Ultrasound Meets Memory: A proposal for a new approach to study TUS-Induced neuroplasticity

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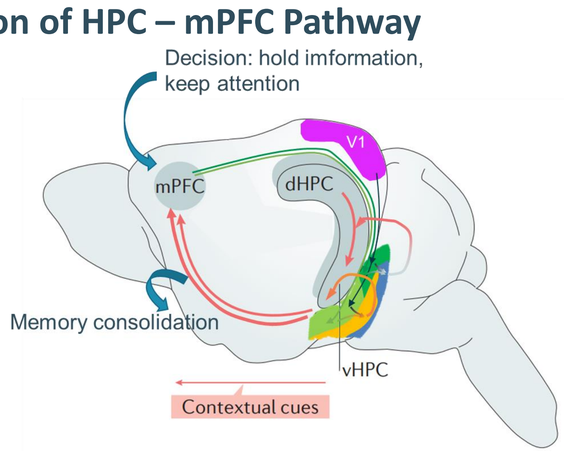
Introduction

- Transcranial ultrasound stimulation (TUS) is an emerging non-invasive neuromodulation technique with high spatial precision and access to deep brain regions.
- In vitro studies suggest that TUS can induce neuroplasticity-related effects, but its in vivo mechanisms remain largely unknown.
- The hippocampus–medial prefrontal cortex (HPC–mPFC) pathway is a monosynaptic connection between ventral CA1 of HPC and Prelimbic Cortex (PrL) of mPFC.
- HPC–mPFC pathway is critical for working memory and long-term memory, where long-term potentiation (LTP) underlies memory encoding and consolidation.
- Long-term potentiation (LTP) is a persistent enhancement of synaptic transmission induced by specific activity patterns. It can be experimentally evoked by electrical stimulation (e.g., high-frequency or theta-burst) and also occurs naturally during learning tasks, making it a core mechanism of memory formation.
- This study proposes a rodent model to examine how TUS modulates LTP within the HPC–mPFC pathway, integrating electrophysiological recording and neurochemical analysis.
- By optimizing stimulation parameters and monitoring glutamate and dopamine dynamics, this work aims to clarify the mechanisms of TUS-induced plasticity and its potential for cognitive enhancement and clinical interventions.

Function of HPC – mPFC Pathway

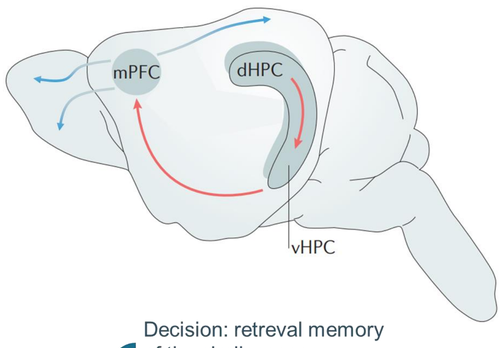
A

- Working memory
- Memory formation



B

- Long-term memory storage



C

- Memory retrieval

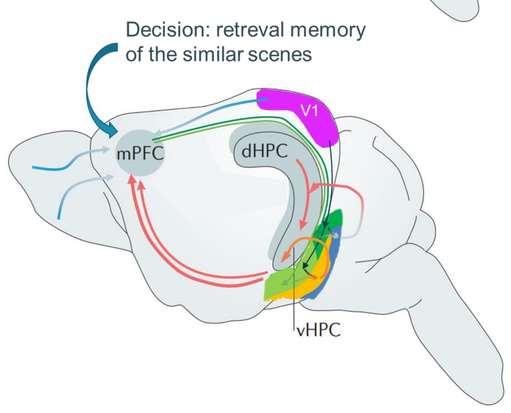


Fig.1: A) Contextual signals from the ventral hippocampus (vHPC) modulate medial prefrontal cortex (mPFC) activity to support working memory functions such as maintaining information and attention[1]. B) newly formed memory is sent to mPFC for Distributed Storage at neo-cortex by HPC-mPFC pathway[1]. C) Contextual inputs from the vHPC activate the mPFC to guide recall of relevant memories. This hippocampal–prefrontal interaction supports decision-making processes by selecting context-appropriate memories[1].

LTP and its functional role

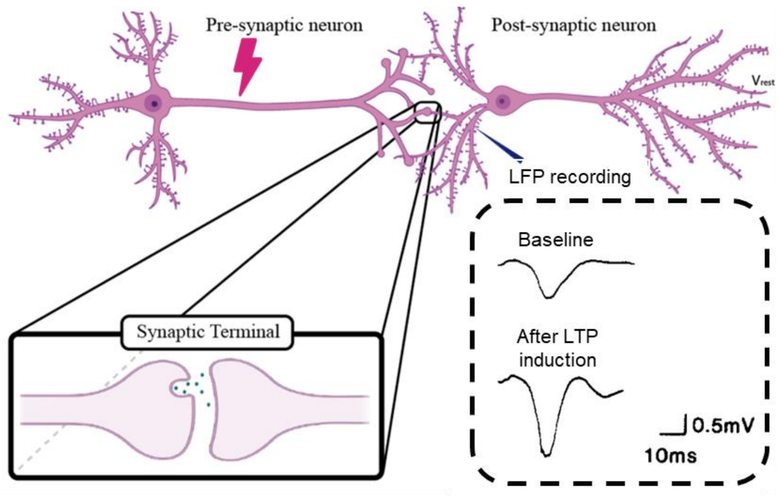


Fig.2: High-frequency stimulation at pre-synaptic neuron enhances glutamate release and strengthens post-synaptic responses, leading to a persistent increase in synaptic efficacy[2].

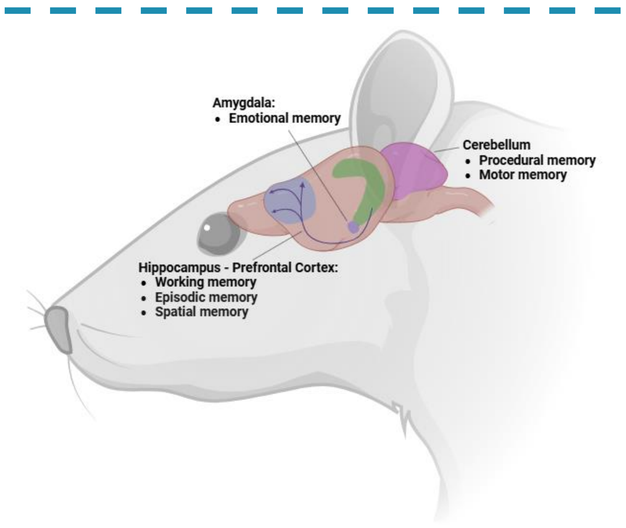


Fig.3: LTP contributes to multiple memory systems across the brain. In the hippocampus–prefrontal cortex circuit, LTP underlies working memory, episodic memory, and spatial memory. In the amygdala, LTP supports emotional memory, particularly fear learning. In the cerebellum, LTP is essential for procedural and motor memory. Together, these mechanisms highlight LTP as a unifying cellular basis of diverse memory functions[3].

TUS modulation LTP in-vitro

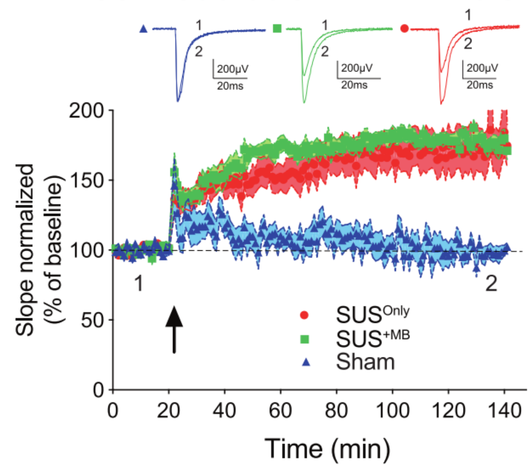


Fig. 4: Field excitatory postsynaptic potentials (fEPSPs) were recorded in hippocampal slices following theta-burst stimulation (TBS, indicated by the black arrow) ***by Blackmore, D. G et al***. No LTP was observed in sham mice, whereas LTP was fully rescued in both scanning ultrasound combined with microbubbles (SUS^{+MB})and SUS treatment without microbubbles (SUS^{only}) groups. Data are normalized to baseline slope (mean ± SEM)[4].

TUS modulation LTP in-vivo

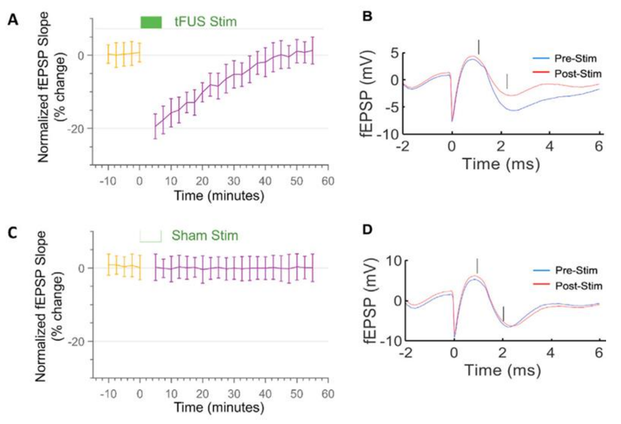


Fig. 5: Average fEPSP waveforms pre and post tFUS stimulation in-vivo ***by Niu X et al***. The blue line represents the fEPSP before the stimulation, and the red line indicates the one after the stimulation. Markers show segments used to measure fEPSP slope. TUS can also cause depression effects to neuroplasticity[5].

Experiment Design

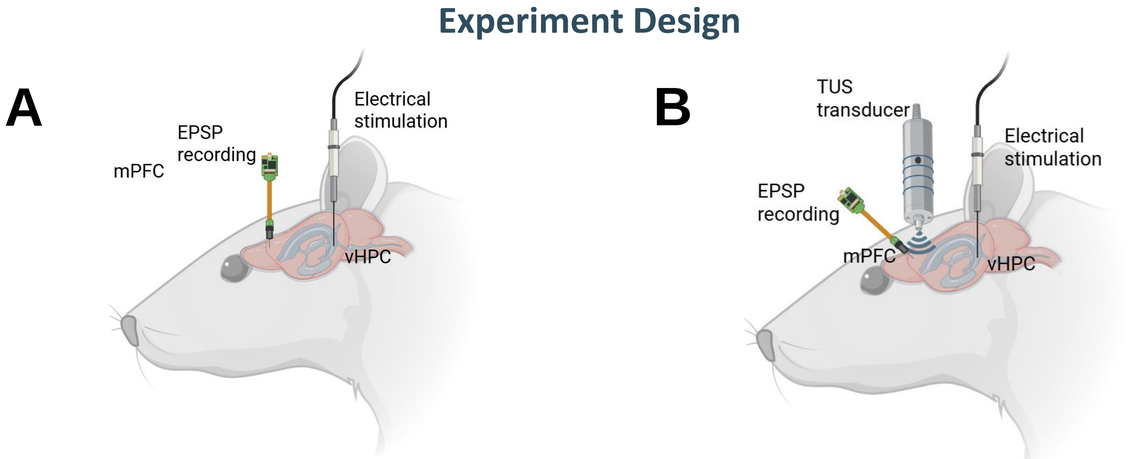


Fig.6: A) In-vivo neuroplasticity recording paradigm. LTP was induced by high-frequency stimulation at CA1 of ventral hippocampus and recorded at the prelimbic cortex (PrL) of mPFC on anesthetized rats. Neuroplasticity was quantified by amplitude and slope of fEPSPs. B) TUS modulation of LTP at the HPC–mPFC pathway. A transducer is positioned above PrL to deliver TUS during LTP induction at the HPC–mPFC pathway. fEPSPs are recorded in PrL to quantify amplitude, slope, assessing TUS effects on synaptic plasticity.

Preliminary Results – in-vivo LTP is induced

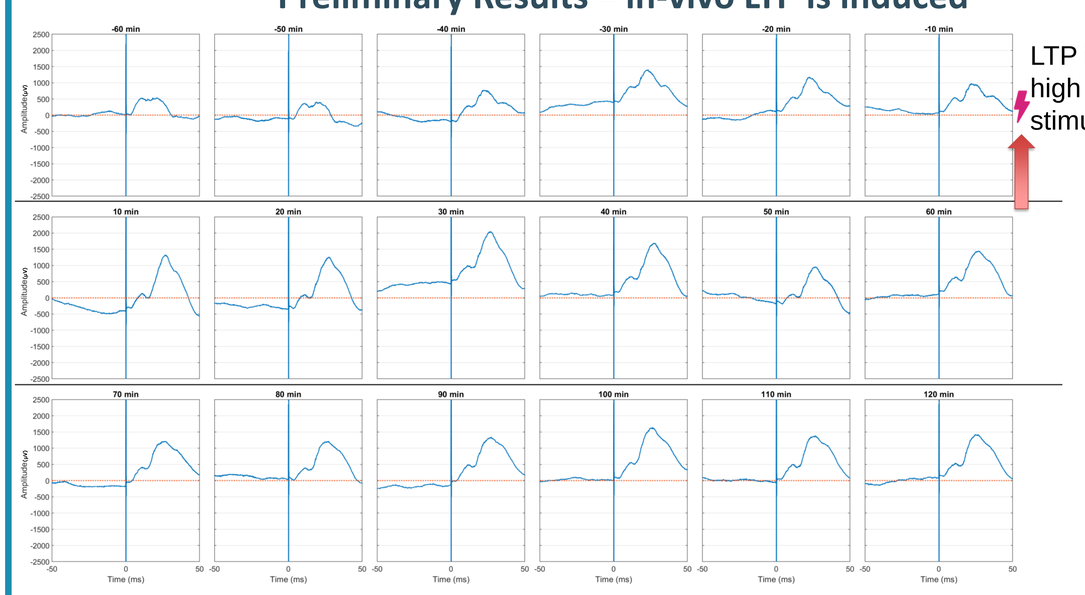
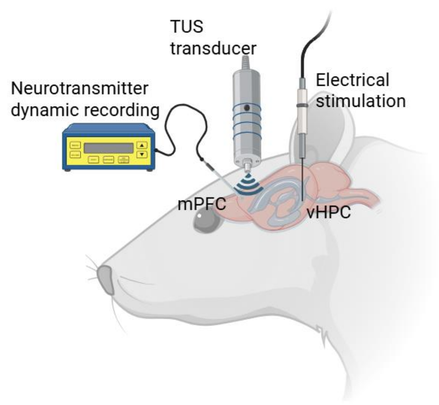


Fig.7: Amplitude of EPSP in mPFC of rat increased after LTP induction by high frequency stimulation

Follow steps:

Fig.8: Neurotransmitter mechanisms of TUS-induced plasticity. To investigate neurotransmitter involvement in TUS modulation of the HPC–mPFC pathway, a matrix of more than 16 parameter combinations (pulse repetition frequency: 50–2000 Hz; pulse duration: 50 μs–1 ms) will be applied for parameters optimization. Changes in dopamine (DA), glutamate (Glu), and release latency will be measured to identify stimulation parameters most relevant to plasticity regulation.



[1]. Preston, A. R., & Eichenbaum, H. (2013). *Current Biology.*
[2]. Schmidgall, S., et al. (2024). *APL Machine Learning*
[3]. Dringenberg, H. C. (2020). *Hippocampus*
[4]. Blackmore, D. G., et al. (2021). *Molecular Psychiatry*
[5]. Niu, X., Yu, K., & He, B. (2022). *Brain Stimulation*

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