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Enhancing the neuroplasticity of statistical learning through brain stimulation and behavioral interventions

PhD Thesis

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List of publications related to this thesis

I. Szücs-Bencze, L., Vékony, T., Pesthy, O., Kocsis, K., Kincses, T. Zs., Szabó, N., & Nemeth, D., (2025). Enhancing retrieval capacity of the predictive brain through dorsolateral prefrontal cortex intervention. *Cerebral Cortex, 35*(2).
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II. Szücs-Bencze, L., Fanuel, L., Szabó, N., Quentin, R., Nemeth, D., & Vékony, T. (2023). Manipulating the rapid consolidation periods in a learning task affects general skills more than statistical learning and changes the dynamics of learning. *eNeuro, 10*(2).
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Other publications

I. Szücs-Bencze, L., Vékony, T., Pesthy, O., Szabó, N., Kincses, Zs. T., Turi, Zs., Nemeth, D. (2023). Modulating visuomotor sequence learning by repetitive transcranial magnetic stimulation: What do we know so far? *Journal of Intelligence, 11*(10), 201.
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II. Veréb, D., Szabó, N., Kincses, B., **Szücs-Bencze, L.,** Faragó, P., Csomós, M., Antal, Sz., Kocsis, K., Tuka, B., Kincses, Zs. T. (2024). Imbalanced temporal states of cortical blood-oxygen-level-dependent signal variability during rest in episodic migraine. *The Journal of Headache and Pain, 25*(1), 114.
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Introduction

Statistical learning (SL) refers to the brain's ability to detect and extract patterns from sensory input, shaping perception, cognition, and behavior. At its core, SL involves tracking the frequency and co-occurrence of elements over time to predict future events. SL operates implicitly—without conscious awareness—and occurs incidentally in everyday life. SL plays a vital role across different domains, including language, motor skills, and social interactions. Neurological conditions such as Parkinson's disease and stroke can severely affect these various cognitive and motor skills. Developing interventions to enhance SL could improve rehabilitation outcomes. This thesis summarizes two studies investigating how different phases of SL—consolidation (storing learned patterns) and retrieval (accessing stored knowledge)—can be modulated using brain stimulation and behavioral interventions. The findings of these studies aim to inform future strategies for enhancing SL in both healthy and clinical populations.

SL involves a dynamic and distributed neural network that integrates cortical and subcortical regions. Regarding cortical areas, both sensory-specific and domain-general cortical areas are engaged in SL. Subcortical structures, including the basal ganglia and hippocampus, play key roles in encoding and consolidation. SL relies on the interactions between multiple cognitive systems supported by these cortical and subcortical areas. The prefrontal cortex (PFC) regulates subcortical structures through the frontostriatal network, which balances habitual and goal-directed learning mechanisms. The hippocampus also interacts with the PFC and striatum, facilitating encoding and consolidation processes. Diffusion tensor imaging studies further support these connections, showing that SL is linked to the integrity of tracts connecting the caudate nucleus and hippocampus to the dorsolateral prefrontal cortex (DLPC).

SL is the process by which individuals acquire knowledge of patterns through repeated exposure. This learning is not limited to active engagement but can continue during offline periods. SL can be measured behaviorally through reaction times (RTs) and accuracy, providing insights into how learning unfolds over time. Regarding acquisition, research indicates that SL occurs rapidly, with participants showing sensitivity to statistical regularities within the first block of trials. This rapid acquisition suggests that SL is an automatic and fundamental process for adapting to environmental regularities. Consolidation stabilizes and strengthens statistical knowledge, allowing for its retention over time. While sleep facilitates consolidation for some forms of learning, evidence suggests that probabilistic sequence learning in the visuomotor domain does not benefit from post-learning sleep. A new era of consolidation research is rapid consolidation, which can occur even within seconds, during short breaks inserted in the learning process. Studies are contradictory about the role of such rapid consolidation in SL. However, studies consistently suggest that once SL is consolidated, it remains stable and can be accessed even after extended delays, ranging from several hours to a year.

Overall, SL involves three key phases: rapid acquisition, stable consolidation, and robust retrieval. Understanding these phases raises important questions about how SL can be modulated through brain stimulation and behavioral interventions. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that influences neural activity by repeatedly delivering magnetic pulses to specific brain regions. It allows researchers to manipulate neural activity with high temporal precision, providing insights into learning and memory. Studies have explored rTMS during the learning and consolidation phase, showing varied effects. For instance, inhibitory rTMS over the dorsolateral prefrontal cortex (DLPFC) applies between learning blocks improved performance, while facilitatory rTMS over the same area led to declines in performance. However, no studies have focused on the retrieval phase of SL, which is one of the primary goals of the current thesis.

Behavioral interventions can also provide insights into the different phases of SL. For example, prioritizing speed over accuracy during learning enhances probability-based learning, while stress can improve acquisition in the early phase. Attention appears to have minimal impact on SL, with studies suggesting that minimal attentional resources are sufficient for learning. Stress and divided attention may even enhance learning in some contexts. The retrieval phase remains less studied. Research has shown that dual-task conditions can slow RTs but do not hinder the retrieval of learned knowledge. Consolidation is influenced by factors such as awareness and sequence complexity. Recent studies suggest a rapid form of consolidation that occurs within seconds. The current thesis aims to investigate the role of this rapid form of consolidation in visuomotor SL.

Aims

This thesis presents two studies addressing gaps in the literature on SL consolidation and retrieval (Table 1). While research shows that inhibitory rTMS over the DLPFC facilitates SL and its consolidation, no study has examined its effects on the retrieval of well-established statistical knowledge. To fill this gap, **Study I** examined the impact of inhibitory TMS on the retrieval of implicit probabilistic sequences. After learning the ASRT sequence and undergoing a 24-hour consolidation period, participants performed the sequence again. Before retesting, they received inhibitory rTMS for 10 minutes over the left, right, or bilateral DLPFC. Their performance was compared to a sham group to assess the effects of rTMS on retrieval.

Study II focused on whether different rest period durations affect SL, as previous studies have shown conflicting results regarding the role of rapid consolidation during short rest periods in SL. Participants completed the ASRT task with the rest durations of 15 seconds, 30 seconds, or self-paced breaks in a between-subjects condition. The study examined how rest period duration influenced implicit learning of probabilistic sequences and general skill learning. Moreover, the effect of rest period duration on the offline and online learning phases was also tested in these two learning processes.

Table 1. The literature gaps and main research questions to fill them

	Literature gap to be filled		Research questions
Study I	The role of the DLPFC in the retrieval of statistical knowledge	a.	Does inhibitory TMS over the DLPFC modulate the retrieval phase of SL?
		b.	Does the effect of DLPFC inhibition on retrieval differ based on hemispheric lateralization (left, right, or bilateral stimulation)?
Study II	The role of rapid consolidation in SL	a.	How does short rest periods of different length affect SL performance?
		b.	Does rest period length influences SL differently in online (within-block) and offline (between-block) phases?

Materials and methods

Study I – Brain stimulation intervention to SL retrieval

A total of 104 healthy adults participated, with 101 completing the study. Participants were randomly assigned to one of four groups: Left DLPFC, Right DLPFC, Bilateral DLPFC, or Sham. All had normal or corrected-to-normal vision and no contraindications for TMS. Written informed consent was obtained, and the study was approved by the Regional Scientific and Research Ethics Committee of the University of Szeged.

Implicit visuomotor SL was assessed using the ASRT task in the E-Prime 3.0 software environment. Participants responded to a visual stimulus appearing at one of four locations on the screen. Unbeknownst to the participants, the sequence of stimuli followed an eight-element probabilistic sequence, with pattern and random elements alternating. High-probability triplets (62.5%) and low-probability triplets (37.5%) were used to assess SL via RT differences between the two types of triplets. A control task, the Paired-Associate Learning Task (PALT) assessed declarative learning.

rTMS was applied using a Magstim Rapid^2 Stimulator. Stimulation (1 Hz, 600 pulses) was delivered for 10 minutes to the DLPFC (left, right, or bilateral in separate groups), with 55% of the maximum stimulator output intensity. Sham stimulation involved tilting the coil 90° away from the skull. Coil positioning followed the 10-20 EEG system for accurate targeting.

The experiment was conducted on two consecutive days. In the Learning Session, participants completed the ASRT task (25 blocks) and PALT learning phase. In the Retrieval Session, after a 24-hour offline period, rTMS was administered, followed by the ASRT retrieval phase (5 blocks) or PALT recall phase. The order of tasks was counterbalanced across participants and sessions.

For the ASRT task, trials with trills, repetitions, RTs below 100 ms, or outliers were excluded. Invalid responses were also removed. For PALT, three learning indices were calculated: item memory, association learning, and recollection. Liner mixed models (LMMs) were used for the ASRT data analysis, with factors including Trial Type, Group, and Block. ANOVAs were conducted for PALT learning indices. Statistical significance was set at 0.05, with Bonferroni correction for post hoc comparisons.

Study II – Behavioral intervention to SL consolidation

A total of 361 university students participated, with 268 included in the final sample. Participants were randomly assigned to one of three groups: 15-second, 30-second, or self-paced breaks. All had normal or corrected-to-normal vision, no neurological or psychiatric conditions, and provided informed consent. The study was approved by Eötvös Loránd University's Research Ethics Committee.

The ASRT task assessed implicit SL and general skill learning. The differences compared to the version described below were as follows: (1) the task was programmed in JavaScript using the jsPsych framework and run online, (2) participants used their own computer keyboard for responses, (3) the length of between-block breaks was manipulated, and (4) practice blocks preceded the learning phase.

The online experiment used the Gorilla Experiment Builder. Participants were randomly assigned to one of three versions of the ASRT task: 15-second, 30-second, or self-paced breaks between the learning blocks. The task included two practice blocks followed by 25 learning blocks of 80 trials each. After the task, participants' awareness of the sequence structure was tested. Additionally, working memory was tested using 0-back and 2-back tasks.

To ensure data quality, participants were excluded based on predefined criteria (e.g., accuracy below 80%, response delays). Inaccurate responses (misses, trills, repetitions) and long RTs were removed. SL scores were calculated by subtracting the median RT of high-probability trials from low-probability trials. General skill learning was assessed based on median RTs. Offline and online changes in learning were calculated by comparing RT differences between high- and low-probability trials across and within blocks, respectively.

Statistical analyses were performed using JASP. Mixed-design ANOVA on SL scores were used to analyze SL across blocks, with Group (self-paced, 15-second, 30-second) as a between-subjects factor. Separate analyses were performed for online and offline SL changes with a within-subjects factor of Learning Phase (offline vs. online). General skill learning was also assessed with ANOVAs. Significance was set at $p < 0.05$, with Bonferroni correction applied to post hoc comparisons.

Results

Study I – Brain stimulation intervention to SL retrieval

In the Learning Session, all groups demonstrated SL, with faster responses to high-probability trials ($F(1,4840) = 278.76$, $p < .001$), and SL increased over time ($F(1,4840) = 33.62$, $p < .001$). However, there were no significant differences between groups in SL ($F(3,4840) = 0.45$, $p = .714$) or general skill learning ($F(3,97) = 0.05$, $p = 0.987$) before DLPFC stimulation.

In the Retrieval Session, SL remained intact after stimulation ($F(1,804) = 199.10$, $p < .001$). The Group × Trial Type interaction was significant ($F(3,804) = 3.62$, $p = .013$), indicating group differences in SL performance. Post hoc tests showed that the Bilateral DLPFC ($p < .01$) and the Left DLPFC ($p < .05$) groups outperformed the Sham group, though only the Bilateral DLPFC group remained significant after correction for multiple comparisons.

In the Retrieval Session, no significant group differences were found in declarative memory performance after stimulation, including item memory ($F(3, 97) = 0.85$, $p = .46$, $\eta^2p = 0.02$), association learning ($F(3, 97) = 0.50$, $p = .67$, $\eta^2p = 0.01$), or recollection ($F(3, 97) = 0.34$, $p = .79$, $\eta^2p = 0.01$).

Study II – Behavioral intervention to SL consolidation

Regarding overall SL, it progressively increased across all participants ($F(4,1060) = 25.68$, $p < .001$, $\eta p^2 = 0.09$), with significant learning between distant task sections but not consecutive blocks. Rest period duration did not affect SL, as no differences were found between the three groups ($F(2,265) = 0.65$, $p = .53$, $\eta p^2 < 0.01$), nor did the time course of learning differ across groups ($F(8,1060) = 0.28$, $p = .97$, $\eta p^2 < 0.01$).

Overall general skill learning was observed ($F(2.73,723.72) = 275.21$, $p < .001$, $\eta p^2 = 0.51$), with continuous RT reductions across the task. The self-paced group had slower RTs compared to the 15-second and 30-second groups ($F(2,265) = 8.69$, $p < .001$, $\eta p^2 = 0.06$), with the difference emerging after the first learning unit ($p < .01$).

Regarding the dynamics of SL, a significant Learning Phase × Group interaction ($F(2,265) = 3.51$, $p = .03$, $\eta p^2 = 0.03$) indicated differences in online and offline changes between the groups. Only the 15-second group showed positive online learning ($t(89) = 3.50$, $p < .001$) and significant offline forgetting ($t(89) = -3.39$, $p < .01$), while no significant online or offline effects were found in the other groups.

In general skill learning, participants showed online learning ($t(267) = 29.14$, $p < .001$) but experienced performance declines during offline periods ($t(267) = -30.60$, $p < .001$) across all groups ($F(2,265) = 920.49$, $p < .001$, $\eta p^2 = 0.77$). Although the Learning Phase × Group interaction was significant ($F(2,265) = 4.38$, $p = .01$, $\eta p^2 = 0.03$), no between-group differences in online and offline changes remained after correction (all $p > .17$).

Discussion

This thesis summarizes the findings of two studies that aimed to modulate SL through brain stimulation and behavioral interventions (Table 2). Both studies focused on manipulating different phases of SL to better understand underlying cognitive and neural mechanisms.

Study I investigated the impact of rTMS in the retrieval of SL. This study addressed a gap in the literature, as no prior research had examined how rTMS affects access to previously acquired statistical knowledge. Participants underwent inhibitory rTMS over the left, right, or bilateral DLPFC (Brodmann 9) immediately before being retested on statistical knowledge learned the previous day. Their performance was compared to a Sham stimulation group. The results revealed that bilateral DLPFC inhibition significantly enhanced SL retrieval. This effect was specific to SL, as performance on a declarative memory task remained unaffected. The study suggests that the DLPFC plays a critical role in regulating SL retrieval, with bilateral inhibition overcoming potential compensatory mechanisms between hemispheres.

Study II explored how the length of rest periods between learning blocks influences the dynamics of SL and general skill learning. Using a between-subjects design, three groups of participants completed the ASRT task with different between-block intervals: 15 seconds, 30 seconds, or self-paced. The study aimed to determine whether rapid consolidation during short breaks affects SL and general skill learning. The length of rest periods did not significantly impact overall SL performance, but it influenced general skill learning. Participants in the self-paced group exhibited slower performance compared to the fixed-duration groups. Furthermore, shorter rest periods (15 seconds) led to SL occurring exclusively online, reducing offline learning gains. In contrast, longer rest periods (30 seconds) maintained balanced learning across both online and offline phases.

The studies summarized here hold theoretical, methodological, and applied significance**. Study I** demonstrated that inhibitory stimulation of the DLPFC reliably modulates SL, confirming the DLPFC's role in SL regulation. Crucially, it extends previous findings by showing this modulation applies not only to acquisition and consolidation but also to the retrieval phase. These findings align with predictive coding frameworks, suggesting that DLPFC inhibition reduces top-down interference, facilitating SL retrieval. They also challenge dual-process theories by revealing more complex interactions between implicit and explicit learning systems.

Study II contributes new evidence on rapid consolidation, revealing that the length of rest periods determines whether this process occurs both online and offline in SL. Moreover, both studies establish causal links through experimental manipulation. **Study I** provides direct evidence of DLPFC involvement in SL retrieval and its antagonistic relationship with executive functions. **Study II** shows that altering rest periods causally affects the dynamics of SL, offering insights into how temporal factors shape learning processes.

Regarding methodological innovations, **Study I** uniquely employs bilateral DLPFC stimulation alongside unilateral conditions, offering nuanced insights into hemispheric contributions**. Study II** refines SL analysis by distinguishing offline and online learning phases and systematically comparing fixed and self-paced conditions.

The findings have potential applications in clinical, educational, and cognitive enhancement contexts. In clinical settings, bilateral TMS protocols may optimize treatments for cognitive impairments, such as post-stroke rehabilitation. Educationally, optimizing rest periods can enhance learning outcomes, especially in procedural learning contexts like language acquisition. More broadly, these insights may inform strategies to maintain cognitive health in aging populations, supporting independent living and delaying institutional care.

Table 2. The main research questions and summary of findings

		Research question	**Results**
Study I	a.	Does inhibitory TMS over the DLPFC modulate the retrieval phase of SL?	DLPFC inhibition leads to enhanced retrieval of statistical knowledge
	b.	Does the effect of DLPFC inhibition on retrieval differ based on hemispheric lateralization (left, right, or bilateral stimulation)?	Bilateral stimulation reaches the most pronounced effect on SL retrieval
Study II	a.	How does short rest periods of different length affect SL performance?	The length of short rest periods does not impact overall SL performance
	b.	Does rest period length influence SL differently in online (within-block) and offline (between-block) phases?	Shorter rest periods shift SL to the online phase

Conclusion

The studies presented in this thesis have theoretical, methodological, and applied significance. Theoretically, they deepen our understanding of the less-explored phases of SL—consolidation and retrieval. Methodologically, they introduce new approaches to capture these processes more comprehensively. Practically, they outline strategies to optimize SL in both healthy and clinical populations.

Study I confirms the DLPFC’s role in SL retrieval. It shows that bilateral stimulation yields stronger effects than unilateral stimulation and suggests neuromodulation as a potential intervention for improving SL in clinical populations.

Study II reveals that rest interval length differentially affects SL and general skill learning, particularly during online and offline phases. This underscores the importance of analyzing learning dynamics rather than relying on overall learning outcomes. Applied insights from his study can guide the design of learning tasks to support both learning phases.

Together, these studies advance our understanding of SL’s neurocognitive mechanisms and suggest neuromodulation and task design as effective strategies for enhancing SL.