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LETTER TO THE EDITOR

Functional Near-Infrared Spectroscopy Neurofeedback of Cortical Target Enhances Hippocampal Activation and Memory Performance

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Dear Editor,

Neuromodulation, a rapidly expanding field attracting wide attention over recent decades, facilitates human cognition, behavior, and pathology by modifying the activity of specific neural targets. Human brain functions can be modified by exogenous brain neuromodulation techniques that deliver physical energy (e.g., electrical current or magnetic pulses) into the brain [1], such as deep brain stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation. In contrast, neurofeedback is considered to be an endogenous form of neuromodulation for regulating human brain function [2], in which individuals use mental strategies to voluntarily regulate the on-going neural activity of target brain regions. Compared to exogenous brain modulation techniques, neurofeedback is relatively safe, side-effect-free, well-tolerated, and acceptable to both healthy and clinical populations (see [3] for review).

Most neurofeedback systems currently utilize electroencephalography (EEG), functional magnetic resonance imaging (fMRI), or functional near-infrared spectroscopy (fNIRS) to acquire the on-going brain activity of individuals. Among these techniques, fNIRS neurofeedback (fNIRS-NF) has several special advantages. In contrast to fMRI, fNIRS devices are much cheaper, having lower purchase and operational costs, are relatively insensitive to movement-related artifacts, have no restrictions on location, have fewer contraindications (e.g., claustrophobia and MRI-incompatible metal implants), and can be used in natural environments [4] and with special populations (e.g., patients and infants) [5, 6]. These features also make fNIRS-NF more suitable for long-term and multi-session applications than fMRI neurofeedback. Besides, fNIRS has a relatively high and acceptable spatial resolution compared to EEG, which allows fNIRS-NF to achieve more precise self-regulation of a local cortical target. Thus, fNIRS-NF is a promising brain modulation technique and has been successfully applied in many areas (see the recent review by Kohl *et al.*, 2020 [7]).

Like other transcranial techniques, fNIRS measures activity near the surface of the brain but not in deep brain regions. However, several regions located in deep areas (e.g., the hippocampus, amygdala, and subgenual cingulate cortex) are critical for brain function, and dysfunction of these regions may lead to certain neurological or psychiatric diseases. These regions usually serve as the targets of deep brain stimulation to treat related diseases but cannot

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be directly modulated by fNIRS-NF. This, therefore, limits the scope of application of fNIRS-NF.

Accumulating evidence has indicated that the modulatory effects of focal neurostimulation can spread from the directly-stimulated region to distant connected regions [8–10]. Fox *et al*. (2014) found that known effective cortical sites used in noninvasive brain stimulation for neurological and psychiatric diseases usually have strong resting-state functional connections with the deep sites usually targeted by invasive brain stimulation [11]. Furthermore, cortico-subcortical functional connectivity can predict the clinical efficacy of neurostimulation [12]. Transcranial magnetic stimulation of a superficial target with robust functional connections with a deep brain region—the hippocampus—selectively enhances the functional connectivity among cortical-hippocampal network regions [13], and increases task activation of the hippocampus and related regions [14]. This evidence suggests that cortico-subcortical connectivity is helpful for cortical target selection and the optimization of transcranial neuromodulation techniques, and superficial cortical regions with robust functional connectivity to key subcortical nodes might be effective targets through which to achieve indirect modulation of deep brain regions.

Here, we aimed to test the feasibility of fNIRS-NF for indirectly regulating deep brain regions. First, knowledge from functional connectomics was used to select a cortical target robustly connected with the key deep brain region. We selected the hippocampus as the deep modulation target for its importance in long-term memory, especially associative memory retrieval [15]. Our hypothesis was: fNIRS-NF of a cortical region connected to the hippocampus will improve associative memory performance by indirectly changing the neural activity of the hippocampus.

We conducted a placebo-controlled real-time multisession fNIRS-NF experiment with behavioral test and task fMRI measurement to test the hypothesis. This study was approved by the Southwest University Brain Imaging Center Institutional Review Board. In the participant screening phase, any individuals with experience in mnemonic strategies or neurofeedback were excluded. Fifty healthy college students (25 males, age range 18–25 years) were recruited to participate in this study, and all participants provided written informed consent.

An overview of the experimental design is illustrated in Fig. 1. To define the cortical target for fNIRS-NF, we first performed a resting-state functional connectivity analysis based on the open-access large sample fMRI database SLIM [16] to find the cortical regions with robust intrinsic connections to the hippocampus (Supplementary Materials). Consistent with previous studies [17], the left lateral parietal cortex (LPC, peak voxel MNI (Montreal Neurological Institute) coordinate: [−45, −69, 33]) exhibited robust positive connectivity with the left hippocampus (FDR-corrected P <0.005, Fig. 1A), and was selected as the cortical feedback target. Then, 30 participants (15 males) from among the recruited participants were assigned to the experimental group and instructed to up-regulate the neural activity of LPC. Control conditions are essential for neurofeedback studies to distinguish whether neuropsychological changes are due to regulation of the target region or due to placebo effects. Therefore, the other twenty participants (10 males) were assigned to the active control group and received placebo neurofeedback of activity in an irrelevant brain region (left premotor area, PMA, mean MNI [−38, −13, 60], Fig. 1A). All participants were blinded to their group allocation. The deep region and cortical targets were located in the left hemisphere (for reasons, see Supplementary Materials). The arrangement of optodes is shown in the Supplementary Materials (Fig. S1A).

The entire experiment was divided into three stages: pre-assessment, 8 fNIRS-NF sessions, and post-assessment (Fig. 1B). Each participant received 8 neurofeedback sessions within 9 days. Each session had ∼30 min of effective feedback time. Changes in oxyhemoglobin concentration were measured using the NIRS system (FOIRE-3000, Shimadzu Corp., Kyoto, Japan). Neurofeedback was performed on our in-house fNIRS neurofeedback platform (Fig. 1C), in which the height of the stone in an on-screen image represented the relative concentration change of oxygenated hemoglobin compared to the baseline in the target brain region (for the calculation of the neurofeedback index see Supplementary Materials). Without providing explicit strategies, participants were asked to raise the stone as high as they could use any strategy they found helpful. Post-assessment was performed on the day after the final feedback session.

To assess the behavioral and neural effects induced by fNIRS-NF, all participants performed a face-noun associative memory test while undergoing functional MRI scanning in the pre- and post-assessment sessions. The day before the first fNIRS-NF session, the face-noun associative memory task and functional MRI scanning were performed to assess the baseline behavioral performance and brain function. The entire associative memory test consisted of four parts: encoding, recognition, immediate recall, and delayed recall (Fig. 1D). The encoding phase and recognition test were performed in an MRI scanner. Participants were instructed to learn the relationships between the human faces and corresponding noun words in the encoding phase, then an 8-min structural imaging scan followed. Afterward, a 4-choice recognition test was given, and participants were asked to recollect the correct noun from four possible alternative nouns containing three distractors and make a response. After leaving the scanner

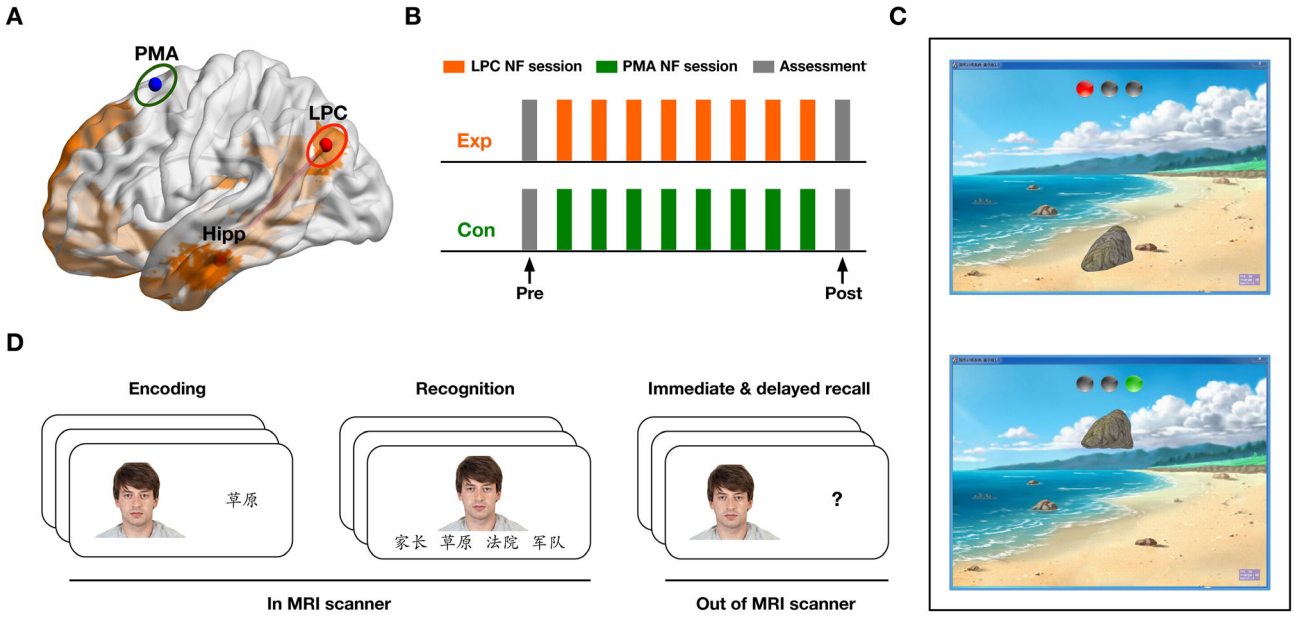

Fig. 1 Experimental design overview. **A** Neurofeedback target identification. Orange shading indicates the hippocampal (Hipp) functional connectivity mask. The experimental group's target (LPC: lateral parietal cortex) is within the hippocampal connectivity network, while the control group's target (PMA: premotor area) is outside of the connectivity network. **B** Experimental procedure. Both experimental (Exp) and control (Con) groups received 8-session neurofeedback (NF) sessions. Before and after the 8-session neurofeedback, all participants completed task fMRI scans and associative memory assessments. **C** Neurofeedback visual interface. Two sample images of the interface depict fixation (upper) and regulation (lower) blocks. **D** Associative memory test.

room, the immediate recall test was given. And the delayed recall test was performed approximately 24 h later. The face-noun associative memory task was performed again with the same procedure and different stimuli on the day after the last fNIRS-NF session. All MRI data were collected on a 3-Tesla Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany) with a 12-channel head coil.

Offline analysis of fNIRS-NF time-course data indicated that both groups succeed in up-regulating the real-time activity of their target brain regions but not non-target regions (Fig. S2 and Table S2). To determine whether fNIRS-NF could induce a neuroplastic change in hippocampal activity during memory processing, relative activation values of task-dependent fMRI within the left hippocampus during the memory recognition task were calculated and then compared between groups. The values for changes in voxel-wise task activation within the left hippocampal region of interest (3 mm radius sphere used in the feedback targeted identification phase) from the delta activation map were extracted and averaged for subsequent neural effect comparison. Though no significant group difference was found ($t_{(43)}$ = 1.10, P = 0.28, Cohen's d = 0.34), a significant increase in hippocampal activation was found in the experimental group after 8 sessions of fNIRS-NF relative to the baseline in pre-assessment session ($t_{(26)}$ = 2.05, P = 0.05, Cohen's d = 0.39), but not in the control group ($t_{(17)}$ = 0.01, P = 0.99, Cohen's d = 0.00, Fig. 2A and Table S1). Meanwhile, no significant pre-post or group differences in task-dependent activation in the LPC and PMA were found (Table S2). Behavioral effect analyses showed that recognition memory performance significantly increased relative to the baseline in the pre-assessment session in the experimental group ($t_{(26)}$ = 2.83, P <0.01, Cohen's d = 0.54, Fig. 2B and Table S1), while the change was not found to be significant in the control group ($t_{(17)}$ = 0.81, P = 0.43, Cohen's d = 0.19). The group difference of the modulation effects in recognition memory performance was significant ($t_{(43)}$ = 2.40, P = 0.02, Cohen's d = 0.73). Similar results were obtained in the immediate recall test after leaving the MRI scanner room and the delayed recall test approximately 24 h later (Table S1 and Fig. S3). Correlation analysis revealed that task activation changes in the left hippocampus were significantly and positively correlated with increases in accuracy of recognition memory performance in the experimental group (r = 0.42, P = 0.03, 95% CI: [0.05, 0.69], Fig. 2C). No significant trend was found in the control group (r = 0.13, P = 0.62, 95% CI: [−0.36, 0.56], Fig. 2C).

Despite being a promising neural modulation technique with several specific advantages, its inability to modulate deep brain regions limits the application of fNIRS-NF. In the current study, we made a preliminary attempt to test whether fNIRS-NF could indirectly modulate the deep

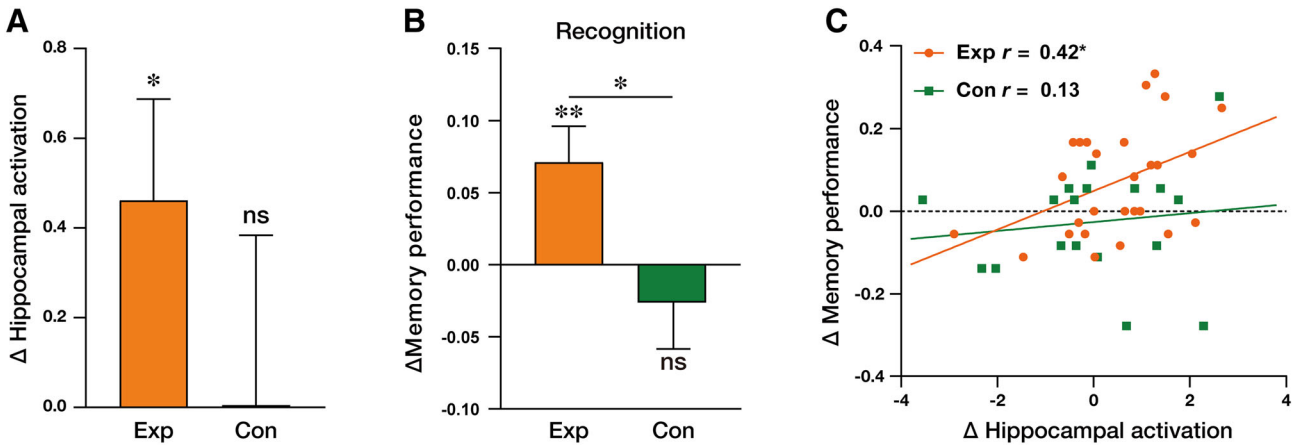

Fig. 2 Experimental results. **A** fNIRS-NF induced task activation in the hippocampus. **B** Recognition test performance of associative memory. **C** Scatter plots showing the relationships between changes in hippocampal activation and changes in memory performance. Error bars indicate SEM. *P ≤0.05; **P ≤0.01; ns, not significant.

brain region *via* directly regulating a cortical region with robust intrinsic connections with the deep region.

The LPC was selected as the direct feedback target because of its robust intrinsic functional connectivity with the hippocampus. Then, multi-session fNIRS-NF training was performed on this region with the aim of enhancing hippocampal activation and improve the subsequent memory performance. Neural effect analysis showed that the activation in the hippocampus during associative memory recognition increased after 8 self-regulation sessions. In addition to neural results, the behavioral effect analysis showed that associative memory performance also increased after training. Furthermore, increased hippocampal activation was significantly correlated with memory improvement. The underlying neural mechanisms for the remote modulation effect and subsequent behavioral improvement induced by fNIRS-NF might be explained as follows. First, self-regulation with mental strategies not only changes the neural activity of the direct target region but also affects the related deep regions within the same network (especially those having strong intrinsic connections with the direct feedback target). Long-term regulation gradually consolidates these influences and finally induces significant changes in neuroplasticity in the connected deep regions. And then the affected key deep regions play their special roles in changing cognitive or behavioral performance. In this study, though the feedback signal from the LPC was regulated directly, the hippocampus having strong functional connectivity with this cortical target could also be activated simultaneously. After 8 fNIRS-NF training sessions, the hippocampal activation was increased significantly. Enhanced hippocampal activation supports more effective associative memory processing, and increases subsequent memory performance. The hippocampus is the core component of the distributed hippocampal-cortical network [18] and plays a crucial role in associative memory processing [19]. Information from various distributed cortical modules is received by the adjacent cortical regions of the medial temporal lobe *via* respective streams, and then these independent elements are rapidly integrated and bound into coherent long-term memory traces by the hippocampus [20]. During retrieval, the presentation of a subset of the original information reactivates the hippocampus and causes the cortical network to reinstate the original pattern of activity, allowing recall of the stored information [21]. Increased hippocampal activation makes these memory processes more efficient and precise, and improves final memory performance [15, 22].

Here, we preliminarily tested the feasibility of using fNIRS-NF to indirectly modulate a deep brain region by directly regulating an accessible cortical feedback target with robust functional connectivity with the deep region. These neural and behavioral results suggested the potential for fNIRS-NF on a functionally-connected cortical region to be used to indirectly modulate the neural activity of a related deep brain regions and improve the desired cognitive functions. However, several limitations should be noted when interpreting our results, and future studies are needed to generalize our method. First, we only tested the feasibility of fNIRS-NF to indirectly modulate a single deep brain region – the hippocampus. And, the results were generated based on a healthy young adult population sample. Future studies are needed to test its feasibility for other deep brain regions (e.g., the amygdala and subgenual cingulate cortex) in different populations, especially before deployment to clinical applications. Second, in the current study, the robust functional connectivity between the superficial cerebral cortex and the hippocampus was identified by using FDR correction (P <0.005) on the

result of group-level resting-state fMRI analysis, but the criteria might be different in other specific studies. The final goal, here, was to identify an accessible cortical region with strong and stable function connectivity with a deep brain target in the same network, which is more likely to affect the deep region and achieve plastic change in that region. Besides, although distal neural modulation was found in the current study and other related research, the underlying mechanism is yet unclear, requiring further study.

In conclusion, self-regulation of a hippocampus-connected cortical region by fNIRS-NF successfully increased task-related hippocampal activation and the associative memory improvement. Furthermore, the change in hippocampal activation was correlated with the behavioral change. Our results suggest the potential of fNIRS-NF to indirectly modulate deep regions *via* regulating a functionally-connected cortical regions and improve the related cognitive functions or clinical symptoms.

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Conflict of interest The authors claim that there are no conflicts of interest.

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