Baseline regional brain volume and resting-state functional connectivity predicts antidepressant outcomes in unipolar depression after intermittent theta-burst stimulation

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Introduction

- **Major Depressive Disorder (MDD)** → high impact in global public health
- **Antidepressants** as first-line treatment for depression → **about 30% of patients are resistant**
- Due to these limitations -> non-invasive brain stimulation (NIBS). This class of treatment is capable of modifying brain excitability in an effective, safe and non-invasive way and includes transcranial direct current stimulation (tDCS) and **repetitive transcranial magnetic stimulation (rTMS).**
- **The intermittent Theta-Burst Stimulation (iTBS)** became a new therapeutic intervention for the treatment of MDD, being advantageous due to the **shorter** treatment session time (3-9 min vs. 40 min in rTMS), and its **non-inferior** antidepressant efficacy compared to rTMS.
- Many studies have shown that the optimal target for rTMS stimulation is the left dorsal prefrontal cortex (DLPFC) area that presents the highest resting-state functional anticorrelation with the right subgenual Anterior Cingulate Cortex (sgACC) → **outcome predictor**
- Any study provided associations between baseline **structural brain measures** and rTMS antidepressant effects → although it has been shown to be consistently altered in patients with MDD

We evaluated the associations between baseline MRI-based measures and iTBS antidepressant effectiveness in unipolar depression patients.

- We focused on MRI-based measures of areas **DLPFC**, as it was the stimulation site, and the **sgACC**, which although outside the stimulation focus, was previously associated with brain changes in MDD patients and related to the antidepressant effects of rTMS.

Material and Methods

- This was an open clinical trial.
- Patients between 18 and 65 years of age, with an initial Hamilton Rating Scale for Depression (HAMD-17) greater than or equal to 14, and treatment resistant depression confirmed by the Mini International Neuropsychiatric Interview (MINI), were recruited through social media and internal disclosures directed at Hospital das Clínicas employees.
- Montgomery-Asberg Depression Rating Scale (MADRS) was also used to evaluate depression. Patients received 20 consecutive days of stimulation and returned one week after the end of treatment for evaluation of clinical outcomes (follow-up). MRI was collected in the week before the start of the stimulation protocol.
- The coil was positioned on the left DLPFC, identified according to the Beam method, using a MagPro X100 device (MagVenture. Denmark) with a butterfly-shaped coil. 1800 pulses were used per session, with 100% of the motor threshold, totaling 9 minutes of duration. MRI images were collected using a 3T machine (Achieva. Philips) located in the Institute of Radiology, HCFMUSP.
- T1-weighted and T2-weighted structural data were acquired. Resting-state fMRI images were collected using EPI sequence.
- The brain segmentation and parcellation were run using the standard FreeSurfer command 'recon-all'. Total intracranial volume was calculated to correct for interindividual differences in total brain size.
- We used in-house scripts to extract the volume from regions of interest (ROI) defined using a contemporary multimodal cortical parcellation scheme[1]. ROIs consisted of the bilateral DLPFC (46, SFL, 8Ad,8C, 8BL, 8Av, 9p, 9a, p9-46v, a9-46v, i6-8, s6-8 and 9-46d), and we considered 4 parts of the sgACC (bilateral 25 and s32) (Fig. 1a).
- Functional MRI was analyzed using the surface-based pipeline from the CONN toolbox.
- Linear mixed models were conducted for each of these ROIs to investigate the relationship between changes in depression scale scores applied throughout the treatment and the MRI-based measures.

Results

- **Fifty patients** (41 females), with a mean 39.02 ± 10.80 years old, were included in the analysis.
- Mean HAMD-17 went from 18.24 ± 3.05 at baseline to 8.64 ± 5.53 in the follow-up.
- Mean MADRS mean went from 24.82 ± 4.63 to 1.08 ± 7.93.
- Baseline DLPFC region **left p9-46v (Fig. 1b, p-FDR = 0.0004)** and **sgACC portion right s32 (Fig. 1c, p-FDR = 0.003) volumes** were statistically significantly **predictive of HAMD-17 scores through time.**
- Only the **left p9-46v (p-FDR = 0.0001)** was statistically significantly **predictive of MADRS scores through time.**
- Baseline connectivity between left a9.46v and right s32 (p-FDR = 0.053) and between left 9a and left 8C (p-FDR = 0.053) were the best predictors of HAMD-17 changes through time, **although not statistically significant.**
- Baseline connectivity between **left a9.46v and right s32 (p-FDR = 0.012)** and between **left 8BL and left 25 (p-FDR = 0.021)** were statistically significantly **predictive of MADRS changes through time (Fig. 1d).**

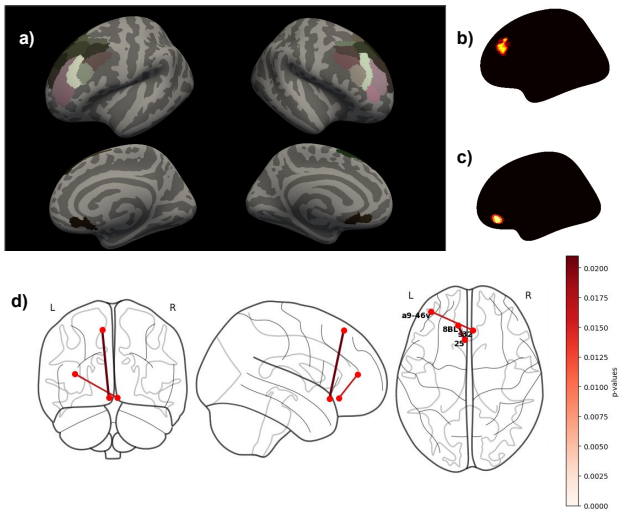

Figure 1: a) Regions of interest (ROI) defined using a multimodal cortical parcellation scheme[1]; b) Left p9-46v; c) Right s32; d) Significant baseline functional connectivity associated with Montgomery-Asberg Depression Rating Scale (MADRS) changes through time. Colorbars are p-values.

Conclusion

- Baseline MRI-based measures from DLPFC and sgACC areas were predictive of iTBS antidepressant effects.
- The fMRI findings resonate with robust previous literature with rTMS, while the structural MRI ones are novel.

Patients with the smallest volumes and highest anticorrelation between left DLPFC and right sgACC areas benefited more from iTBS treatment.

- Future steps include evaluating other brain areas and baseline MRI-based predictors of responders and remitters.

Reference

1. **Glasser et al. (2016). A multi-modal parcellation of human cerebral cortex. Nature, 536(7615), 171–178. https://doi.org/10.1038/nature18933**