Mechanisms of Transcranial Magnetic Stimulation in the Treatment of Anorexia Nervosa

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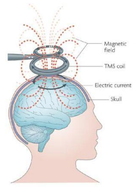
1 Introduction

Severe and Enduring Anorexia Nervosa (SE-AN) is a challenging condition to treat, with limited therapeutic options, high morbidity, and the highest mortality rates of any psychiatric illness[1].

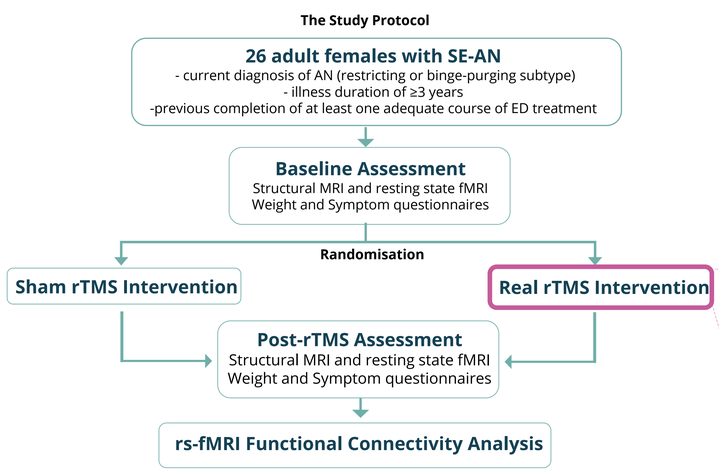
Repetitive Transcranial Magnetic Stimulation (rTMS) is an emerging treatment option, as evidence demonstrates promising efficacy in improving mood and reducing core AN symptoms, as well as safety and tolerability to patients[2,3].

However, the **neurophysiological mechanisms** underlying this treatment effect in AN are poorly understood. We therefore performed the first functional neuroimaging analysis investigating rTMS effects in AN patients.



Transcranial Magnetic Stimulation[4]

2 Methods



Resting state functional connectivity analysis was performed using a seed-based approach with 3 regions of interest: L-dlPFC and bilateral amygdalae. FC differences were analysed using t-contrasts in a mixed ANOVA (flexible factorial analysis) to assess interactions between treatment group (real rTMS vs sham) and time-point (pre or post TMS).

3 Results

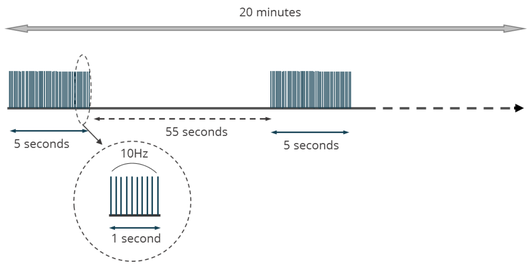
The below figure demonstrates resting state functional connectivity changes that were observed post-TMS compared to pre-TMS, and were only observed in the active rTMS group, not in the sham group, therefore indicating changes in FC which *may* be caused by rTMS intervention.

Seed Region	Functionally Connected Brain Region	MNI Coordinates			T	K_E	$P_{uncorrected}$	P_{FWE}
		X	Y	Z				
Left dlPFC	Left Inferior temporal gyrus	-58	-26	-24	5.25	172	0.027	0.196
Left Amygdala	**Left Pre-supplementary motor area**	-4	26	56	6.12	308	0.005	**0.039**
Right Amygdala	Right Precentral gyrus	34	-10	38	4.17	38	0.249	0.884

Differences in Resting State Functional Connectivity Between Active and Sham rTMS Groups, Post vs Pre rTMS

Shown are T values indicating differences between groups in resting state functional connectivity between the 3 seed regions of interest and the indicated brain regions. The number of voxels in the cluster with altered functional connectivity is indicated by the K_E value, MNI (montreal neurological institute) coordinates refer to the peak of the cluster, and both the uncorrected P value and family wise error rate corrected P value are shown.

Increased FC between the left amygdala and left pre-supplementary motor area reached cluster-wise significance (P_{FWE}<0.05). However after Bonferroni correction for multiple comparisons (3 seed regions), none of these results reached the significance threshold P_{FWE} <0.017.



The High Frequency Repetitive Transcranial Magnetic (HF-rTMS) Stimulation Intervention Protocol
Participants received 20 sessions of HF-rTMS to the left dorsolateral prefrontal cortex (L-dlPFC) at 110% of their resting motor threshold. This was delivered as 5 second trains of stimuli at 10Hz, repeated 20 times, with an inter-train interval of 55 seconds. In total 1000 pulses of TMS were delivered each session, with total duration of 20 minutes. Sham stimulation used a sham coil which only stimulates peripheral nerves of the face and scalp.

4 Significance

This study did not observe any statistically significant changes in resting state functional connectivity after HF-rTMS to the L-dlPFC in SE-AN patients. This may have been due to small sample size and lack of stratification by treatment response, resulting in lack of power.

Increased FC between left amygdala and pre-supplementary motor area (pre-SMA) reached cluster-wise significance. The amygdala is a key limbic region for emotional reactivity, whilst the pre-SMA is implicated in a network associated with reappraisal of emotional stimuli[5]. **Therapeutic benefit in AN may therefore be derived from improved top-down cognitive control over emotional processing.** This is supported by evidence from studies in major depressive disorder[6], obsessive compulsive disorder[7], and binge-purge behaviours[8] which also suggests that HF-rTMS may modulate frontostriatal FC, resetting a dysfunctional imbalance between executive control and reward/emotion processing networks.

Improved top-down control may have indirect or direct effects on AN symptoms:

Indirect Effect
by reducing comorbid depressive symptoms and negative affect, with secondary improvements in ED symptomatology.

?

Improved top-down cognitive control over emotional processing

?

Direct Effect
on ED symptomatology by facilitating a shift from bottom-up, habit/ emotionally driven ED behaviours, towards top-down goal-directed behaviours

5 Conclusion

HF-TMS may have therapeutic benefit in SE-AN by modification of functional connectivity between prefrontal and limbic brain regions, resulting in improved top-down cognitive control over emotional processing,

Acknowledgements: everyone involved in the TIARA trial who collected the neuroimaging data analysed in this study, Professor Iain Campbell and Ms Lucy Gallop of the IOPPN

References: 1. Smink, F.R.E. et al. (2013) *Curr Opin Psychiatry*. 26(6):543-8; 2. Dalton, B. et al. (2018) *BMJ Open*. 8(7); 3. McClelland, J. et al. (2016) *Eur Eat Disord Rev*. 24(2):157–63; 4. Ridding, MC. et al. (2007) *Nat Rev Neurosci*. 8(7):559–67; 5. Etkin, A. et al. (2015) *Nat Rev Neurosci*. 16:693–700; 6. Salomons T V. et al. (2014) *Neuropsychopharmacology*. 39(2):488–98; 7. Dunlop, K. et al. (2016) *Neuropsychopharmacology*. 41(5):1395–403; 8. Dunlop, K. et al. (2015) *NeuroImage: Clinical*. 8:611–8.