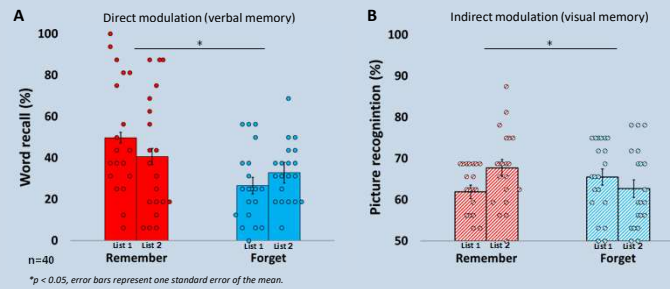


Introduction

- Maladaptive memories underlie mental conditions such as posttraumatic stress disorder (PTSD), depression and fear disorders. However, negative emotional memories show resistance to direct modulation.
- We propose to **modulate negative memories indirectly**.
- We demonstrated **indirect modulation of neutral visual memory**, utilizing behavioral instructions to intentionally remember or forget verbal information, in order to indirectly target an embedded visual memory (Fig. 1) [1].

Figure 1 - Indirect modulation of neutral visual memories [1]



- To indirectly modulate **emotional memories**, we leverage **non-invasive brain stimulation**, paired with memory reactivation, in which long-term memories enter a flexible state and susceptibility to neuromodulation [2-3].
- Transcranial magnetic stimulation (TMS)** over the right prefrontal cortex (PFC) after memory reactivation [3-4] will be applied to enhance verbal memory, and indirectly downregulate negative visual memory.

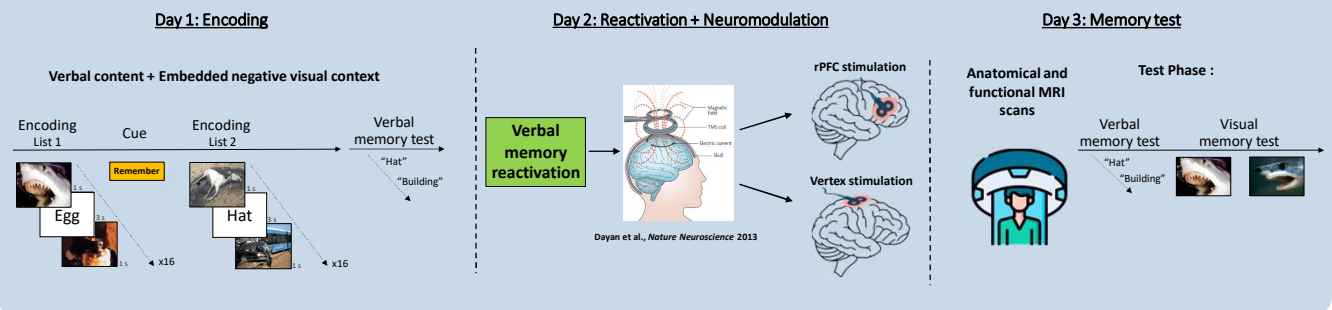
Research question

How can neuromodulation indirectly modify long term negative visual memory, and what are the underlying neural mechanisms?

Methods

- Participants will perform a three-day indirect neuromodulation experiment (Fig. 2).
- Prior to the experiment, participants will complete anatomical and functional Magnetic Resonance Imaging (MRI) scans for TMS localization and neuronavigation, and measurement of PFC resting-state functional connectivity.
- On the first day participants will study neutral words embedded with negative pictures and complete a verbal memory test (Fig. 2, Day 1).
- On the next day, participants will undergo verbal memory reactivation [3-4] in the same experimental room (spatial contextual reminder).
- Next, participants will undergo 1Hz repetitive TMS over the right PFC to enhance verbal memory strength or a control stimulation over the vertex [3] (Fig. 2, Day 2).
- On the third day participants will complete an additional set of MRI scans, and verbal and visual memory will be tested (Fig. 2, Day 3).

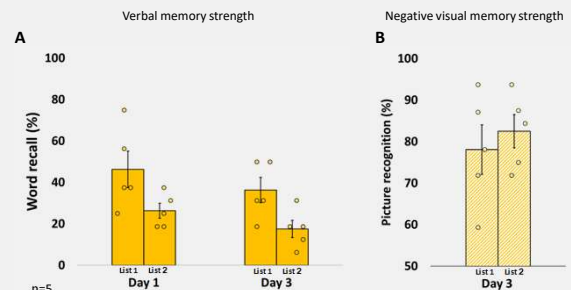
Figure 2 – Study design and procedures



Preliminary Results

Figure 3 – Verbal and negative visual memory strength without neuromodulation

- To establish the behavioral paradigm, we first evaluated participants' verbal and visual memory performance without neuromodulation.
- Consistent with dominance of negative visual memory, preliminary results show that negative emotional context reduced verbal memory strength (Fig. 3A left panel), in contrast to the effect of the remember instruction in the neutral context experiment (Fig. 1A left panel).
- On the third day, negative visual memory strength (Fig. 3B) was greater than neutral visual memory strength (Fig. 1B left panel).



Summary and Future Directions

- This study explores the neurobehavioral mechanisms of learning and memory occurring under negative context.
- Preliminary results demonstrate that negative visual memory dominates neutral verbal content, emphasizing the challenges associated with negative memory modulation.
- To address these challenges, we now examine the effects of memory reactivation combined with neuromodulation on long-term visual negative memory.
- This study seeks to discover novel approaches to downregulate long-term negative memories, potentially opening a new avenue for treating psychopathologies such as PTSD.

References

- Kozak, S., Herz, N., Bar-Haim, Y., & Censor, N. (2021). Indirect modulation of human visual memory. *Scientific reports*, 11(1), 1-7.
- Nader, K., & Hardt, O. A single standard for memory: The case for reconsolidation. *Nature Reviews Neuroscience* vol. 10 224–234 (2009).
- Sandrini, M., Censor, N., Mishoe, J., & Cohen, L. G. (2013). Causal role of prefrontal cortex in strengthening of episodic memories through reconsolidation. *Current Biology*, 23(21), 2181-2184.
- Bos, M. G., Schuijjer, J., Lodestijn, F., Beckers, T., & Kindt, M. (2014). Stress enhances reconsolidation of declarative memory. *Psychoneuroendocrinology*, 46, 102-113.

