Toward state-of-the-art personalized brain stimulation: precision, feasibility and relation to clinical outcome

Robin Cash1,2, Luca Cocchi3, Jinglei Lv1,2, Paul Fitzgerald4, Andrew Zalesky1,2

1. Melbourne Neuropsychiatry Centre, The University of Melbourne, Australia; 2. Department of Biomedical Engineering, The University of Melbourne; 3. Clinical Brain Networks group, QIMR Berghofer, Brisbane; 4. Epworth Centre for Innovation and Mental Health, Epworth Healthcare & Monash University Central Clinical School

BACKGROUND:
- Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) is an established treatment for refractory depression, but 50-70% of individuals do not respond.
- Clinical response depends on functional connectivity (FC) with the subgenual cingulate cortex (SGC) at the DLPFC stimulation site.
- The topography of DLPFC-SSG FC varies across individuals.
- FC-guided DLPFC target personalization might improve rTMS response.
- Intraindividual reproducibility of optimal targets across scans is limited to 3.5cm (Ning et al., 2018), rendering personalization impossible.

AIMS:
1. Develop & test computational personalization methods
2. Assess relation to clinical response in a depression cohort

METHODS:
- Personalization methodology was evaluated in 1000 individuals with repeat scans from the Human Connectome Project.
- Relation to clinical response was evaluated in 26 individuals who previously received rTMS for treatment refractory depression (targeted to F3).
- Seedmap method: To increase the signal to noise ratio, the SGC time series was computed from the weighted spatial average of the fMRI data across all gray matter voxels, excluding the DLPFC.

RESULTS:
1. Precision
2. Ratio
3. Heritability
4. Proximity to opt. target vs. clinical response
5. Clinical response & proximity to personalised vs. group target
6. Individual FC profiles are stable & unique

CONCLUSION:
- Personalised connectivity-based cortical stimulation targets can be pinpointed with a median accuracy of ~2mm between scans repeated one year apart. The previous published benchmark was an order of magnitude greater (3.5cm; Ning et al., 2018).
- Interindividual spatial variation in personalised targets exceeded intraindividual variation by a factor of up to 6.85.
- Personalized targets were heritable, suggesting that connectivity-guided rTMS personalization is stable over time and under genetic control [MZ: monozygotic; DZ dizygotic; NT: non-twin siblings; *P=0.008; †P=3.2x10^-5, ‡P=1.3x10^-19].
- Clinical response was consistently better when patients were serendipitously treated closer in proximity to the personalised connectivity-based DLPFC target (P=0.001, R=0.56).
- Divergence from 12 ‘one-site-fits-all’ fixed group-level coordinates demonstrated no relation to treatment response.
- Individual SGC FC profiles are unique but relatively stable across repeat scans.