Let's Shape Learning Into Lasting Memories

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ABSTRACT: Recent experiments in rats and humans have indicated that the effects of non-invasive electrical stimulation are primarily due to transcutaneous stimulation of peripheral nerves, specifically the greater occipital nerve. This stimulation pathway activates communication gateways from the periphery to the brain, impacting memory consolidation. In this invited commentary, I delve into and offer additional insights concerning the enhancement of episodic memory through transcutaneous electrical stimulation of the greater occipital nerve, building upon the findings published by my laboratory in both *Science Advances* and *Elife*. Our research on non-invasive transcutaneous electrical stimulation of the greater occipital nerve (NITESGON) has shown to enhance episodic memory consolidation and promote communication between the locus coeruleus (LC) pathway and the hippocampus based on resting connectivity functional MRI. The LC, primarily responsible for releasing noradrenaline and dopamine, plays a crucial role in post-encoding memory stabilization. This suggests that NITESGON can improve memory but does not affect immediate learning. The concept of behavioural tagging, where weak memories can be stabilized through strong or novel events, and how NITESGON activates a memory consolidation through this mechanism are discussed. The role of NITESGON in enhancing memory stabilization is highlighted, providing a non-pharmaceutical solution with minimal side effects. The potential application of NITESGON in neurological conditions, including Alzheimer's disease, attention deficit hyperactivity disorder and post-traumatic stress disorder, is also discussed, emphasizing its promising therapeutic prospects.

KEYWORDS: Learning, memory, electrical stimulation, greater occipital nerve, locus coeruleus

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There is an ongoing debate about whether non-invasive electrical stimulation of the scalp modulates the excitability of neurons directly.[1] Interestingly, a series of experiments in rats and humans isolated the transcranial and transcutaneous mechanisms of non-invasive electrical stimulation and showed that the reported effects are mainly caused by transcutaneous stimulation of peripheral nerves.[2] Our recent work indicates that non-invasive transcutaneous electrical stimulation of the greater occipital nerve (NITESGON) using direct current utilizes a pathway that arises from the C2 spinal nerve to establish communication gateways from the periphery to the brain via afferent fibres that project to the brainstem and synapse onto the nucleus tractus solitarius.[3] From the nucleus tractus solitarius, the information is then integrated among networks within the complex reticular formation and relayed across noradrenergic locus coeruleus (LC) in the brainstem through major cortical and subcortical regions[3] (see Figure 1). In this invited commentary, I discuss and provide further research avenues related to our research on NITESGON enhancing episodic memory that was published by my lab in both *Science Advances*[4] and *Elife*.[3]

In a series of memory recall experiments, university students who received NITESGON during their initial visit exhibited improved memory recall 7 days after the initial learning of a word association task.[4,5] Intriguingly, NITESGON yielded a long-term memory effect but did not trigger an immediate effect on learning, suggesting that the effect is generated during the consolidation of memories as opposed to during the learning or encoding of new memories.[5] A neurobiological model for long-term memory suggests a mechanism in which initially unstable memories can be reinforced through subsequent novel experiences. We demonstrated that NITESGON has the capacity to enhance memory consolidation when applied before, during, or immediately after the learning phase.[5]

Memory Stabilization is Driven via Locus Coeruleus – Dopamine

The majority of newly acquired memories are forgotten, while certain episodic-like memories are kept for extended periods of time and are susceptible to memory stabilization.[6] This is referred to as synaptic consolidation, a process that stabilizes new episodic information into memory over a timespan of minutes to hours. A prevailing hypothesis is that episodic-like memory stabilization is mediated by a subiculum–accumbens–pallidum–ventral tegmental area (VTA) pathway via dopamine. However, research suggests that hippocampal projections in the VTA are sparse and only have a limited role in late-phase synaptic plasticity. Interestingly, previous research has shown that electrical and pharmacological stimulation of the LC modulated hippocampal synaptic transmission, whilst

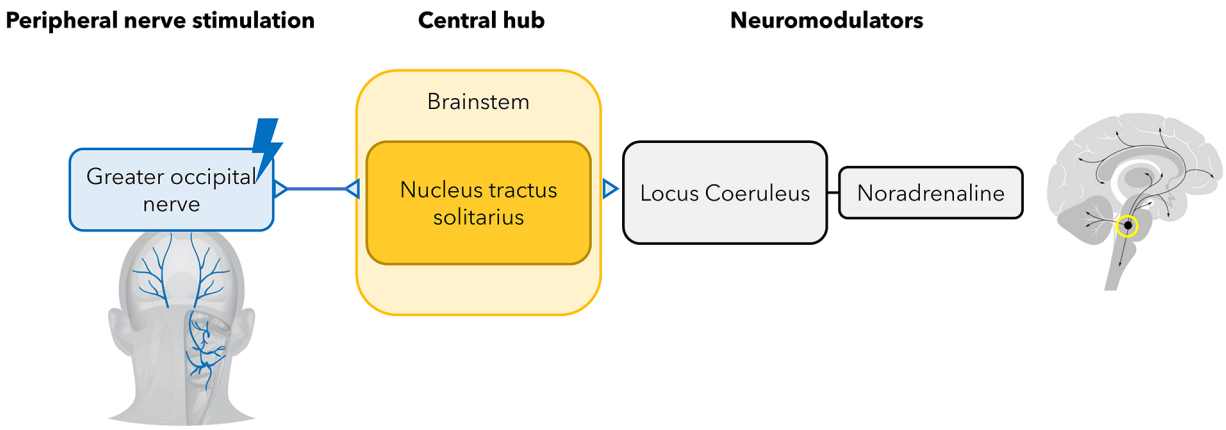

Figure 1. Schematic figure showing the stimulation pathway for NITESGON.

modulation of the VTA did not significantly mediate synaptic transmission.[7] Using regional amplitude of low-frequency fluctuations of rest-state MRI, our results indicated that the VTA as well as the LC was activated during NITESGON, however, the VTA activation ceased post-stimulation while continued activation was revealed for the LC. In addition, resting connectivity functional MRI revealed no increased connectivity between the VTA and hippocampus during or after NITESGON, while this was the case between the LC and the hippocampus.

A key neuromodulator in memory stabilization is dopamine (DA).[8] DA affects plasticity, synaptic transmission, and network activity in the hippocampus, and plays a critical role for hippocampal-dependent mnemonic processes by selectively enhancing consolidation of memory information.[9] Suggestions are made that the signal transduction processes catalysing this synthesis of plasticity-related proteins require DA to stabilize new memories.[10] To regulate synaptic plasticity, the hippocampus receives dopaminergic input from the VTA and the LC.[9] However, recent research revealed that mainly LC DA mediates post-encoding memory enhancement in the hippocampus, while the VTA does not respond to arousal.[7] Animal studies identified activation of the LC via optogenetic stimulation caused more synaptic consolidation 45 minutes after stimulation.[8] This can explain why NITESGON applied while learning a memory task generated a long-term memory effect but did not modify immediate learning.[4,5] Furthermore, our results corroborate this, indicating that utilizing a DA antagonist can reduce the effect of NITESGON and that spontaneous eye blink responses, a proxy for DA, increases after NITESGON.

Although the LC can release both dopamine and noradrenaline across the brain in parallel to facilitate memory stabilization, understanding the precise role of these 2 specific neuromodulators is crucial for the development of effective interventions. Initial research suggests that DA might be involved in neural-gain related memory selectivity, while NA is involved in arousal-related memory enrichment.[11] However, further characterization of their interdependence would reveal fundamental principles of how the brain captures and stores specific information in memory.

Behavioural Tagging Versus Synaptic Tag-and-Capture Mechanism

To elucidate the neurobiological basis of synaptic consolidation, Frey and Morris introduced a plasticity model called the synaptic tag-and-capture hypothesis. This model provides a cellular mechanism that explains how initially weak and unstable memories can be tagged for capture by late-phase long-term potentiation, ultimately making them stable.[10] This synaptic tag-and-capture mechanism has been adapted into a learning and memory concept known as behavioural tagging.[10] Behavioural tagging suggests that weak training, which typically results in short-term memory, can leverage the tag-and-capture process to transform into a stable long-term memory when a weak event is either preceded or followed by a strong or novel event within a specific time frame.[12] The neural system responsible for this novelty response is the locus coeruleus-noradrenaline (LC-NA) pathway.[13] Animal studies further support the idea that direct electrical stimulation of the locus coeruleus (LC) can modulate hippocampal synaptic consolidation.

Our experiments provide evidence that NITESGON targeting the LC might inducing a memory consolidation via a behavioural tagging mechanism.[5] The idea behind behavioural tagging suggests that weak memories that are relatively unstable and likely to be forgotten will solidify following a novel experience.[12] That is, consolidation is facilitated by applying a strong stimulus alongside a weak stimulus within a critical time window. Recent research revealed a direct link between the LC and behavioural tagging, attributable to the pivotal role the LC plays during the presentation of a salient or arousing event (ie, strong stimulus), as well as being at the helm of regulating the synthesis of new proteins required for memory consolidation in the hippocampus. Our findings revealed that NITESGON induced a proactive and retroactive memory effect.

More intriguingly, when we introduced an interference task we found that NITESGON diminished the interference effect. Interestingly, according to the cellular mechanism of the

behavioural tagging model (called the synaptic tag-and-capture hypothesis), memory interference has been proposed to be the result of synaptic competition, a proposed 'fight for proteins' that arises between tagged synapses among limited proteins that leads to one memory converting to long-term memory at the expense of the other. Therefore, it could be postulated that NITESGON could enable optimal availability of plasticity-related proteins, thus decreasing synaptic competition and subsequent interference. However, research is needed to confirm the hypothesis that NITESGON's memory effect is achieved by specifically activating the synaptic tag-and-capture's neural mechanism.

Conclusion

Our study provides evidence demonstrating the power of NITESGON-directed plasticity for improving memory consolidation. Unlike pharmaceutical approaches, NITESGON offers the possibility of long-lasting and stimulus-specific changes to neural circuits with minimal side effects (eg, temporary headache, itching). Several studies have suggested that the memory deficit of Alzheimer's disease patients is due to ineffective consolidation of new information. NITESGON is a novel approach that could contribute to a solution to this issue. This approach can easily be expanded to other neurological problems and disorders. For instance, the LC-NA pathway also plays a role in the regulation of attentional stability, responsiveness, and cognitive reserve. Specifically, insufficient LC-NA function can lead to attention deficit hyperactivity disorder, post-traumatic stress disorder, affective disorders, mild cognitive impairment, and chronic pain.

Author Contributions

SV is responsible for writing and editing the manuscript.

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