Prefrontal theta burst stimulation modulates metabolic activity in the core depression network

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BACKGROUND

- Intermittent theta burst stimulation (iTBS) has emerged as a promising new repeated transcranial magnetic stimulation (rTMS) treatment for depression.
- Therapeutic effects of rTMS are thought to be related to its effect on the subgenual anterior cingulate cortex (sgACC).
- In depression, metabolic activity of the sgACC is increased (measured as increase of ^{18}F-labeled fluorodeoxyglucose).[2] The metabolic activity of the sgACC appears to be a general marker for treatment response.[4]
- Effects of iTBS in humans are not well understood and acquiring a better understanding of its mechanism of action may lead to further improvements in its administration.

OBJECTIVE

- Improve our understanding of the mechanisms of action of iTBS by comparing its neuronal effects to sham treatment in 16 healthy controls using positron emission tomography (PET) and magnetic resonance imaging (MRI) in a double-blind cross-over experiment.

HYPOTHESIS

- Based on previous findings[1,3], we hypothesize that a single session of iTBS will decrease metabolic activity in the subgenual anterior cingulate cortex (sgACC) and the magnitude of decrease will be related to the strength of connectivity between target site and sgACC.

REFERENCES

1. Baeken, C. et al. The impact of accelerated HF-rTMS on the subgenual anterior cingulate cortex in refractory unipolar major depression: insights from 18FDG PET brain imaging. Brain stimulation 8, 808-815 (2015).
2. Drevets, W. C., Savitz, J. & Trimble, M. The subgenual anterior cingulate cortex in mood disorders. *CNS spectrums* **13**, 663 (2008).
3. Fox, M. D., Buckner, R. L., White, M. P., Greicius, M. D. & Pascual-Leone, A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biological psychiatry 72, 595-603 (2012).
4. Pizzagalli, D. A. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology* **36**, 183 (2011).

METHODS

Participants:

- Planned unblinding and interim analyses were carried out on 8 healthy individuals (6 females, age 27.5 ± 8.2).

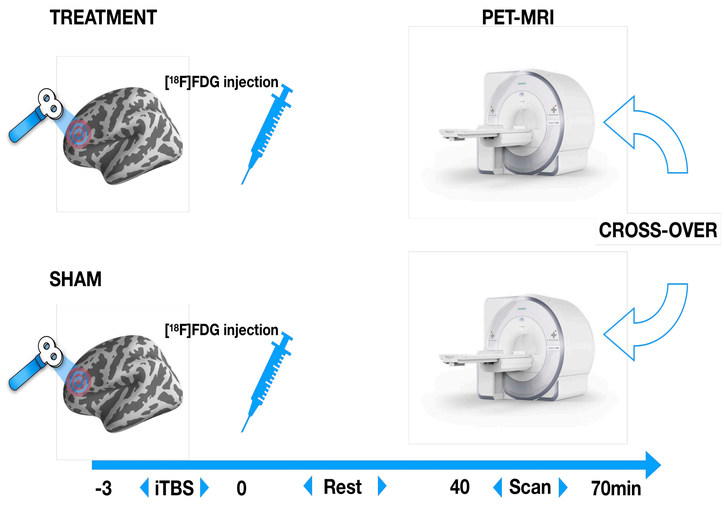
iTBS procedure:

- With an intensity of 80% of the active motor threshold biphasic burst of 3 pulses at a 50Hz frequency applied at a 5Hz burst repetition rate repeated every 10sec for 190sec.

Experimental design:

- Two separate sessions, where each participant receives 3 minutes of iTBS or sham stimulation targeted on the left dorsolateral prefrontal cortex.
- [^{18}F]FDG is injected immediately after iTBS and sham stimulation.
- [^{18}F]FDG-PET/fMRI scan is performed 40 minutes post-injection.

iTBS-[^{18}F]FDG-PET

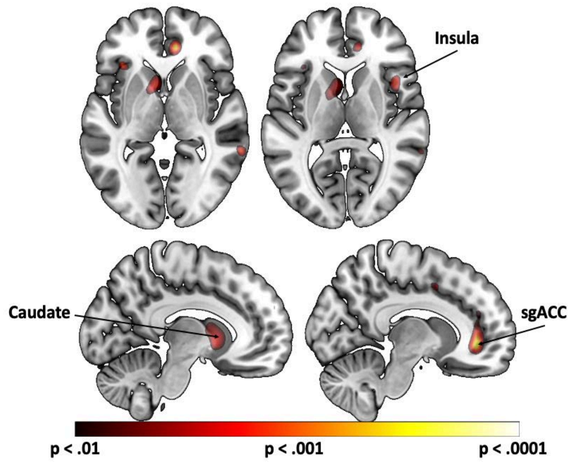


Equipment:

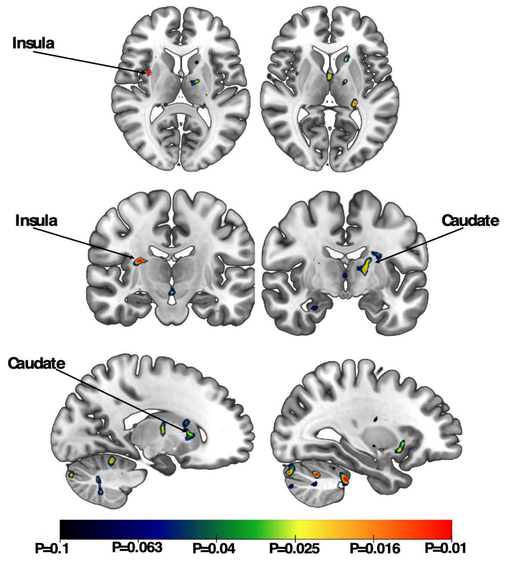
- TMS, MagPro X100 w/ MagOption Stimulator with a 70 mm figure-of-eight coil (MagVenture, Denmark).
- Stereotactic neuro-navigation system, Brainsight, Rogue Research Inc., Montréal.
- Siemens mMR Biograph PET-MR system at the Brain Imaging Centre of the Royal's of Mental Health Research.

RESULTS

PET brain glucose metabolism



Functional connectivity



- Difference between iTBS and sham in SUVRs and rsfMRI was calculated, and effects of stimulation were analyzed using voxel-wise one sample t-tests. All tests were thresholded at voxel-wise p-values < 0.01, uncorrected.
- iTBS decreased [^{18}F]FDG uptake in the subgenual anterior cingulate cortex (sgACC), the anterior insula, and the left caudate.
- iTBS decreased rsfMRI connectivity between the stimulation site and the insula, and the caudate.

Discussion

- To our knowledge, this is one of the first studies that simultaneously uses PET and fMRI to study the effects of iTBS on brain metabolism and connectivity.
- Our interim analysis suggests that a single session of iTBS is sufficient to modulate the metabolic activity of the core depression network. These results are in line with previous studies and if confirmed in the final sample, they will help design more personalized iTBS treatments in clinical populations.
- Acquiring a better understanding of the neural response to iTBS could help develop optimized rTMS treatments for clinical populations, leading to more personalized protocols, increased response rates and reduced suffering.