Personalized functional imaging identifies brain stimulation target for a patient with trauma-induced functional disruption

Dear editor

Non-invasive neuromodulatory techniques such as transcranial magnetic stimulation (TMS) have been increasingly used to treat a wide range of psychiatric and neurological disorders [1]. Recent studies have shown that personalized functional MRI (fMRI)-guided neuromodulation may outperform conventional anatomy-guided stimulation for patients with treatment-resistant major depressive disorder (MDD) [2,3]. In these studies, subject-specific targets identified in the dorsolateral prefrontal region by their robust functional anti-correlations with the subgenual anterior cingulate cortex (sgACC) achieved better treatment outcomes than those target regions showing scant sgACC anti-correlations. This empirically-driven approach to TMS target identification is advantageous in MDD, but for a variety of brain disorders without an empirically defined circuit, identification of personalized TMS targets is challenging. We designed a strategy for personalized brain stimulation based on abnormal RSFC assessed by resting-state fMRI (rsfMRI) and applied it to a 21-year-old patient suffering from severe motor, cognitive and mood impairments due to brain trauma. We stimulated the personalized target using TMS and evaluated the RSFC changes along with symptom improvement following treatment. Here, we leveraged fMRI and TMS to provide proof of concept for personalized fMRI-guided closed-loop stimulation that includes functional brain assessment for target identification, neuromodulation, and reassessment of functional connectivity.

1. Case report

The patient was a 21-year-old male snowboard athlete who sustained severe trauma during training that resulted in an intracranial venous sinus thrombosis, cerebellar hematoma, and obstructive hydrocephalus. A structural MRI revealed a large lesion along his cerebellar vermis that extended into both cerebellar hemispheres (Nov 20th, 2019, Fig. 1A). The patient suffered from a severe disorder of consciousness and underwent craniotomy with hematoma evacuation twice within a week. After stabilization of vital signs, the patient was transferred to our hospital (Feb 19th, 2020) and underwent a rigorous rehabilitation regimen to Jun 8th, 2020 (6.5 months following the initial injury, see supplementary methods) by comparing the patient’s fMRI with 1000 healthy subjects’ data. High abnormality was observed in the left DMPFC region (Fig. 1B), which is functionally associated with multiple cognitive and emotional symptoms [5–7] and is anatomically connected to the cerebellum via cerebello-thalamo-cortical pathways [8,9]. Stimulation to the DMPFC might impact the functional networks and cortico-cerebellar circuits associated with aforementioned symptoms. On Jun 8th, 2020, treatment began with an efficient form of high-frequency TMS known as intermittent theta burst stimulation (iTBS) using a Magstim Rapid magnetic stimulator (Magstim, Whitland, U.K.) with a figure-of-eight coil placed over the left DMPFC (Fig. 1B). Each iTBS session contained a total of 600 pulses (50 Hz triplets delivered at 5 Hz) at 90% resting-state motor threshold (see supplementary methods).

After 20 sessions of iTBS extending across a period of 4-weeks, the patient was administered the same battery of neuropsychiatric tests and fMRI examinations. We found remarkable improvements in his general cognitive functioning and mood, with 38.3–84.6% increases in testing scores (Fig. 1C and Tables S1 and S2). In addition, the patient was able to ambulate independently. Remarkably, over the course of three months following iTBS treatment, the patient’s motor abilities continued to improve to the point that he was able to run without assistance (see Video. S2 for running performance). At the one-year follow-up visit (June of 2021), the patient’s cognitive functions showed steady or continued improvement compared to the baseline, and the mood scores showed a modest increase, with 46.2%–97.5% increases in testing scores (Fig. 1C).

To determine how the above-mentioned symptom improvements related to changes in the RSFC, we placed seeds in the PCC, canonical parietal nodes of the default mode network (DMN). PCC showed significant improvement in long-distance RSFC and anti-correlations with attention networks (Fig. 1D, S1A-B; p < 0.001, Wilcoxon signed rank tests). The absence of anti-correlations between DMN and attention networks has previously been linked with symptoms associated with various brain disorders [10]. The appearance of long-distance correlations and anti-correlations within the DMN and attention networks after iTBS might be
Fig. 1. (A) The patient’s anatomical MRI image demonstrates a massive lesion in the cerebellar vermis, extending into both cerebellar hemispheres, which was sustained as a result of ischemic stroke following trauma-induced injury indicated by red arrows. (B) The iTBS target was determined in the left DMPFC showing high abnormality in functional connectivity. (C) A neuropsychological battery was applied to measure cognitive and mood-related changes before (Pre-TBS) and after iTBS (Post-TBS) treatment and in one year after treatment (Follow-up), including MoCA, a measure assessing cognitive status, WAIS, a measure of intelligence, WMS, a measure of memory function, HAMA and HAMD measuring symptoms of anxiety and depression. The percentages above the bar indicate the improvement comparing to the pre-TBS. The observed clinical changes after iTBS treatment are consistent with the efficacy of iTBS treatment. (D) The RSFC changes associated with behavioral improvements were revealed by contrasting the RSFC maps derived from seeds (white filled circles) placed in the DMN (i.e., the PCC seed) prior to (pre-TBS) and following (post-TBS) treatment. The long-distance functional connections, indicated by arrows, emerged after iTBS treatment. (E) For the motor seed, contralateral cortico-cortical and cortico-cerebellar RSFC, indicated by arrows, appeared after iTBS treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
associated with the patient’s improvements in cognitive functioning and mood. Moreover, the RSFC between the primary motor cortex and contralateral cortical and cerebellar sensorimotor areas emerged after iTBS treatment (Fig. 1E, S1C–D; p < 0.0001, Wilcoxon signed rank tests), which temporally coincided with patient’s improvements in motor function. Although the mechanisms of neural recovery are not yet understood, it may be that the tailored stimulation led to cortical and cerebellar neuroplastic changes above and beyond the threshold that could be achieved from conventional rehabilitation, thereby overcoming the local optimal state (i.e., the plateau in recovery) to reorganize functional networks on a global scale, which might explain the continued improvements observed in both motor functions after treatment.

In summary, we present a novel pipeline to detect functional abnormalities using fMRI which can guide neuromodulation, and to assess normalization of the brain networks following the treatment. When applying this pipeline to a case with severe functional impairments, our approach shows sensitivity in its ability to detect functional abnormalities in RSFC prior to treatment and normalization of these network abnormalities following fMRI-guided TMS modulation, which temporarily coincided with improvements in cognition, mood and motor function. The practical application of our approach extends RSFC from a research tool for retrospective studies to a practical tool for threading the pipeline. Furthermore, the post-treatment assessments based on RSFC closes the loop along the continuum from initial diagnosis, to treatment, and final assessment. The conceptual framework that combines rsfMRI and TMS interconnects each of these components into a personalized, non-invasive, closed-loop brain stimulation system.

Declaration of competing interest

HL is on the chief scientific advisory board for Neural Galaxy LLC and is listed as an inventor in issued patents on brain imaging that are unrelated to this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.11.005.

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