# Modulating learning and memory processes by transcranial magnetic stimulation over the dorsolateral prefrontal cortex

Ph.D. Thesis Summary

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2020

**Original publications directly related to this thesis:**

**I. Vékony, T.**, Németh, V. L., Holczer, A., Kocsis, K., Kincses, Z. T., Vécsei, L., & Must, A. (2018). Continuous theta-burst stimulation over the dorsolateral prefrontal cortex inhibits improvement on a working memory task. *Scientific Reports*, *8*(1), 1-9. **IF = 4.011**

**II.** Ambrus, G. G., **Vékony, T.***, Janacsek, K., Trimborn, A. B., Kovács, G., & Nemeth, D. (2020). When less is more: enhanced statistical learning of non-adjacent dependencies after disruption of bilateral DLPFC. *Journal of Memory and Language*, 114, 104144. **IF = 3.893**

* = shared first authorship

**III. Vékony, T.**, Marossy, H., Must, A., Vécsei, L., Janacsek, K., & Nemeth, D. (2020). Speed or accuracy instructions during skill learning do not affect the acquired knowledge. *Cerebral Cortex Communications*, tgaa041. **IF = expected in 2022**

**Cumulative impact factor of publications related to this thesis: 7.904**

# Introduction

The dorsolateral prefrontal cortex (DLPFC, Brodmann 9/46 regions) has been connected to a wide range of cognitive functions (e.g., Barbey, Colom, & Grafman, 2013; Heekeren, Marrett, Ruff, Bandettini, & Ungerleider, 2006; Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2011; MacDonald, Cohen, Stenger, & Carter, 2000), including different learning and memory processes, such as working memory (WM) (e.g., Owen, McMillan, Laird, & Bullmore, 2005) and implicit probabilistic learning (e.g., Bennett, Madden, Vaidya, Howard, & Howard, 2011; Simon, Vaidya, Howard, & Howard, 2012; Stillman et al., 2013). WM is typically associated with the activation of frontal and parietal regions (e.g., Owen et al., 2005). Nevertheless, the role of connections between the striatal regions and the dorsal prefrontal cortex is also emphasized in WM processes (Riley, Moore, Cramer, & Lin, 2011). Procedural learning processes (e.g., implicit probabilistic learning) is also associated with the activity of the fronto-striatal networks; the role of the basal ganglia and medial temporal structures such as the hippocampus are particularly emphasized (e.g., Bennett et al., 2011; Gheysen, Van Opstal, Roggeman, Van Waelvelde, & Fias, 2011; Janacsek et al., 2020; Rieckmann, Fischer, & Bäckman, 2010; Simon et al., 2012). Connections between the DLPFC, the basal ganglia, and the medial temporal lobe were found to be related to implicit probabilistic learning performance (e.g., Bennett et al., 2011; Stillman et al., 2013), suggesting a potential mediating role of the DLPFC between the areas involved in procedural learning. The present thesis aims to investigate the causal role of DLPFC in these memory processes.

Neuroimaging and electrophysiological techniques could provide correlational but not causal evidence to support the roles of distinct brain areas/networks in memory processes. The use of non-invasive brain stimulation methods may overcome this limitation. One of such methods, *transcranial magnetic stimulation* (TMS) works by creating an intense magnetic field via a wire coil that induces a current flow in the targeted cortical tissue leading to neural firing and changes in cortical excitability (Deng, Lisanby, & Peterchev, 2013; Hallett, 2000). *Repetitive transcranial magnetic stimulation* (rTMS) has been found to modulate cortical activity beyond the stimulation duration (Klomjai, Katz, & Lackmy-Vallée, 2015), making it an ideal tool to study learning and memory processes. A more recently developed alternative to rTMS is *theta-burst stimulation* (TBS) with two widely-used forms: continuous (cTBS) and intermittent TBS (iTBS) exert inhibitory and excitatory effects, respectively (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Although TBS operates with theta-gamma coupling, which is associated with WM-related processes (Lisman, 2010), a direct comparison of the effects of iTBS and cTBS on WM, as well as the comparison of effects over the left and right DLPFC is still missing in the literature.

Only a few TMS studies aimed at revealing the role of DLPFC in procedural learning mechanisms, and they typically found enhanced performance following the inhibition of DLPFC, and decreased performance after facilitation (Galea, Albert, Ditye, & Miall, 2010; Pascual-Leone, Wassermann, Grafman, & Hallett, 1996; Smalle, Panouilleres, Szmalec, & Möttönen, 2017). These results are in line with the competition theory that memory processes can compete with each other (Daw, Niv, & Dayan, 2005; Hardwick, Forrence, Krakauer, & Haith, 2019; Poldrack & Packard, 2003). So far, studies investigated deterministic rather than ecologically more valid, probabilistic learning (Remillard, 2008), and assessed the learning performance at a single time point, not the whole learning process over multiple time points.

The idea of testing at multiple time points can easily lead us to a methodological issue. In cognitive neuroscience, learning and memory functions are typically measured within a single context of learning. That is, we often draw conclusions about the relationship between the brain and human behavior based on either the long-term learning (competence) or the temporary fluctuation in behavior (performance) (Heideman, van Ede, & Nobre, 2018; Rose, Haider, Salari, & Buchel, 2011; Thomas et al., 2004; Turk-Browne, Scholl, Johnson, & Chun, 2010). Many examples show that performance and competence can be separated from each other (Soderstrom & Bjork, 2015). If we only measure performance, it could easily lead to wrong conclusions on brain-behavior relationships; therefore, we should test how fragile the memory representations are that we are measuring.

## AIMS AND OBJECTIVES

The current thesis presents three studies to address some of the issues mentioned above concerning WM and implicit probabilistic learning:

- **I.** **Study I** aimed to compare the effects of TBS on WM-related processes after stimulation over the left and right DLPFC.
- **II.** **Study II** aimed to investigate the involvement of the DLPFC in the acquisition and retrieval of implicit probabilistic knowledge.
- **III.** **Study III** aimed to test the effect of instruction on implicit probabilistic learning to test a potential methodological problem and the robustness of this type of learning.

## Study I – The effect of TBS on working memory

### *How do cTBS and iTBS over the left and right DLPFC affect WM performance?*

Fifty-two healthy participants took part in the study, but the final analyses were carried out on 51 participants due to technical failure in one case (25 males, $M_{age} = 23.68 \pm 3.06$ SD years). The experiment consisted of two separate sessions (Fig. 1). Participants received neuronavigated cTBS ($n = 17$), iTBS ($n = 18$), or sham stimulation ($n = 16$) over the left or right DLPFC. Before and after the stimulation, they completed three levels of a verbal n-back WM task (Fig. 2). Participants were presented with capital letter stimuli continuously and instructed to press the space bar if the letter on the screen was identical to the letter presented one (1-back task), two (2-back task), or three (3-back task) trials earlier.

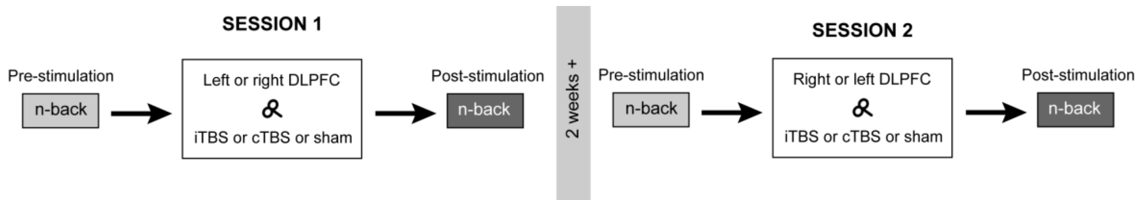


***Fig. 1. Experimental design of Study I.*** The study consisted of two sessions. In the first session, participants practiced three levels of the n-back WM task. After that, we administered iTBS, cTBS, or sham stimulation over the left or right DLPFC. After the stimulation, they completed the n-back task again. The second session occurred at least two weeks later; here, the experimental design was the same, except that we stimulated the other hemisphere (the type of stimulation remained the same for the given participant).

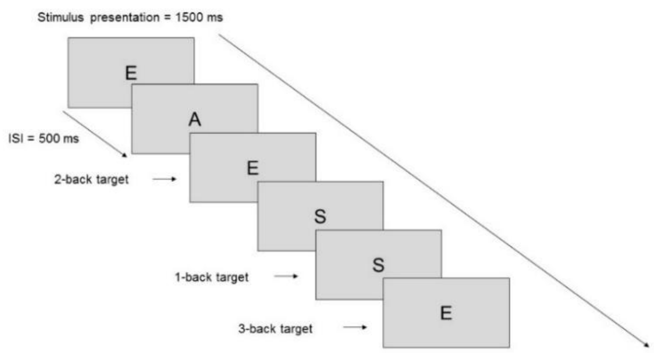


***Fig. 2. The structure of the n-back WM task.*** The participants' task was to press a button if they perceived the same letter as presented one (1-back), two (2-back), or three (3-back) trials earlier. The three levels were completed consecutively. Each stimulus was presented on the screen for 1500 ms, with an interstimulus interval of 500 ms. *Figure 2 of Vékony et al. (2018) see Appendix I of the Ph.D. thesis.*

WM performance was primarily evaluated by the discriminability index (*d'*). We detected increased *d'* scores following the stimulation, as participants performed better at the second administration, possibly due to practice effects. However, this increase in performance was only detected in the iTBS and the sham group, but not in the cTBS group. Equal results were found after stimulating both hemispheres (Fig. 3).

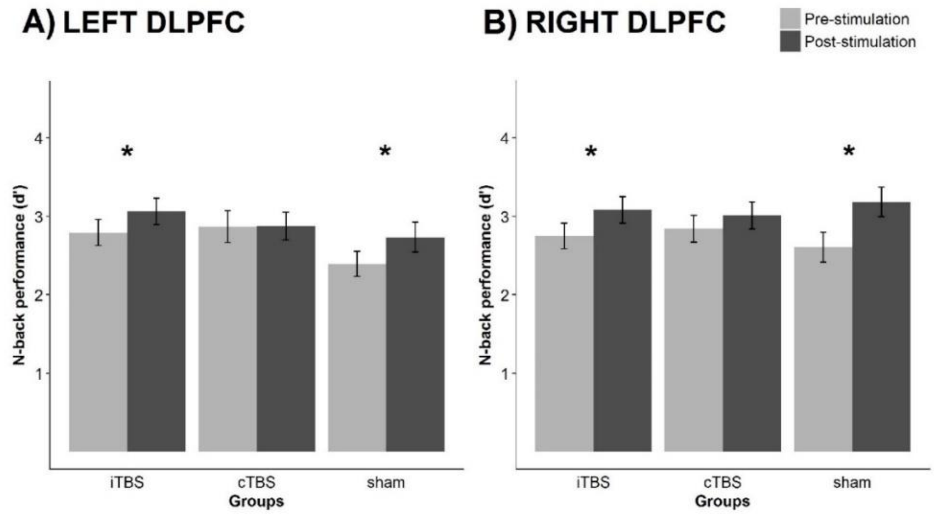


***Fig. 3. N-back performance of the three groups before and after the stimulation of (A) the left and (B) right DLPFC.*** The horizontal axes denote the three groups, and the vertical axis the discriminability index (*d' = Z(hit rate)* – Z*(false alarm rate))*. The error bars indicate SEM. The results were the same after the stimulation of both hemispheres: after iTBS and sham stimulation, practice effect occurred, i.e., the performance enhanced compared to the pre-stimulation measurement. However, after the cTBS, a lack of change was observed. * $p < .05$ *Figure 1 of Vékony et al. (2018), see Appendix I of the Ph.D. thesis.*

**Study II – The effect of rTMS on probabilistic learning**

***How does inhibitory rTMS over bilateral DLPFC affect implicit probabilistic sequence learning performance?***

Thirty-two right-handed participants took part in the study. The final analyses were carried out on 31 participants due to exclusion based on executive function performance (four males, $M_{age} = 22.16 \pm 3.01$ SD years). The experiment consisted of four sessions (Fig. 4). In the first session, participants practiced the Alternating Serial Reaction Time Task (ASRT) (Training/rTMS phase) (Howard et al., 2004; Song, Howard, & Howard, 2007). Before starting the task, participants received 1 Hz neuronavigated rTMS ($n = 16$) or sham stimulation ($n = 15$) bilaterally over the DLPFC (5 minutes over the left and 5 minutes over the right hemisphere, 300 pulses/run). This procedure was repeated after every approximately five minutes of learning. The second, third, and fourth session took place 10 min, 2 h, and 24 h after the end of the Training/rTMS Phase, respectively. Participants completed ca. 5 more minutes of practice on the ASRT task in every session.

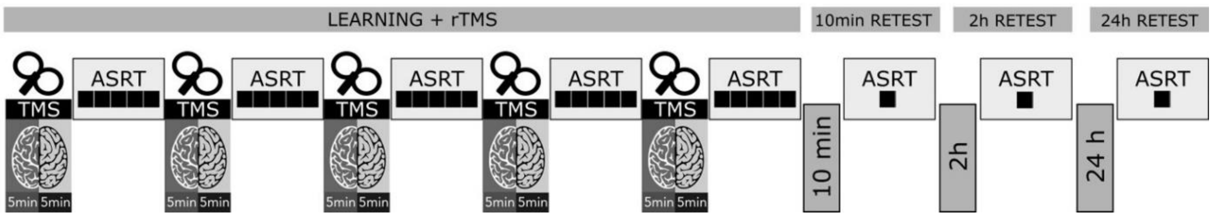


*Fig. 4.* ***Experimental design of Study II.*** The experiment consisted of four sessions. In the first session, participants received 1 Hz rTMS or sham stimulation bilaterally over the DLPFC for 5-5 minutes. After that, they practiced on the ASRT task and received 5-5 minutes of rTMS between each unit of five blocks (25 blocks, i.e., 5 runs of stimulations were completed). After the last stimulation, a 10 min break followed, and then five more blocks of ASRT were administered. We also measured the performance on the ASRT task 2 hours and 24 hours after the end of the rTMS. *Modified version of Figure 1 of Ambrus et al. (2020), see Appendix II of the Ph.D. thesis.*

In the ASRT task, four circles were presented on a computer screen in a horizontal arrangement. A target stimulus appeared in one of the four possible locations (Fig. 5A). The participants were instructed to press the response key corresponding to the position of the target stimulus as fast and as accurately as possible. Eighty-five stimuli were presented in a block. In the first session (Training/rTMS phase), 25 blocks were completed. Five blocks were completed in each of the 10 min, 2 h, and 24 h retest phases.

During the task, an eight-element alternating sequence of pattern and random elements was repeated ten times (e.g., 2r4r3r1r, where "r" indicates a random element). Due to this structure, some combinations of three consecutive elements (referred to as *triplets*) appeared with higher probability than others (Fig. 5B and 5C).

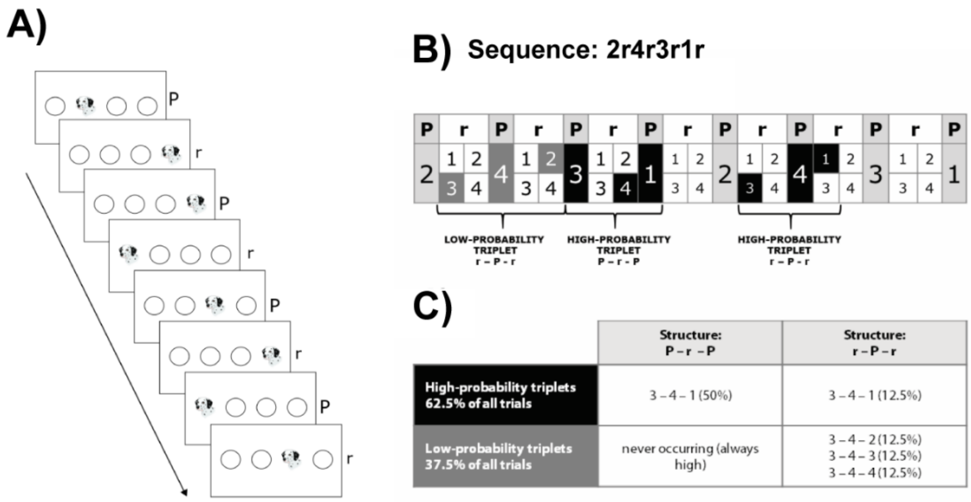


*Fig. 5.* ***Structure of the ASRT task.*** (A) In the ASRT task, a stimulus (a head of a dog) appears at one of four possible positions. The task of the participants was to press the corresponding button as quickly and as accurately as possible. The stimulus remained on the screen until the first correct response, and then, after a 120-ms long interstimulus interval, the next item appeared. (B) The order of appearance follows a predetermined, 8-element sequence: every first element of this sequence was part of the pattern (P), and every second element appeared at a

truly random position (r). Because of this hidden sequence, specific triplets (three consecutive elements) appear with higher probability than other triplets. For instance, if the sequence was 2r4r3r1r, the 2X4, 4X3, 3X1, and 1X2 triplets (where "X" indicates any middle element) occurred with higher probability because the third element of the triplet could be derived mostly from the pattern elements. The triplets of, for example, 2X1 or 3X2 could appear with less probability because the third element could only be random. (C) High-probability triplets can be formed by two pattern elements and one random element in the middle. Two random elements and a pattern element in the middle can form high-probability triplets; however, much less frequently. Low-probability triplets always consist of two random and one pattern element. *Modified version of Vékony et al. (2020), see Appendix III of the Ph.D. thesis.*

Probabilistic learning was evaluated by the difference in reaction times for high- and low-probability triplets. We found an overall increase in the 10 min retest session in the Sham Group compared to the Training/rTMS session, but the performance of the DLPFC Group was also enhanced in the 2 h and 24 h retest sessions. Most importantly, the learning indices between the two groups were similar at all measurements except for the 24 h retest session, where the DLPFC Group showed better probabilistic knowledge (Fig. 6).

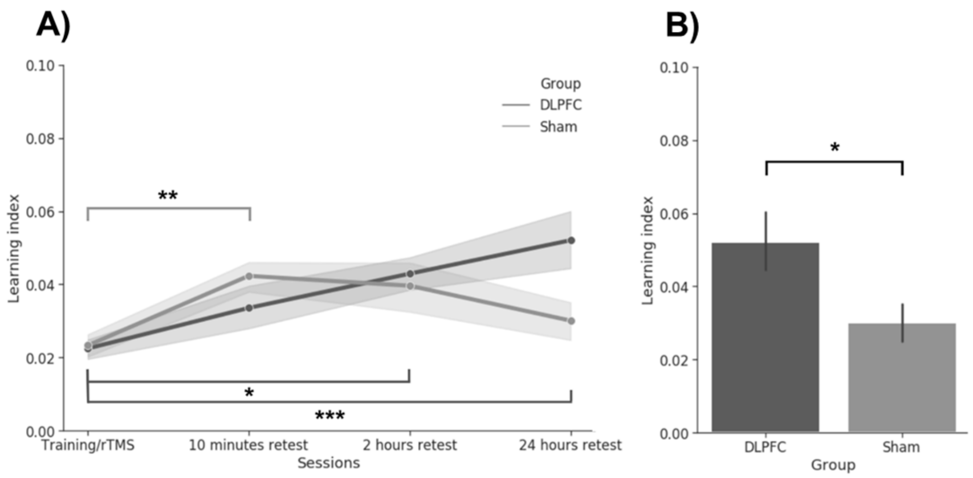


***Fig. 6. Learning performance of the two groups on the ASRT task.*** (A) Changes in performance over the four sessions. The horizontal axis shows the four measurement points. The vertical axes show the learning indices (calculated as [mean RTs for low-probability triplets – mean RTs for high-probability triplets]/mean RTs for low-probability triplets). Thus, higher scores indicate better learning of the sequence. In the Sham Group, performance improved from the Training/rTMS session to the 10 min retest session. In the DLPFC Group, on the other hand, performance enhanced between the Training/rTMS session and the 2 h retest session, and also between the Training/rTMS session and the 24 h retest session. (B) Performance of the two groups at the 24 h retest session. DLPFC Group showed significantly higher probabilistic knowledge than the Sham Group. * $p < .05$ *Modified version of Figure 2 of Ambrus et al. (2020), see Appendix II of the Ph.D. thesis.*

## Study III – The effect of instructions on probabilistic learning

### *How do instructions affect learning and retrieval of implicit probabilistic knowledge, i.e., how fragile are the statistical representations?*

Sixty-six healthy young adults were recruited for the study. The final analysis was carried out on 61 participants due to exclusion because of the misunderstanding of instructions

(40 females, $M_{age}$ = 21.18 ± 2.13 SD years). The experiment consisted of two major sessions: in the *Different Instruction Phase*, participants completed four epochs (20 blocks) of the ASRT task (the ASRT task was used with the same settings as in **Study II,** Fig. 5). The Accuracy Group ($n$ = 31) were instructed to be as accurate as possible during the task, and the Speed Group ($n$ = 30) to be as fast as possible. In the *Same Instruction Phase*, participants completed one more epoch of ASRT (five blocks). Here, both groups were instructed to complete the task quickly and accurately (Fig. 7).

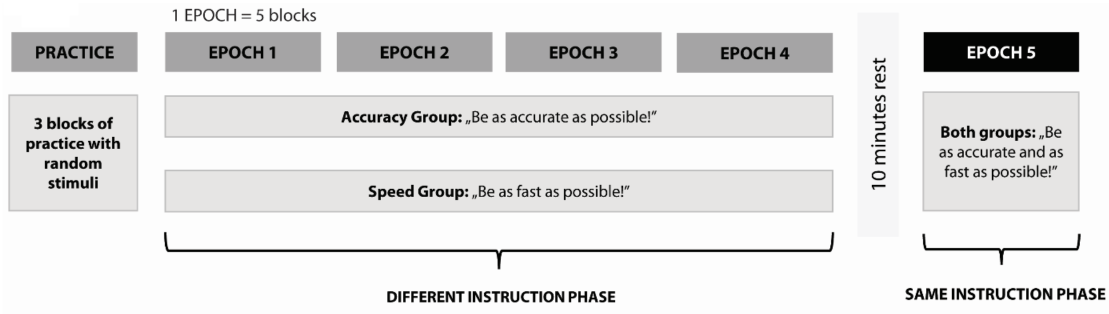


***Fig. 7. Experimental design of Study III.*** First, three blocks of practice with random stimuli were completed. After that, four epochs of the ASRT task were administered. The Accuracy Group received the instruction to be as accurate as possible, and the Speed Group to be as fast as possible (Different Instruction Phase). After that, 10 min rest period followed. After the rest period, participants completed another epoch of the ASRT task, but this time, both groups were instructed to be fast and accurate at the same time. *Modified version of Figure 1 of Vékony et al. (2020), see Appendix III of the Ph.D. thesis.*

In terms of RTs, we found similar probabilistic learning between the two groups in the Different Instruction Phase (Fig. 8). After the change of the instructions, we also found a similar level of probabilistic knowledge (Fig. 10).

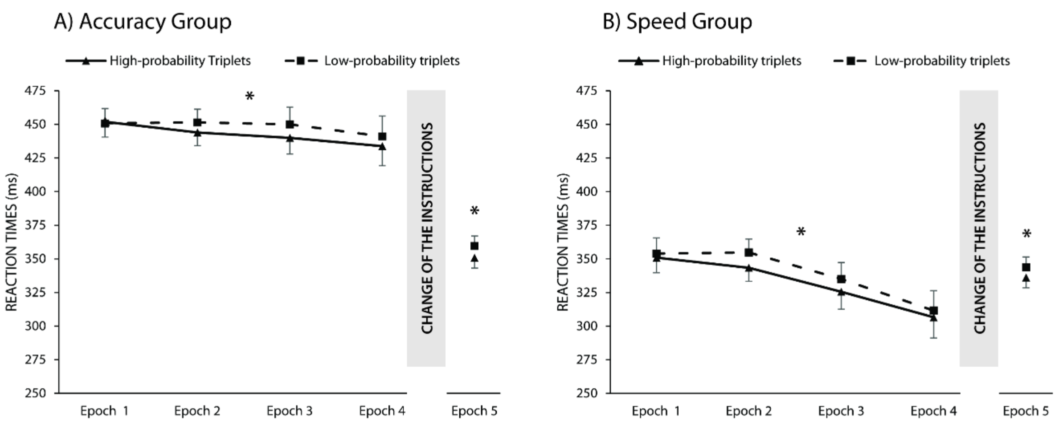


***Fig. 8. Performance of the (A) Accuracy Group and (B) Speed Group in RT measures.*** The horizontal axes indicate the five epochs of the task (Epoch 1 - 4 as part of the Different Instruction Phase, and Epoch 5 as part of the Same Instruction Phase). The vertical axes denote RTs. The solid lines represent RTs for high-probability triplets, and the dashed lines the same for low-probability triplets. Implicit probabilistic learning was detected in both groups, and it was similar in both groups, in both phases. * $p < .05$. *Figure 3 of Vékony et al. (2020), see Appendix III of the Ph.D. thesis.*

In terms of accuracy, no learning of probabilistic regularities was found in the Accuracy Group (Fig. 9). However, equal probabilistic knowledge was detected after the change of the instructions (Fig. 10).

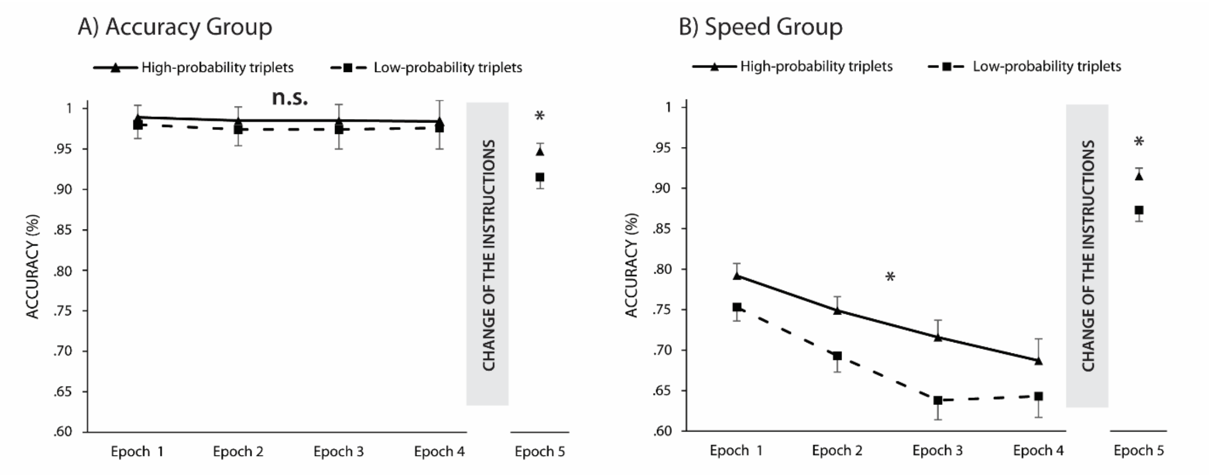


***Fig. 9. Performance of the (A) Accuracy Group and (B) Speed Group in accuracy measures.*** The horizontal axes indicate the five epochs of the task (Epoch 1 - 4 as part of the Different Instruction Phase, and Epoch 5 as part of the Same Instruction Phase). The vertical axes denote accuracies. The solid lines represent accuracies for high-probability triplets, and the dashed lines the same for low-probability triplets. Implicit probabilistic learning was detected only in the Speed Group during the Different Instruction Phase but in both groups in the Same Instruction Phase, and here, no difference was found between groups. *: $p < .05$, ns: $p > .05$. *Figure 4 of Vékony et al. (2020), see Appendix III of the Ph.D. thesis.*

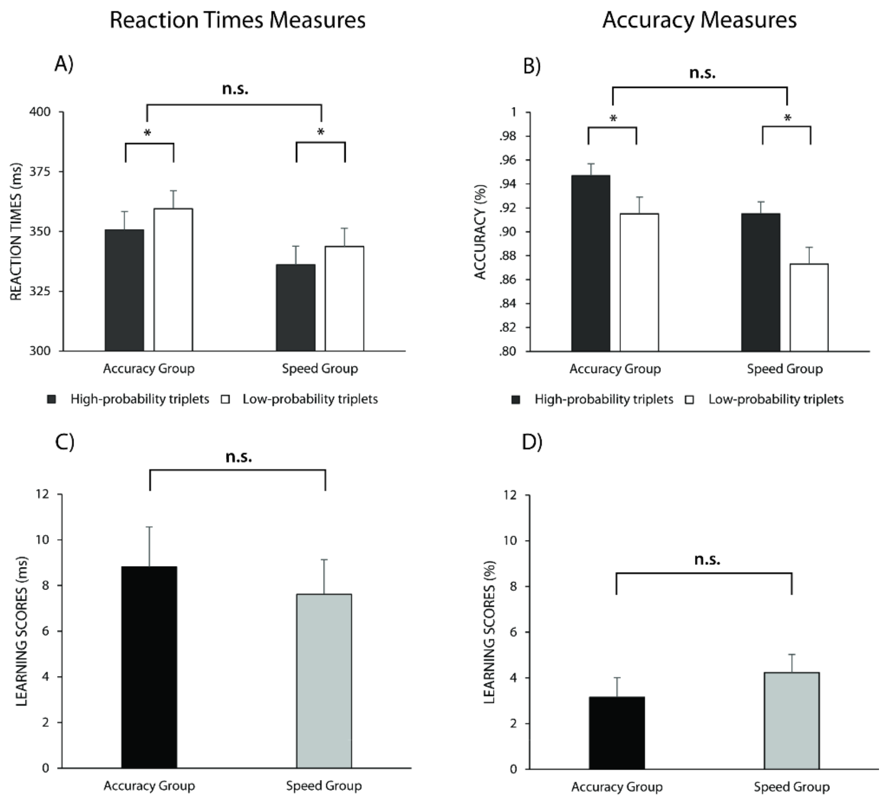


***Fig. 10. Comparison of the high- and low-probability triplets (A and B), and the learning scores in the Same Instruction Phase (C and D).*** The vertical axis denotes the RTs (A), accuracy (B), or the learning scores (C and

D). The horizontal axis indicates the two groups. The error bars denote the SEM. Although probabilistic knowledge was detected in both groups, a lack of significant difference was found in the learning scores. *: $p < .05$, ns: $p > .05$. *Figure 5 of Vékony et al. (2020), see Appendix III of the Ph.D. thesis.*

## DISCUSSION

We investigated the effect of TMS methods over the DLPFC (Brodmann 9/46) on WM and implicit probabilistic (statistical) learning, and also a potential methodological problem in learning and memory studies in clinical and cognitive neuroscience. In **Study I**, we showed that cTBS (both over the left and right DLPFC) hindered the practice effect and, by that, reduced WM performance (the difference was accompanied by a large effect size). This result is in line with previous studies (Lee & D'Esposito, 2012; Schicktanz et al., 2015); however, surprisingly, we did not find any effect of iTBS compared to sham stimulation. So far, iTBS over the DLPFC was found to lead to altered WM-related oscillatory activity or event-related potentials rather than strong behavioral aftereffects (Chung, Rogasch, Hoy, & Fitzgerald, 2018; Chung et al., 2017; Hoy et al., 2016). Another explanation for the lack of iTBS-related effects might be that cTBS methods were shown to lead to more stable cognitive aftereffects than iTBS (Lowe, Manocchio, Safati, & Hall, 2018). We found similar results when stimulating over the left and right DLPFC, supporting that TBS can equally modulate WM-related processes over both hemispheres.

**Study II** showed that probabilistic knowledge became better 24-hour after the disruptive stimulation of bilateral DLPFC. The difference was obtained with a medium effect size. This result is in line with previous studies finding facilitating stimulation to hinder, whereas inhibitory stimulation to improve deterministic sequence learning (Galea et al., 2010; Pascual-Leone et al., 1996; Smalle et al., 2017). We went beyond previous results by verifying the disruptive effect of DLPFC also on probabilistic non-adjacent dependencies, and by comparing the effect of rTMS over a longer period. Another novelty in our study is that we used bilateral stimulation of the DLPFC, and proved its efficacy in modulating learning processes. We hope that future studies will benefit from using both unilateral and bilateral stimulation to get a holistic picture of the role of different brain areas and networks in cognitive functions.

Summarizing the results of **Study I** and **Study II**, we can claim that the disruptive stimulation of DLPFC could lead to worse WM performance but improved implicit probabilistic learning. These results support further the existence of competitive neurocognitive networks underlying learning and memory between habit-like, incidental vs. more controlled forms of learning (e.g., Daw et al., 2005; Hardwick, Forrence, Krakauer, & Haith, 2019; Smittenaar, FitzGerald, Romei, Wright, & Dolan, 2013; Yin & Knowlton, 2006). Prefrontal cortical areas, more specifically, the DLPFC was suggested to play a mediating role between these competitive learning processes (e.g., Smittenaar et al., 2013). The DLPFC might have a pivoting role in more controlled forms of learning, such as accessing long-term memory representations and in higher-level functions supporting such processes, e.g., WM. These processes might be disadvantageous during the incidental learning of new patterns or statistics. If there is only limited access to these controlled forms of learning, then the balance will change in favor of the more incidental forms of learning; thus, the learning of probabilistic regularities will be enhanced. We propose that the DLPFC might have realized these processes by modulating the activity of the prefrontal-hippocampal circuitry, shifting the advantage in this competition in favor of the incidental learning processes.

The findings of study **Study I** can be interpreted similarly: although the results can be viewed as a change in WM *itself*, we should notice that the change was not in *WM performance*, but in the *improvement on WM* due to practice. Thus, we can speculate that the disruptive effect of cTBS over the DLPFC might have affected the short-term consolidation of task-specific knowledge, i.e., the learned information about task completion. Following this reasoning, practice effects on cognitive tasks could be interpreted as task-related knowledge helping the individuals improve their performance over multiple testing. This interpretation is supported by the lack of practice effect in neurocognitive disorders characterized by deficits in memory consolidation and acquiring new information (Duff et al., 2007; Ivnik et al., 2000; Pace-Schott & Spencer, 2015; Weintraub, Wicklund, & Salmon, 2012). These consolidation processes might have been modified by the disruption of DLPFC, similarly to how it changed the consolidation of probabilistic sequential regularities in **Study II**.

Finally, **Study III** showed that although the instructions affected general speed and accuracy during learning with large effect sizes, the level of probabilistic knowledge was not affected by them when measured by RTs. The degree of the acquired knowledge was not affected by the instructions whenever we measured by RTs or accuracies. From a theoretical viewpoint, these results underlie that implicit probabilistic learning is a robust learning mechanism, and the acquired representations remain stable independently of the strategy used during learning (Kóbor et al., 2017; Vékony et al., 2019). From a methodological perspective, the difference between the two measures should be highlighted; it warns us that differences in the momentary (measured) performance and the actual competence can emerge. Future studies should explore how RTs and accuracy measures differ when using different learning strategies in other cognitive tasks, as general speed-up and changes in accuracy are typically detectable in various cognitive tasks requiring fast decision-making. Until that, although multiple testing seems essential to reveal all potential differences of the tested effects, we highly recommend taking into consideration the possible variances between the competence and the momentary performance when planning learning studies, especially if they involve the evaluation of accuracy measures.

## CONCLUSIONS

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**I.** Compared to sham stimulation, cTBS but not iTBS over the left and right DLPFC affects improvement on a WM task.

**II.** Bilateral inhibitory rTMS over the DLPFC enhance probabilistic learning performance after a 24-h offline period.

**III.** Speed and accuracy instructions during probabilistic sequence learning result in stable statistical representations.

## ACKNOWLEDGEMENT

First of all, I would like to thank Anita Must for her support during my Ph.D. studies. I am deeply grateful to Professor László Vécsei, previous Head of the Department of Neurology, for the opportunity to work at the department and for his continuous support of my research activities. I would like to thank Professor Péter Klivényi, Head of the Department of Neurology, for the opportunity to work at the department.

I am also grateful to Professor Zsigmond Tamás Kincses, and the members of the Neuroimaging Research Group for the opportunity to work at the Neurophysiological Lab and their help during my Ph.D. studies.

I wish to express my gratitude also to Professor Dezső Németh and the members of the Brain, Memory and Language Lab of the Eötvös Loránd University for the fruitful collaborations and their help during my research.

I would like to thank all of my co-authors for their work on our projects and all the valuable knowledge they shared with me.

I am also grateful to my undergraduate supervisors, Gábor Csifcsák and Emese Szegedi-Hallgató, for all the things they taught me about science and also for their encouragement to pursue a scientific career.

Last but not least, I would like to thank my family for their patience and support during this journey.

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