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

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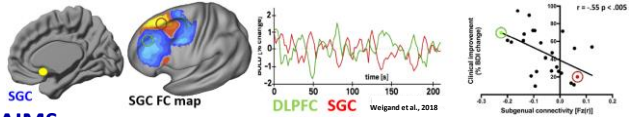
BACKGROUND:

- 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-SGC 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.



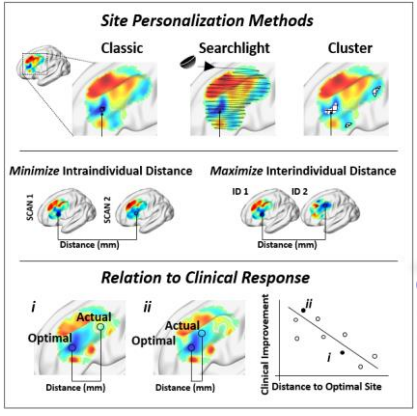
AIMS:

1. Develop & test computational personalization methods

2. Assess relation to clinical response in a depression cohort

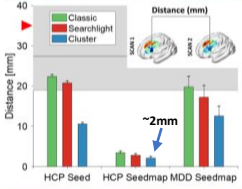
METHODS:

- 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 as a weighted spatial average of the fMRI data across all gray matter voxels, excluding the DLPFC.

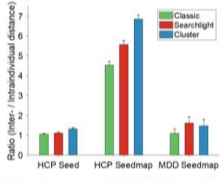


RESULTS:

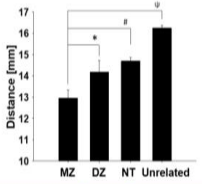
1. Precision



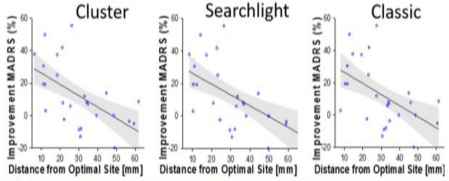
2. Ratio



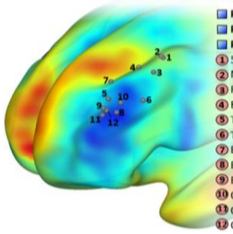
3. Heritability



4. Proximity to opt. target vs. clinical response

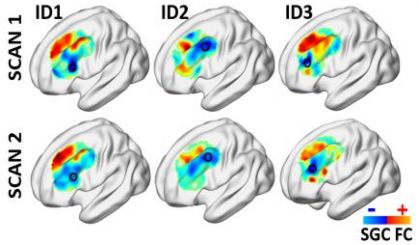


5. Clinical response & proximity to personalised vs. group target



Target	x	y	z	Rho	P Value
Personalised FC Optimal Target ('Cluster')				-0.56	0.0013**
Personalised FC Optimal Target ('Searchlight')				-0.54	0.0020**
Personalised FC Optimal Target ('Classic')				-0.52	0.0034**
1 5cm average (Fox et al., 2012)	-41	16	54	0.13	NS
2 Non-responders (Herbsman et al., 2009)	-41	17	55	0.13	NS
3 Responders (Herbsman et al., 2009)	-46	23	49	0.09	NS
4 EEG F3 site (Herwig et al., 2003)	-37	26	49	0.16	NS
5 TMS Target (Fitzgerald et al., 2009)	-46	45	38	-0.17	NS
6 TMS Target (Rusjan et al., 2010)	-50	30	36	-0.02	NS
7 BA9 Definition (Rajkowska et al., 1995)	-36	39	43	0.17	NS
8 BA46 Definition (Rajkowska et al., 1995)	-44	40	29	-0.25	NS
9 Beam F3 (Cash et al., 2019)	-43	46	32	-0.22	NS
10 Optimal FC Group Target #1 (Fox et al., 2012)	-44	38	34	-0.10	NS
11 Optimal FC Group Target #2 (Fox et al., 2012)	-38	44	26	-0.15	NS
12 Optimal FC Group Target #1 (Weigand et al., 2017)	-42	44	30	-0.23	NS

6. Individual FC profiles are stable & unique



1. 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).

2. Interindividual spatial variation in personalised targets exceeded intraindividual variation by a factor of up to 6.85.

3. 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, ΨP=1.3x10^{-19}].

4. 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).

5. Divergence from 12 'one-site-fits-all' fixed group-level coordinates demonstrated no relation to treatment response.

6. Individual SGC FC profiles are unique but relatively stable across repeat scans.

CONCLUSION:

- Clinical response was significantly better when patients were treated closer to *personalized connectivity-guided targets*.
- Critically, there was no relation between therapeutic outcome and proximity to *non-personalized* group-average stimulation targets.
- Future prospective randomized controlled trials are warranted to quantify the clinical efficacy of fMRI-guided personalized rTMS.
- Our methodology provides capacity to robustly pinpoint unique and stable individualized optimal targets with unprecedented accuracy.

PUBLISHED IN: Cash et al. 2021, Human Brain Mapping • Cash et al. 2020, JAMA Psychiatry • Cash et al. Biol. Psychiatry 2020 & 2019