

Focal neural perturbations reshape low-dimensional trajectories of brain activity supporting cognitive performance

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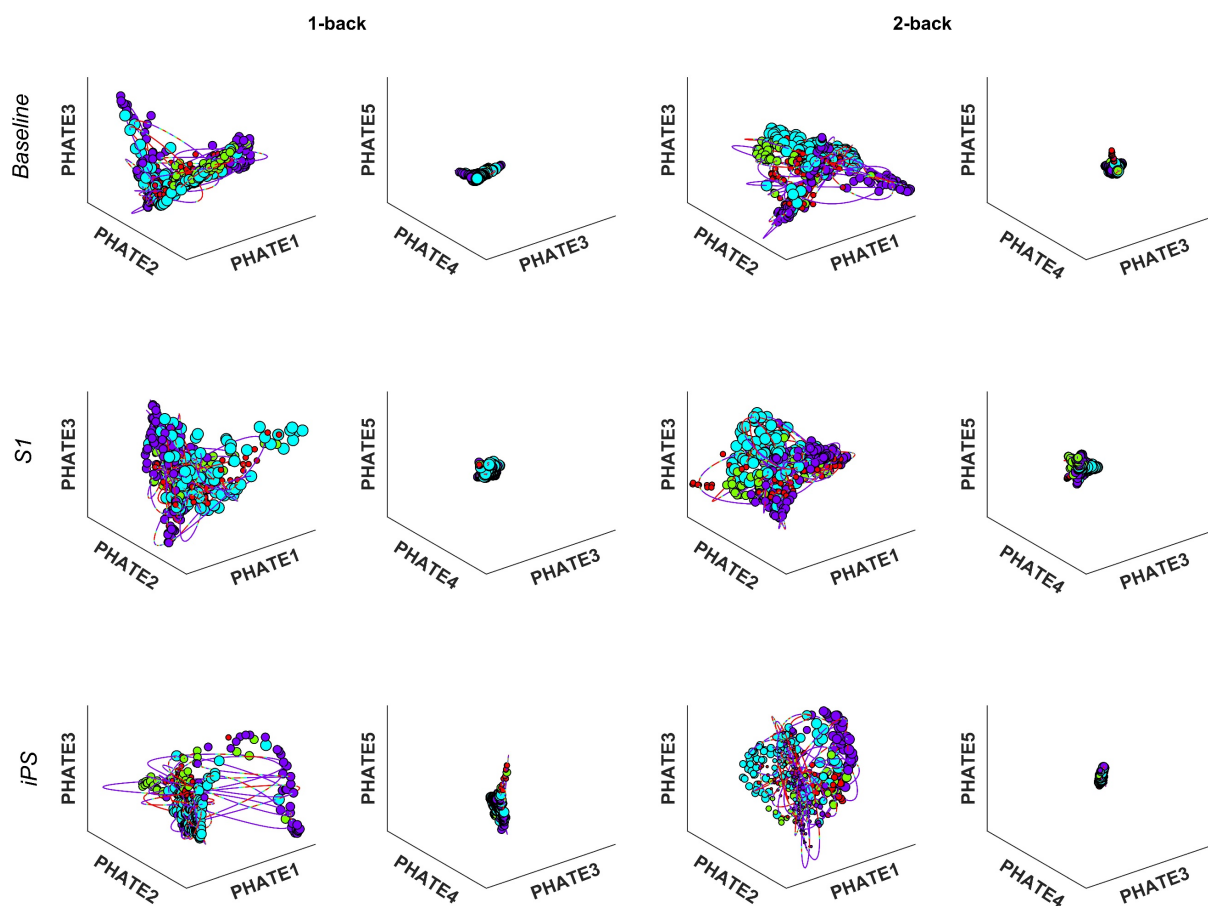
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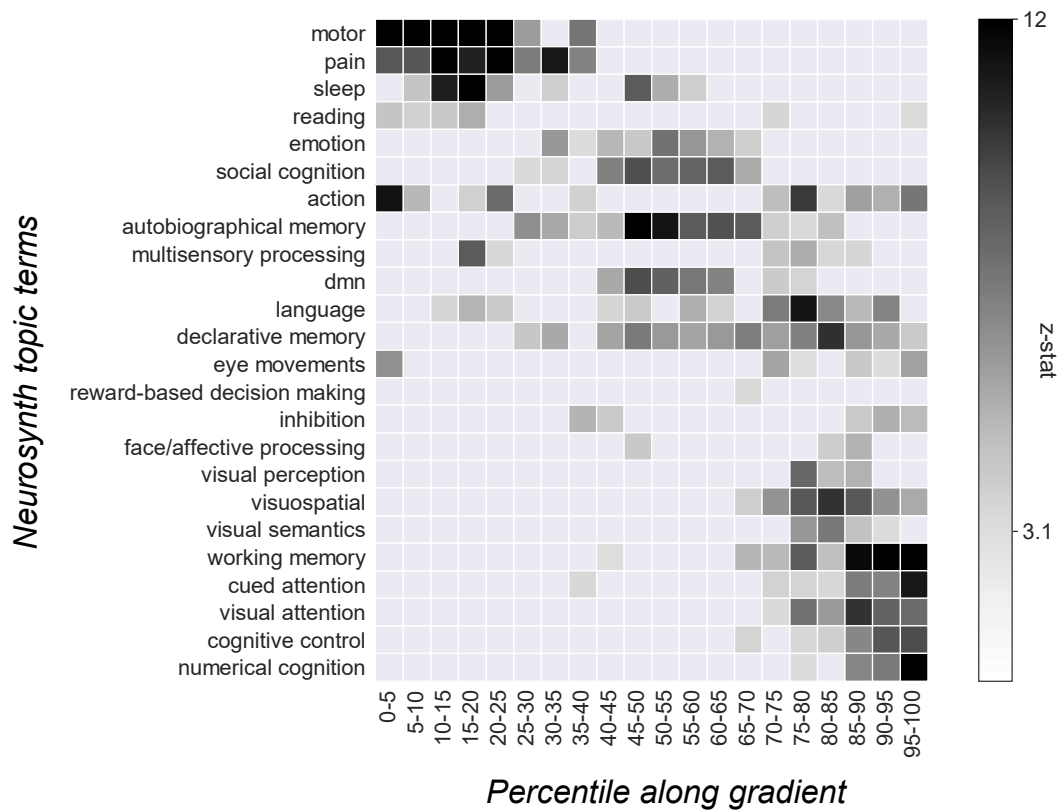
Supplementary Table and Figures

	<i>Baseline</i> <i>1-back (%)</i>	<i>Baseline</i> <i>2-back</i>	<i>S1</i> <i>1-back</i>	<i>S1</i> <i>2-back</i>	<i>iPS</i> <i>1-back</i>	<i>iPS</i> <i>2-back</i>
<i>PHATE1</i>	82.75	82.18	86.11	81.90	67.47	76.72
<i>PHATE2</i>	13.08	13.68	6.73	15.17	31.22	20.64
<i>PHATE3</i>	3.18	2.93	5.59	1.64	1.13	2.02
<i>PHATE4</i>	0.44	0.80	1.06	0.92	0.08	0.35
<i>PHATE5</i>	0.29	0.20	0.28	0.17	0.05	0.14

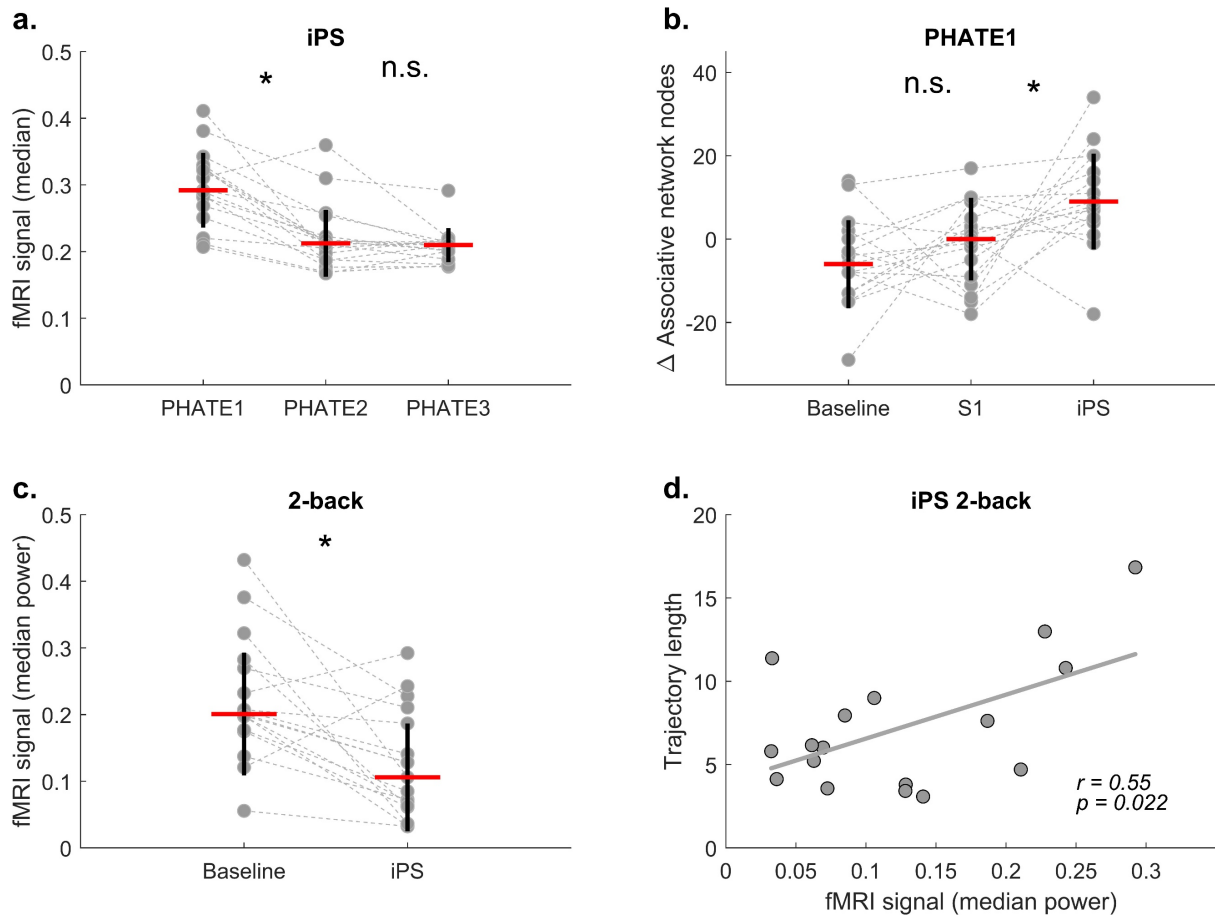
Supplementary Table 1. *Explained variance of PHATE components as captured by a denoised affinity-based transition embedding space.* This table summarizes the variance explained (%) by the top five PHATE dimensions. The first three dimensions explain >98% of the variance in the data. The variance explained by the three first dimensions remain consistent for the baseline and the S1 sessions, across 1-back and 2-back conditions. In contrast, TMS on iPS causes a shift in the overall variance captured by the PHATE dimensions (particularly the first and second dimensions). See Methods and Moon et al.¹² for further details.



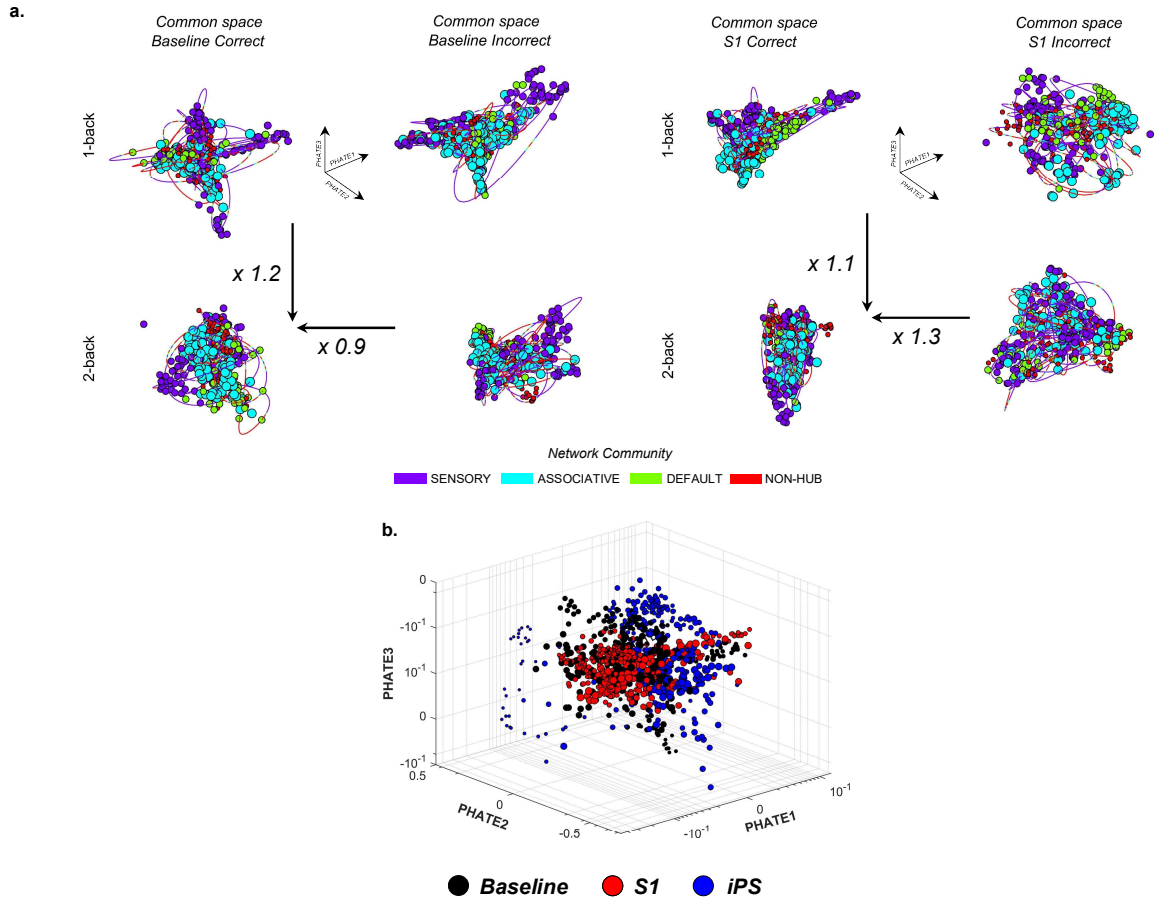
Supplementary Figure 1. Session and working memory load effects on PHATE4 and PHATE5. The figure highlights the contribution of low-dimensional trajectories defined by the first three dimensions (PHATE1, PHATE2, PHATE3) as a function of working memory load ('correct' responses from trial conditions shown). Low-dimensional trajectories defined by control dimensions (PHATE4 and PHATE5) remain unchanged for 'correct' responses in the same trial conditions. Source data are provided as a Source Data file.



Supplementary Figure 2. High-dimensional projections of the low-dimensional embedding linked to associative-cognitive processes defined by meta-analytic data (NeuroSynth). This figure highlights the association of the overall spatial weights (average across PHATE1, PHATE2, PHATE3 dimensions for correct 2-back trials, all experimental sessions) with 24 NeuroSynth topic terms aggregated from over 5000 neuroimaging studies. The figure shows that spatial weights estimated from low-dimensional brain activity were highly associated with cognitive processes such as working memory and numerical cognition.



Supplementary Figure 3. System-level and local-level changes for correct 2-back trials following stimulation of iPS. **a.** For median fMRI signals recorded during the iPS session, a within-subject ANOVA showed a significant effect ($F_{(2, 48)}=18.5$, $p=1.1 \times 10^{-6}$; $n=17$ examined within the iPS session across PHATE1, PHATE2 and PHATE3 dimensions; median represented by red line; within-dimension S.D. shown with black lines). No significant differences in fMRI signal across PHATE dimensions were detected for baseline and S1 sessions ($p>0.3$; not shown). The effect detected in the iPS session was driven by increased fMRI signal in key brain regions (top 20%) contributing to PHATE1 compared to fMRI signal in key regions contributing to PHATE2 and PHATE3 (paired t-test, PHATE1 > PHATE2 $p_{FDR}=8.4 \times 10^{-5}$, PHATE1 > PHATE3 $p_{FDR}=2.1 \times 10^{-6}$, and PHATE2 versus PHATE3 $p_{FDR}=0.18$; two-sided test). **b.** Analysis of changes in brain regions attributed to the associative network (cyan in Fig.1b) as a function of working memory load and session showed a significant interaction ($F_{(2, 96)}=8.64$, $p=3.5 \times 10^{-4}$, $n=17$ examined over the three experimental sessions). Positive values in the panel indicate recruitment of brain regions (number of nodes) comprising the associative network in the 2-back condition compared to 1-back condition. That is, the interaction was driven by an increased number of brain regions contributing to PHATE1 in correct 2-back trials (paired t-test, iPS > baseline $p_{FDR}=0.0007$, iPS > S1 $p_{FDR}=0.027$, and baseline versus S1 $p_{FDR}=0.26$; two-sided test). No significant differences were detected in all other network communities. Within-session median values represented by red lines and within-session S.D. shown with black lines. **c.** The fMRI signal (median power) of iPS was reduced in the iPS session (correct 2-back trials) compared to the baseline session (paired t-test, $p=0.0023$ two-sided test, $n=17$ examined between the baseline and iPS sessions). Each dot in the panel represents a participant (within-session S.D. shown with black lines). **d.** Pearson's correlation between iPS fMRI signal (2-back condition, correct trials) and length of the low-dimensional trajectory. Individuals with lower task-induced fMRI signal in iPS (following cTBS) showed shorter low-dimensional trajectories ($r=0.55$, $p=0.022$, two-tailed) and higher 2-back accuracy (see Fig. 3b). For all panels, asterisks (*) indicate statistical significance, adjusting for multiple comparisons where appropriate. Source data are provided as a Source Data file.



Supplementary Figure 4. Low-dimensional trajectories for baseline (no TMS) and S1 (following TMS on S1) sessions in the common embedding space. **a**, Results suggest that a measured degree of expansion (that does not reach statistical significance) of low-dimensional trajectories in the task embedding space is required to successfully accommodate an increase in working memory load in both baseline and S1 sessions. **b**, Representation of low-dimensional trajectories for 1-back correct trials in the common embedding space for baseline, S1 and iPS sessions (visualized in log space, same embedding space across experimental sessions). Source data are provided as a Source Data file.