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Techniques and Methods

Personalized brain stimulation of memory networks

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ABSTRACT

Background: The finding that transcranial magnetic stimulation (TMS) can enhance memory performance via stimulation of parietal sites within the Cortical-Hippocampal Network counts as one of the most exciting findings in this field in the past decade. However, the first independent effort aiming to fully replicate this finding found no discernible influence of TMS on memory performance.
Objective: We examined whether this might relate to interindividual spatial variation in brain connectivity architecture, and the capacity of personalisation methodologies to overcome the noise inherent across independent scanners and cohorts.
Methods: We implemented recently detailed personalisation methodology to retrospectively compute individual-specific parietal targets and then examined relation to TMS outcomes.
Results: Closer proximity between actual and novel fMRI-personalized targets associated with greater improvement in memory performance.
Conclusion: These findings demonstrate the potential importance of aligning brain stimulation targets according to individual-specific differences in brain connectivity, and extend upon recent findings in prefrontal cortex.
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1. Introduction

An important source of outcome heterogeneity following transcranial magnetic stimulation (TMS) may stem from inter-individual spatial variation in brain network architecture. This provides a rationale to align the position of stimulation targets according to person-specific differences in brain connectivity. Recent research indicates that personalized targeting of prefrontal cortex associates with better therapeutic outcomes to TMS for treatment resistant depression [1–4]. A fundamental question is now whether the significance of personalized targeting generalizes to other clinical and behavioural applications of brain stimulation outside of the prefrontal cortex, potentially influencing outcome efficacy and reproducibility.

We addressed this question in the context of TMS of parietal sites within the cortical-hippocampal memory network. A series of seminal studies demonstrated the capacity of parietal cortex stimulation to enhance memory performance, with potential utility across cognitive and psychiatric disorders [5,6]. However, the first independent effort aiming to fully replicate this finding found no discernible influence of TMS on memory performance at the group level and no variable that could account for individual variation [7]. We considered whether this might be attributed to interindividual spatial variation in brain connectivity architecture, and the capacity of personalisation methodologies to overcome the noise inherent across independent scanners and cohorts [2,8]. While a personalized targeting approach was previously implemented [5–7], we investigated whether recently detailed precision personalisation methodology might increase the propensity of the original findings by Voss and colleagues to generalize and replicate [2,8]. We

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implemented this computational methodology [2,8] to retrospectively compute individual-specific connectivity-guided targets. We then assessed whether proximity between actual and novel fMRI-personalized targets associated with improvement in memory performance.

2. Methods

We analysed data previously acquired from 36 healthy participants (20 female, mean age±SD of 24.9 ± 8.9 years), who underwent T1 and resting-state fMRI prior to and following multi-day TMS [7]. In brief, participants completed two TMS conditions across two separate weeks; an experimental condition targeting LLPC and another targeting SMA as a comparison site. Each condition included four sessions of TMS delivered daily (2s trains of 20 Hz biphasic stimulation every 30s for 20 min, 100% of resting motor threshold, 1600 pulses/day). Stimulation targets were derived from a seed-based analysis of each participant's baseline resting-state fMRI scan. The order of stimulation conditions was counterbalanced across participants, and each condition was separated by an interval of at least one week. Associative memory was assessed at baseline and ~24 h post-TMS using a face-cued word task [5], with performance scored as the percentage of correctly recalled face-word pairs out of a total of 20.

We retrospectively computed personalized TMS targets within the left lateral parietal cortex (LLPC) by adapting recently described personalisation methodology [2] for the present purposes (Fig. 1A). This involved first computing a robust group-average hippocampal connectivity seedmap [2,8] from Human Connectome Project [9] data (N = 1000, 28-min resting-state fMRI scan) seeded at a hippocampal ROI (MNI -24, −18, −18; 3 mm radius sphere [5,7]). The hippocampal seedmap time series for each individual [7] was then computed as a seedmap weighted spatial average of their fMRI data across *all* grey matter voxels [2,8], excluding the LLPC ROI. This 'seedmap methodology' improves the signal-to-noise ratio [2,8] because data from most of grey matter was used to estimate the hippocampal seedmap time series, rather than the approximately 20 voxels comprising the conventional hippocampal ROI as utilized in the original work [5–7]. More specifically, averaging across a larger number of data points (voxels) increases the SNR of the average by a factor of $\sqrt{N}$, where N is the number of voxels across which the average is taken (seedmap: 163620 vs seed: 19 voxels). The seedmap provides a weighting for each voxel, computed from the voxel-specific connectivity with the hippocampus, and is not thresholded [2,8]. Next, voxels of the LLPC, within a 15 mm radius of MNI -47, −68, 36 [5,7], that were most positively correlated with the hippocampus were spatially clustered using a connected component finding algorithm based on a 26-voxel connectivity neighbourhood. and the centre of the largest cluster was defined as the personalized coordinate. This clustering approach previously demonstrated advantages in precision, reproducibility and relation to outcome compared to the conventional approach of identifying the single most functionally connected voxel [1,2]. The cluster threshold was set at 2.5% [1,2]. We measured the proximity between previously applied [7] and personalized targets using Euclidean distance [1,2,4] and correlated this distance with percentage change in associative memory performance (face-cued word recall) following LLPC stimulation.

We additionally computed this relation for proximity between previously applied and *'one-site-fits-all' group-level* targets, namely the (i) spatial group-average of actual stimulation coordinates, (ii) spatial group-average of optimal stimulation coordinates, (iii) 'optimal' target derived by applying cluster methodology to the hippocampal seedmap. Lastly, we applied a general linear model to determine whether optimized personal coordinates explained more variance in behavioural outcome relative to group-level coordinates.

An additional control analysis was performed in which we used an identical process, but using the voxels that were most negatively correlated with the hippocampal seedmap time series.

3. Results

Memory enhancement was associated with closer proximity between the experimentally applied and optimized personal targets ($r = -0.30$; $P = 0.038$; Fig. 1B). This association remained significant even after controlling for proximity between the experimentally applied and any of the three candidate group-level LLPC targets. Moreover, there was no significant correlation when optimized personal targets were substituted with any of the three group-level LLPC targets ($P > 0.05$, Table 1). A general linear model supported the hypothesis that a combined model comprising distance to individually optimized and group-level coordinates did not explain additional variance relative to proximity to individualized coordinates alone ($P < 0.05$).

The relation was tested at different cluster thresholds and the resultant curve (Fig. 1C) demonstrates that the relation remains highly consistent across a broad range of thresholds and cannot be attributed to parameter tuning. Indeed, for the cortical-hippocampal memory network interrogated here, a stronger relation is evident at a cluster threshold of 10%, rather than the 2.5% threshold we had selected a priori based on our recent work [1,2].

Our final control analysis demonstrated that there was no significant relation when the optimal target was defined according to voxel clusters that were most negatively (rather than positively) correlated with the hippocampal seedmap time series. There was no significant relation at any cluster threshold, and the cluster threshold curve demonstrates an uncharacteristic and arbitrary relation between cluster threshold, Pearson's correlation and statistical significance (Fig. 1E).

4. Discussion

These findings demonstrate that memory performance following multi-session TMS was significantly improved only when individuals serendipitously received stimulation closer in proximity to optimized personal connectivity-guided targets. This relation was highly robust as indicated in Fig. 1C. Our data demonstrated specificity to clusters having positive FC with the hippocampal seedmap time series. Critically, there was no relation between memory outcome and proximity to non-personalized group-average stimulation targets. The present findings thus provide support for the behavioural significance of aligning stimulation targets with *individual-specific* brain network architecture.

The present methodology provides a potential avenue to enhance the reliability and reproducibility of TMS induced improvements in memory performance across basic and clinical applications. The hippocampus has a poor fMRI signal-to-noise ratio and is subject to signal distortion. The personalisation methodology employed here is particularly beneficial in situations where data is prone to a low signal-to-noise ratios [2,8], and is thus well placed to improve reproducibility and generalisability across studies and scanners.

Prefrontal and parietal cortices show some of the highest levels of interindividual variation in brain network architecture [10; see also Fig. 1F]. Personalized targeting based on functional brain network architecture therefore provides a compelling and neurobiologically principled opportunity to advance behavioural and therapeutic outcomes when stimulating these brain regions [2,4]. However, it is important to acknowledge that the body of evidence

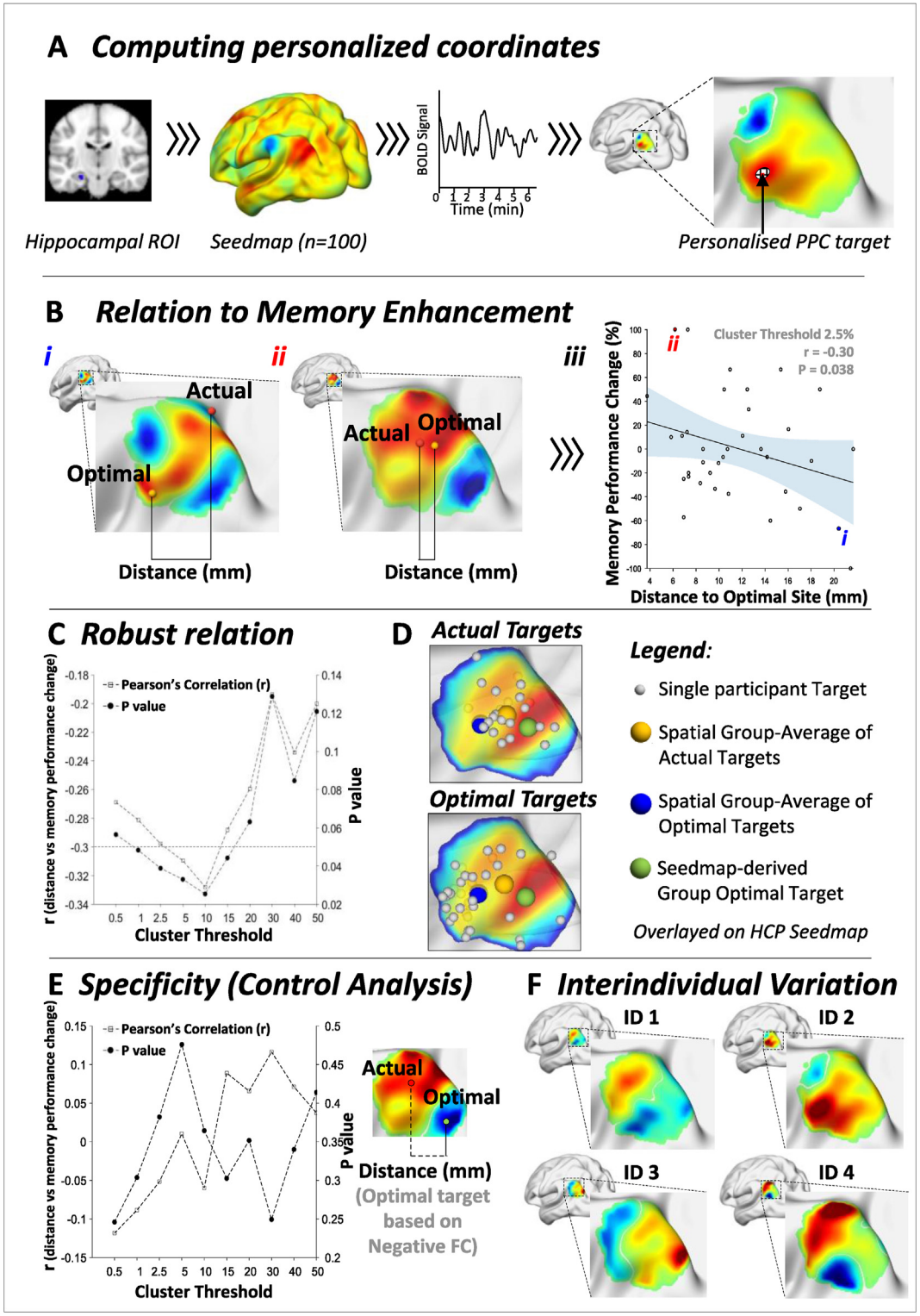


Fig. 1. A: The optimal personalized PPC stimulation coordinate was retrospectively computed for 36 participants who previously underwent a course of TMS designed to enhance memory performance. We implemented recently described methodology adapted for the present application [1,2]. A normative hippocampal functional connectivity seedmap was first constructed using data from the human connectome project. This whole-brain weighted FC map was then used to compute each participant's hippocampal seedmap timeseries. Personalized coordinates were subsequently computed using cluster-based methodology [2]. **1B**. The hippocampal FC map is depicted for two individuals (**i** and **ii**). As indicated in the third panel (**iii**) improvement in memory performance was related to closer proximity to the personalized coordinates ($R = -0.30$, $P = 0.04$; shaded region represents 95% confidence interval). **1C**. The relation was highly robust. This is indicated by varying a key parameter termed 'cluster threshold'. The relation would be further enhanced by parameter optimization, with a cluster threshold of 10 ($R = -0.33$, $P = 0.02$.). This optimal threshold could not have been fully predicted a priori. **1D**. Distribution of actual and optimal targets. Note the disparity between group-level targets and optimal personalized targets. Accordingly, there was no relation of memory performance outcome with the distance between actual targets and any of these group-level optimal targets, indicating the importance of personalized connectivity-based targeting. The blue edging is an artefact caused by spatial interpolation in the plotting software. Visibility of some participant coordinates is restricted by overlying coordinates or submersion below the cortical surface. Minor distortion of coordinate positions occurs during overlay on brain surface. **1E**. Cluster threshold curve derived from defining optimal targets according to voxel clusters that were most negatively (rather than positively) correlated with the hippocampal seedmap time series. There was no significant relation at any cluster threshold and the cluster threshold curve demonstrates an uncharacteristic and arbitrary relation between cluster threshold, Pearson's correlation and statistical significance. **1F**. Interindividual spatial variation in hippocampal FC across the LLPC. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Relation between memory performance changes and proximity to personalized and group-average stimulation target sites.

Stimulation target	x (mm)	y (mm)	z (mm)	R	p-value
Personalized target (Cluster Threshold 2.5%)	–	–	–	−0.30	0.04
Personalized target (Cluster Threshold 10%)	–	–	–	−0.33	0.02
Group-average targets					
Actual Target − group spatial mean	−46	−70	36	−0.13	0.23
Optimal Target - group spatial mean	−48	−65	33	−0.18	0.14
HCP seedmap derived optimal group-target	−44	−74	33	−0.01	0.46

Abbreviations: Human Connectome Project (HCP); Functional connectivity (FC). Coordinates are provided in Montreal Neurological Space (MNI) space.

supporting personalized targeting remains limited. The case for personalized targeting in the context of depression comprises retrospective research akin to the present work [1,4,11], and a number of prospective studies with relatively small sample sizes [3,4,12–16]. Similarly, while personalized targeting was previously assumed to be important in the context of memory enhancement [5], a causal relation has yet to be explicitly demonstrated in prospective comparator-controlled work. Nonetheless the present findings add to a growing body of evidence that personalized targeting based on individual-specific brain network architecture might have capacity to enhance the efficacy of non-invasive and invasive forms of brain stimulation [1,3,4,11–17].

CRediT authorship contribution statement

Robin F.H. Cash: Conceived and designed the analysis, Contributed data or analysis tools, Performed the analysis, Wrote the paper. **Joshua Hendrikse:** Conceived and designed the analysis, Collected the data, Wrote the paper. **Kavisha B Fernando:** Conceived and designed the analysis, Contributed data or analysis tools, Performed the analysis. **Sarah Thompson:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools. **Chao Suo:** Conceived and designed the analysis, Contributed data or analysis tools, Performed the analysis. **Alex Fornito:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools. **Murat Yücel:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools. **Nigel C. Rogasch:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools. **Andrew Zalesky:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools. **James P. Coxon:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Wrote the paper.

Declaration of competing interest

The authors report no conflicts of interest.

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