

Media Release: European College of Neuropsychopharmacology (ECNP)

“For the science and treatment of disorders of the brain”

[Scientists show how magnetic pulses change the brain in treatment for depressed patients: may open door to individualised treatment](#)

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A group of UK scientists have found a way of understanding how transcranial magnetic stimulation (TMS) can give relief to severely depressed patients. TMS is used as an alternative to Electro-Convulsive Therapy (ECT)*, but it is not known how it achieves its therapeutic effect. Understanding how it works may open the door to better, more targeted treatment for depression and other conditions.

Transcranial magnetic stimulation works by applying a magnetic pulse to the frontal part of the brain of depressed patients. Like ECT, it seems to ‘reset’ the brain, but is easier to use because it does not require an anaesthetic, and has few side effects. Because of this, it is increasingly used in treatment of depression. However, TMS, like ECT, is something of a blunt instrument, as scientists have limited idea how it works. Now a new study has shown that targeted magnetic pulses causes biochemical and connectivity changes across the brain.

In a placebo-controlled study, researchers from the University of Nottingham applied MRI-guided targeted bursts of magnetic pulses to the dorsolateral prefrontal cortex in the brains of 27 healthy volunteers (see illustration). This is the first time that MRI-guided TMS pulses have been used to look at changes in individual brain networks and brain chemistry. Using the same MRI scanner, they were able to measure the subtle functional changes in the brain caused by the magnetic pulses. They were also able to measure the changes in brain chemistry, using magnetic resonance spectroscopy

Lead researcher Dr Sarina Iwabuchi (Nottingham) said;

“We found that one session of TMS modifies the connectivity of large-scale brain networks, particularly the right anterior insula, which is a key area in depression. We also found that TMS alters concentrations of neurotransmitters, such as GABA, which are considered important for the development of depression.

These results mean that for the first time, we have an understanding of the direct effects TMS has on the brain. If we can see the change caused by the treatment, then treatment can be smarter. It also means that treatment can be better tailored to each individual’s brain; in other words, this could be personalised treatment for depression.

The work presented in Amsterdam describes a healthy control study. It has shown that personalised TMS treatment is possible, and does indeed lead to brain changes. The next step is to use it as a practical treatment for patients with depression in a clinical trial setting, and in fact this trial is now underway in Nottingham. These are the first steps to personalising this treatment.

Commenting for the ECNP, Professor Catherine Harmer (Oxford) said:

“These findings are an exciting step in understanding how targeting the brain directly with magnetic stimulation may exert beneficial effects in the treatment of depression. TMS techniques are still evolving and their efficacy in treating depression remains to be fully validated and optimized. This kind of experimental medicine study is therefore essential for the improved personalization and treatment of depression in the future”

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Notes for Editors

[Please mention the ECNP Congress in any stories which result from this press release.](#)

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The European College of Neuropsychopharmacology

The ECNP is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe. Website: www.ecnp.eu

The annual ECNP Congress takes place from 29th August to 1st September in Amsterdam. It is Europe's premier scientific meeting for disease-oriented brain research, annually attracting between 5,000 and 8,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: <http://www.ecnp-congress.eu/>

**Note:* ECT is a safe and effective treatment, but requires a general anesthetic, and has other side-effects, such as possible short-term loss of memory. TMS does not have these side effects.

ABSTRACT P.1.i.016 Fronto-insular network and prefrontal GABA levels following targeted transcranial theta-burst magnetic stimulation S.J. Iwabuchi¹, D.P. Auer², F. Raschke², S. Lankappa³, L. Palaniyappan¹ *1The University of Nottingham, Division of Psychiatry and Applied Psychology, Nottingham, United Kingdom; 2The University of Nottingham, Division of Clinical Neuroscience, Nottingham, United Kingdom; 3Nottinghamshire Healthcare NHS Trust, Psychiatry, Nottingham, United Kingdom*

Background and Aims: Recent neuroimaging studies have identified the insula as a key brain region in the pathophysiology of depression and may be a crucial target for the treatment of depression [1]. The modulation of insular networks may have widespread effects on the connectivity of other disrupted networks, and ultimately reduce symptom burden in depression. In addition, patients with depression have also shown to have altered neurochemistry (e.g. glutamate and GABA) [2]. Neurostimulation approaches have demonstrated that modulation of both cortical connectivity [3] and neurochemistry [4] is possible, though the precise nature of these effects is uncertain. Using a connectivitybased approach, we sought proof of concept for the neuromodulation of the insula through transcranial magnetic stimulation (TMS) and how these effects may be related to GABA changes in the frontal cortex. Our aim was to develop a connectivityinformed neuromodulation

approach for TMS to reduce depressive symptom burden. To this end, we report a proof of concept study in healthy controls.

Methods: In a sample of 27 healthy controls, we investigated the effects of intermittent theta-burst TMS (iTBS) on fronto-insular effective connectivity using resting-state functional MRI and Granger causal analysis (GCA). We also measured GABA levels in a voxel placed in the left dorsolateral prefrontal cortex (DLPFC) using magnetic resonance spectroscopy. Images were acquired on a GE 3T MR750 scanner and preprocessed using standard procedures. For each subject, GCA was seeded from the right anterior insula (rAI) to locate the highest peak intensity within the left DLPFC, which was used as the neuronavigation target location for iTBS. We also ran an inverse GCA from each individual's DLPFC target region to the rAI to form a reciprocal fronto-insula network. The Granger coefficients were extracted from 6mm spherical regions of interest from both rAI and DLPFC target regions and compared between placebo and real iTBS. GABA (relative to creatine) levels were also compared between placebo and real iTBS and correlated with changes in Granger coefficients.

Results: Results showed significant dampening of the putative negative influence of the DLPFC on the rAI following iTBS ($p = 0.043$). Levels of GABA were also significantly reduced following iTBS ($p = 0.041$). Furthermore, absolute changes in fronto-insular connectivity induced by iTBS were significantly correlated with absolute changes in GABA ($p = 0.002$). This suggests that iTBS has a direct effect on the effective connectivity between the DLPFC and rAI via an inhibitory mechanism on the influence of the DLPFC on the rAI, and this functional change may be mediated by changes in GABA levels in frontal regions.

Conclusions: Our results demonstrate that the application of a single session of targeted iTBS on the frontal cortex can modulate the effective connectivity of the rAI, a key target region in depression, and additionally produce changes in frontal GABA levels. Moreover, we showed that these changes were inter-related, suggesting that changes in both the fronto-insular circuitry and neurochemistry may underlie the therapeutic effects of iTBS. These findings raise the possibility of targeted Brain Network Modulation to optimise the outcomes of TMS treatment in patients with depression.

References [1] Sliz, D., Hayley, S., 2012. Major Depressive Disorder and Alterations in Insular Cortical Activity: A Review of Current Functional Magnetic Imaging Research. *Front Hum Neurosci* 6, 1–14. [2] Sanacora, G., Mason, G.F., Rothman, D.L., Behar, K.L., Hyder, F., Petroff, O.A., Berman, R.M., Charney, D.S., Krystal, J.H., 1999. Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Arch. Gen. Psychiatry* 56, 1043–1047. [3] Liston, C., Chen, A.C., Zebley, B.D., Drysdale, A.T., Gordon, R., Leuchter, B., Voss, H.U., Casey, B.J., Etkin, A., Dubin, M.J., 2014. Default Mode Network Mechanisms of Transcranial Magnetic Stimulation in Depression. *Biol Psychiat* 76, 517–526. [4] Tremblay, S., Beaulé, V., Proulx, S., de Beaumont, L., Marjanska, M., Doyon, J., Pascual-Leone, A., Lassonde, M., Théoret, H., 2013. Relationship between transcranial magnetic stimulation measures of intracortical inhibition and spectroscopy measures of GABA and glutamate+ glutamine. *J. Neurophysiol* 109, 1343–1349.