 475 patients (active rTMS: $n = 242$, sham rTMS: $n = 233$). The panel concluded a lack of efficacy of active HF-TMS compared to sham (mean difference on Hamilton Depressive Rating Scale (HDRS) = -2.02 points; $p = 0.17$). Thus, they reported that ECT was superior to rTMS (mean difference (HDRS) = -6.26 points; $p = 0.0001$) and therefore that rTMS cannot be an alternative to ECT. Finally, they stated that no conclusion can be made on rTMS maintenance protocols. In line with the initial request from the French organization that manages the reimbursement of cares, the HAS qualitatively addressed the question of medico-economics associated with rTMS environment in the context of its practice in France. The HAS emphasized that rTMS significantly increases the cost of care by engaging caregiver resources as well as the need of training which results to a non-viable economic model.

There are significant methodological weaknesses in the HAS work which limits the relevance of their conclusions. The overall rationale behind including only 8 studies in regards to the incredibly rich available data in the literature is at best unclear if not confusing. Moreover, not all of these studies were designed to test superiority of active rTMS over sham. One study [1] had a significant proportion of highly comorbid patients (post-traumatic stress disorder, substance abuse, neurological disorder). In 6/8 studies, the sham technique (90° tilted coil) was known to be inappropriate because potentially active [2]. Finally, the included studies were heterogeneous in terms of methodological quality, particularly concerning the co-prescription of AD medication and treatment resistance severity. Then, the HAS meta-analysis, based on studies with restrictive inclusion criteria and reporting a very small proportion of currently available data, but with a

highly variable set of designs and participants, does not reflect the reality of the rTMS practice neither in France nor internationally. Most importantly, the time window chosen for their meta-analytic work is questionable since it does not include any TMS study prior to 2017, thereby excluding the most well-powered and well-designed pivotal trials in the field such as the pivotal Neuronetics trial that resulted in FDA approval and the independent NIH-funded replication of that trial [3,4]. The conclusion of the HAS analysis therefore seems inappropriate and suffers from obvious lack of representativeness. Thus, the work of the HAS did not meet the reference standards for meta-analyses, as required for registration in PROSPERO or PRISMA databases. Evidence of rTMS efficacy has been reported reproducibly in large randomized clinical trials [3,4], naturalistic studies [5], and meta-analyses [6], regardless of the device used to perform prefrontal rTMS. Safety has also been demonstrated [7] and it is certain that rTMS produces less side effects than drugs [8]. Contrary to what has been stated by the HAS, rTMS can be cost-effective from a medico-economic point of view if we consider the potential benefits of effective management of depression on direct (less medications, fewer hospitalizations) and indirect (improvement of professional functioning) cost-savings, rather than considering only the economic burden of the technique. The cost-effectiveness ratio was evaluated in a meta-analysis which concluded in favor of rTMS over medications [9]. As it stands, the HAS report raises serious concerns in terms of access to care and ethical issues. By not recommending rTMS for the treatment of TRD, the HAS decision therefore exposes France to serious consequences. Firstly, such a decision discredits an entire field of clinical activity based for years on this therapeutic innovation in the domain of psychiatry and depression and may cause patients and their families to lose a potentially valuable treatment option. Secondly, not recommending the therapeutic practice of rTMS in a structured way exposes the risk of heterogeneous and uncontrolled practice without any guarantee of quality and regulation. This point is a crucial issue because official recognition, by such a regulatory agency, could require the establishment of a sub-specialty of practitioners properly trained in neuromodulation therapy with high expected benefits for patients and therefore for public health [10]. Thirdly, it will handicap France in this promising field of clinical research which is rapidly evolving internationally. For nearly 20 years, and not being limited to the last 5 years as HAS done, the scientific literature has provided sufficient data on the efficacy, safety, cost-effectiveness of prefrontal rTMS in the treatment of TRD to be considered as a relevant therapeutic option. Although, there is ongoing research on new stimulation paradigms, including multi-daily sessions, which may provide greater and longer lasting benefit, the efficacy of conventional high-frequency rTMS of the left DLPFC should be

* https://www.has-sante.fr/jcms/p_3211966/fr/stimulation-magnetique-transcranienne-dans-le-traitement-de-la-depression-de-l-adulte.

considered sufficient to validate this technique as a therapeutic option and not as a technique in development. There is an urgent need to revise this position of health regulatory agencies in France.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JMB has served as a scientific consultant for Magnus Medical.

RG has received compensation as a member of the scientific advisory board of Janssen, Lundbeck, Roche, SOBI, Takeda. He has served as consultant and/or speaker for Astra Zeneca, Boehringer-Ingelheim, Pierre Fabre, Lilly, Lundbeck, LVMH, MAPREG, Novartis, Otsuka, Pileje, SANOFI, Servier and received compensation, and he has received research support from Servier. Co-founder and stock shareholder : Regstem.

DS is a principal investigator of several rTMS research protocol (Centre Scientifique de Monaco), member of board in the STEP section of the AFPBN (French Association of Biological Psychiatry and neuropsychopharmacology), member of Task force for ECT (WSFPB), member of the European Society of Brain Stimulation (ESBS).

SB is a principal investigator of several rTMS research protocol (CHU Nantes and DGOS grants), he serves as instructor in the STEP (Stimulation in Psychiatry) section of the AFPBN (French Association of Biological Psychiatry and Neuropsychopharmacology) and is a member of the European Society of Brain Stimulation (ESBS).

MA is unpaid chairman of the Brainclinics Foundation, holds equity/stock in neurocare, serves as consultant to neurocare and Numinous.

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SP report the following potential conflict(s) of interest: 2020 Recordati, The Forensic Panel, L.E.K. Consulting, Biohaven Pharmaceuticals, inc, EMBS Group spółka z ograniczoną odpowiedzialnością spółka komandytowa, Angelini Pharma, GEDEON RICHTER Plc, Association of Analytical Child and Adolescent Psychotherapists in Germany (Vereinigung Analytischer Kinder- u. Jugendlichen-Psychotherapeuten in Deutschland e. V., VAKJP), Swiss National Science Foundation (SNSF) Innova Pharma; 2021 Recordati, Biohaven Pharmaceuticals, inc, Angelini Pharma, GW Research Limited, Innova Pharma, Swiss National Science Foundation (SNSF) for Spark funding instrument, Lundbeck, Otsuka Pharmaceutical, Aboca, Biogen, Menarini; 2022 Neopharmed Gentili, Lundbeck, Biohaven Pharmaceuticals, Inc, Beckley Psytech, Medpace, Acsel Health, Biogen; 2017 – 2022 R21 Grant, The National Institute of Mental Health: "Modulating Inhibitory Control Networks in Gambling Disorder with Theta Burst Stimulation". MPI: Nikolas Makris; Role: Co-I. Clinical Trial NCT03669315.

BM is SYNEIKA (neuronavigation system applied to TMS) shareholder; and has served as consultant for Brainsway.

NRW is a named inventor on Stanford-owned intellectual property relating to accelerated TMS pulse pattern sequences and neuroimaging-based TMS targeting; he has served on scientific advisory boards for Otsuka, NeuraWell, Nooma, and Halo Neuroscience; and he has equity/stock options in Magnus Medical, NeuraWell, and Nooma.

The other co-authors do not report any COI related to this this work.

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