Graph Analysis To Explore The Effect Of Transcranial Magnetic Stimulation On Functional Connectivity In Patients With Major Depressive Disorder

D.C.W. Klooster1,2, S.L. Franklin1, R.M.H. Besseling1,2,3, R. Duprat3, A.P. Aldenkamp1,2,3, A.J.A. de Louw1,2, P. Boon1,2,3, C. Baeken3

1 Eindhoven University of Technology, Department of Electrical Engineering, Eindhoven, the Netherlands; 2 Academic Center for Epileptology Kempenhaeghe, Heeze, the Netherlands; 3 University hospital Ghent, Ghent, Belgium

**Background:** Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique which is FDA approved for the treatment of major depressive disorder (MDD). The mechanism of action of TMS is not yet fully understood, which limits its clinical efficacy. To gain a better understanding of how TMS affects the brain, this study investigates the changes in functional connectivity it induces.

**Methods:** 42 MDD patients were randomly assigned to undergo either excitatory intermittent theta burst stimulation (iTBS a special TMS protocol, n=21) or sham stimulation (n=21) using a real or sham stimulation coil, respectively. The left dorsolateral prefrontal cortex was stimulated on four consecutive days (total 32400 stimuli). An MRI scan protocol was performed before stimulation (baseline), and three days after the sham or real stimulation session, consisting of an anatomical scan (MPRAGE, TR=2530ms, TE=2.58ms, FA=7deg) and resting-state functional MRI (TR=2000ms, TE=29ms, FA=90deg, 300 volumes). Medication was tapered off during the total treatment period.

Functional connectivity was investigated by means of graph parameters: clustering coefficient and global efficiency. To investigate the spatial distribution of the TMS effect, the graph parameters where calculated on whole brain level, and also in two subnetworks known to be involved in MDD: the default mode network (DMN) and the central executive network (CEN). Nodes belonging to the subnetworks were selected based on overlap with the DMN and CEN templates generated by Smith et al. (2009). Paired t-tests were used to compare the graph measures before and after real or sham stimulation (significance level set to p < 0.05).

**Results:** The clustering coefficient was significantly decreased after iTBS in the whole brain, the DMN, and the CEN. In the whole brain and in the CEN, no significant effect of sham stimulation was found. The global efficiency did not show any significant changes in the whole brain. In the DMN and CEN, the global efficiency significantly decreased after iTBS and not after sham stimulation.

**Conclusions:** iTBS decreases the graph parameters clustering coefficient and global efficiency. The fact that the effects of TMS are found beyond the site of stimulation, for example within the CEN comprising the stimulation area, emphasizes the potential network effect of TMS. Correlation of the change in graph parameters with clinical outcome measure and direct comparison between sham and real iTBS (using a cross-over design) will be investigated in the future.