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The effect of repetitive transcranial magnetic stimulation and the brain-derived neurotrophic factor genotype on resting-state functional network connectivity

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This thesis studied the interaction of neural stimulation and genotype on functional connectivity in 67 healthy subjects. Neural stimulation was performed using repetitive transcranial magnetic stimulation (rTMS) of the right dorsolateral prefrontal cortex (DLPFC). The effect of genotype was studied for a well-known polymorphism in the brain-derived neurotrophic factor (BDNF), which is implicated in neuronal plasticity. Functional connectivity was assessed as the degree of correlation between well-established functional networks during resting-state. In short, this thesis investigated the effect of rTMS and the genotype for a polymorphism in the BDNF on the connectivity between resting-state functional connectivity networks in 67 healthy subjects.

Functional connectivity networks represent reproducible patterns of temporally correlated hemodynamic signal fluctuations in the human brain, which are involved in fundamental neurocognitive processes and show alterations in psychiatric disorders such as schizophrenia and depression. rTMS of the right DLPFC has been shown to produce lasting effects on functional connectivity and has emerged as an effective treatment in these disorders. Another mechanism affecting functional connectivity is the valine^{66}methionine (val^{66}met) polymorphism in the gene for the BDNF. Both mechanisms have been linked to neuronal plasticity. However, the combined effect of BDNF genotype and rTMS on functional connectivity is not known. To fill this gap, this thesis studied the interaction of rTMS and genotype on functional connectivity in a sample of 67 healthy subjects. Subjects received 5Hz stimulation of the right DLPFC during one data collection session and sham stimulation of the identical stimulation site during the other session. Following both true and sham stimulation, a resting-state functional magnetic resonance imaging scan was performed. Subjects were genotyped for the val^{66}met single-nucleotide polymorphism (rs6265) in the 5' proregion of the gene for the BDNF. Met^{66}met homozygotes and val^{66}met heterozygotes were grouped as met^{66} carriers for further analysis, due to the low number of homozygotes. The sample population consisted of 26 met^{66} allele carriers and 41 val^{66} homozygotes.

Independent component analysis was used to generate independent components from the resting-state functional magnetic resonance imaging data. These independent components were spatially correlated with canonical samples of resting-state networks to determine best matches for the default-mode network (DMN), executive control network (ECN) and salience network (SLN). The DMN was represented by three independent components, comprising predominantly superior posterior, inferior posterior and anterior nodes respectively. The ECN was split into two components, corresponding to left-hemispheric and right-hemispheric network nodes, respectively. The SLN was covered by a single independent component. Functional connectivity between the networks was measured by the correlation of their voxel time series. Statistical analysis of the networks' Fisher r-to-z-transformed correlation coefficients was performed using a mixed analysis of variance approach.

The results of this study are as follows: rTMS did not result in significant changes in inter-network connectivity compared to sham stimulation. This concurs with published studies, which also reported a lack of effect of repetitive transcranial stimulation of the right DLPFC on inter-network connectivity. There was also no effect of the BDNF polymorphism on connectivity between the networks of interest, which contrasts with a publication, utilizing a different approach to functional connectivity analysis, that reported altered connectivity between nodes of two networks in met^{66} carriers. However, an interaction effect emerged which suggests that rTMS effects are influenced by the BDNF genotype. Following stimulation, met^{66} allele carriers showed stronger connectivity between superior posterior parts of the DMN and left-hemispheric parts of the ECN compared to the sham condition. This finding remained

significant after correction for multiple comparisons and the effect was not observed in val^{66} homozygote individuals.

This is the first study to demonstrate that the BDNF val^{66}met genotype modulates rTMS effects on inter-network functional connectivity. A tentative interpretation could be that the observed stimulation effect may be implicated in previously observed adverse effects of rTMS in patients with schizophrenia involving increased severity of hallucinations, as it mirrors functional connectivity abnormalities observed in schizophrenic patients that correlate with symptom intensity. Variations in the therapeutic effectiveness of rTMS in major depressive disorder could also conceivably be associated to genotype-associated differences in functional connectivity modulation, although the observed effects did not align with published findings concerning the influence of this genotype on presumed therapeutic mechanisms of action of rTMS involving functional connectivity.

The results from this investigation should be used to guide further research into the mechanisms of action underlying the therapeutic, and adverse, effects of rTMS and into the genotype for BDNF as a potential cause for interindividual differences in therapeutic response. These results also suggest that the BDNF val^{66}met genotype of subjects should be routinely determined in rTMS studies, especially in those observing therapeutic effects of rTMS in patients suffering from major depressive disorder and schizophrenia.