Supplementary Material 1

The technical difficulty: How to stimulate connection/circuit?

Connectivity-based segmentation

DTI data were processed in the Camino (http://www.cs.ucl.ac.uk/research/medic/camino/) and FMRIB Software Library (FSL) v5.0 (University of Oxford Center for Functional MRI of the Brain, http://www.fmrib.ox.ac.uk/)1 software. The probabilistic index of connectivity (PICo) algorithm was used in HCs to obtain the nodal brain regions of the “hippocampus-cortex” network based on probabilistic fiber tracking. The procedure was performed as follows: 1) Preprocessing: including eddy currents correction, head movement correction, stripping of nonbrain tissue, and calculation of fractional anisotropy (FA) values, and so on. 2) Determination of seed and target areas: seed and target maps were determined using the automated anatomical labeling (AAL) template, including two voxel-based seeds (left and right hippocampus) and two voxel-based target area maps (left and right cortical brain area maps). All seed and target areas acquired in the standard atlas were converted to subject-specific native space. We registered FA maps to the corresponding T1-weighted scans in native space using FMRIB’s Linear Image Registration Tool (FLIRT) and nonlinearly transformed to register the T1-weighted images to standard MNI space. Subsequently, the transformation parameters estimated above were inversed and then applied to the seed and cortical areas in standard space. 3) Probabilistic tracking: fiber tracing was started 5000 times in diffuse space (threshold: single voxel $\leqslant 80^\circ$ or FA of voxel $\geqslant 0.1$) starting with each voxel within the seed point, and PICo was derived from the total number of seed point voxels reaching the target area. 4) Segmentation based on voxel connectivity: To minimize noise, we thresholded the average PICo and selected only voxels with probability connectivity index >1%.

A pilot study aimed to explore the feasibility of the paired-stimulus regulation on the “hippocampus-cortex” circuit.

The parameters for paired-stimulus regulation on the “Hebbian model” were developed based on existing research, preliminary research foundations, and clinical experience. In our clinical work, we found that the pain threshold in the forehead is lower than that in the posterior parietal lobe. Therefore, we first applied stimuli with an intensity of 80% of the resting motor threshold (RMT) in the left frontal lobe, followed by stimuli with an intensity of 120% RMT in the left precuneus.

Ma J, *et al. J Neurol Neurosurg Psychiatry* 2024; 95:902–911. doi: 10.1136/jnnp-2023-333152

Based on the rTMS treatment plan for existing cognitive disorders, high-frequency stimulation was selected. Considering the important adverse reaction of TMS, seizure. Meanwhile, the hippocampus is the most common site of seizure onset and is also an important brain region of interest in this study. Therefore, to be safe, 5 Hz was chosen as the stimulation frequency.

The interval between the stimuli (ISI) in the two brain regions is another important parameter that affects the effect. Therefore, we collected 9 subjects and randomly assigned them to the ISI = 1, 2, and 3ms groups, and performed TMS intervention according to the above plan. The results showed that the AVLT long-term delayed recall score improved the most when the ISI was 2ms. Therefore, this study chose an ISI of 2ms.

To verify whether the above parameters could achieve the goal of stimulating the "hippocampus-cortex" connection, we collected 6 normal subjects (age: 68.33 ± 10.67 years, education: 11.17 ± 3.19 years, Hamilton Anxiety Rating Scale: 1.67 ± 1.36 points, Hamilton Depression Rating Scale: 0.67 ± 1.21 points) and gave them 2 weeks (5 times per week, a total of 10 times) of TMS intervention.

The specific protocol involved paired stimulation of the left frontal and left precuneus, with 80% RMT intensity to the left frontal gyrus followed by 120% RMT intensity to the left precuneus, at a frequency of 5 Hz, with an ISI of 2 ms, for a total of 900 pulse pairs.

Neuropsychological assessments of overall cognition, memory, attention, and executive function were performed before and after treatment, along with functional magnetic resonance imaging to observe clinical effects and changes in the "hippocampus-cortex" network.

It should be noted that treatment began two weeks after completion of the baseline evaluation for two reasons: first, to reduce learning effects on the cognitive measures; and second, to calculate individualized stimulation targets for each participant.

After performing paired t-tests, it was found that there were significant improvements in mini-mental state examination (MMSE), AVLT total score, and AVLT long-term delayed recall score after treatment ($p < 0.05$) (**Table S1-1**). Comparison of brain functional changes before and after treatment revealed alterations in brain region function and functional connectivity (**Figure S1-1 to S1-4**) with the new neurostimulation strategy. All results were significant at the voxel level (p < 0.01) and cluster level (p < 0.01, *AlphaSim* corrected). This pilot study demonstrates the feasibility of this new method.

Table S1-1: Comparison of cognitive scales before and after "Hebbian pattern" paired stimulation modulation of the "cortico-hippocampal" circuit.

index	Before treatment	After treatment	*t* value	*p* value
MMSE	26.5±1.87	28.33±1.03	-3.05	0.03
AVLT	28.5±7.00	43.17±5.74	-7.06	0.00
AVLT_N5	5.67±2.07	8.00±1.67	-4.72	0.00
SDMT	26.17±18.35	31.17±10.11	-0.97	0.38
STT	208.79±81.72	168.33±96.02	1.75	0.14
BNT	24.17±2.04	23.5±3.02	0.70	0.52

MMSE: mini-mental state examination；AVLT: auditory verbal learning test；AVLT_N5: AVLT long-term delayed recall score；SDMT: symbol digit modalities test；STT: shape trail test；BNT: Boston naming test.

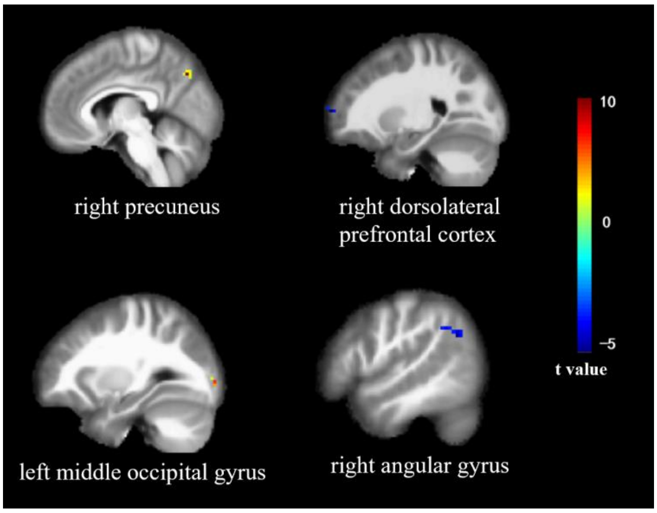

Figure S1-1 showed a comparison of the amplitude of low-frequency fluctuations (ALFF) before and after treatment. Following the "Hebbian pattern" paired-stimulation treatment, the ALFF values of Left middle occipital gyrus and right precuneus increased in healthy subjects, while the ALFF values of the right dorsolateral prefrontal cortex and the right angular gyrus decreased (p < 0.01 at voxel level and p < 0.01 with AlphaSim correction).

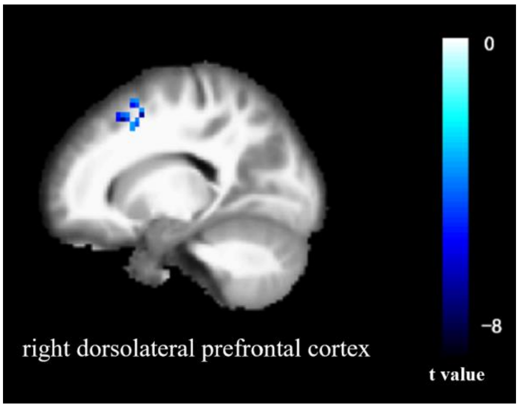

Figure S1-2: Comparison of regional homogeneity (ReHo) before and after treatment. After the paired stimulation treatment, the ReHo value was decreased in the right dorsolateral prefrontal cortex of healthy subjects ($p < 0.01$ at voxel level and cluster level with AlphaSim correction).

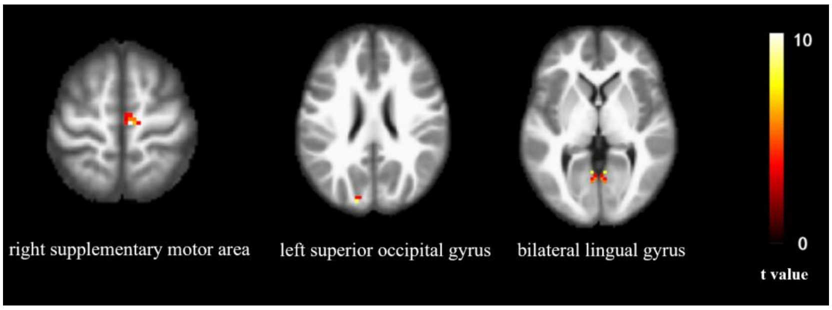

Figure S1-3 Comparison of voxel-mirrored homotopic connectivity (VMHC) before and after treatment. After the "Hebbian pattern" paired stimulation treatment, the VMHC values in the left superior occipital gyrus, right supplementary motor area, and bilateral lingual gyrus were increased in healthy subjects (voxel-level $p < 0.01$ and cluster-level $p < 0.01$ AlphaSim correction).

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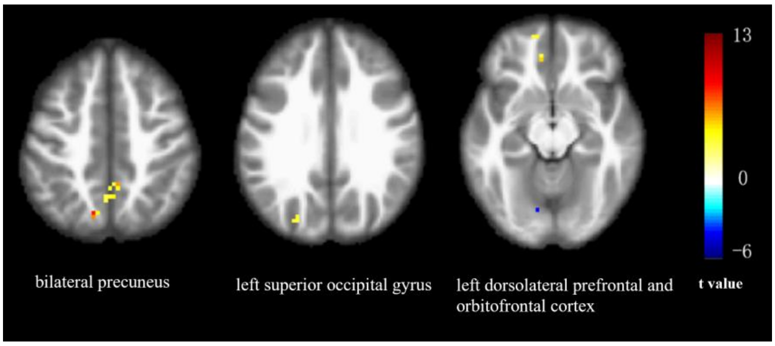

Figure S1-4 Comparison of functional connectivity (FC) before and after treatment. Following pairing stimulation treatment, FC between the left hippocampus and bilateral precuneus, left superior occipital gyrus, left dorsolateral prefrontal cortex, and left orbitofrontal cortex increased in normal subjects (voxel-level $p < 0.01$ and $p < 0.01$ AlphaSim corrected).

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