When Less is More: Enhanced Statistical Learning After Disruption of Bilateral DLPFC

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Abstract

Human learning depends on multiple cognitive systems related to dissociable brain structures. These systems interact not only in cooperative but also in competitive ways in optimizing performance. Previous studies have shown that manipulations reducing the engagement of frontal lobe-mediated control and attentional processes can lead to improved performance in striatum-related learning processes. These studies, however, used correlational methods only. The aim of the present study was to directly test the causal role of the prefrontal cortex (PFC) in striatum-mediated implicit statistical learning and its consolidation using brain stimulation. Healthy young adults were trained on a probabilistic sequence learning task. 1 Hz transcranial magnetic stimulation (TMS) or sham stimulation of both the left and right dorsolateral PFCs (DLPFC) was applied intermittently during the learning session to disrupt frontal lobe functions. To assess the lasting effects of TMS on learning and consolidation, statistical learning performance (i.e., increased reaction times for sequences with high as compared to low probabilities) was tested ten minutes, two hours, and 24 hours later. In line with the predictions of a competitive relationship between DLPFC functions and statistical learning, the DLPFC stimulation group showed better performance compared to the sham group after the 24-hour consolidation period. This finding suggests that the disruption of DLPFC induced qualitative changes in picking up statistical regularities during learning that became salient in behavior after a stabilization period. Our results support an antagonistic relationship between the brain networks of automatic and controlled processes.

Significance statement

Here we demonstrate the role of the dorsolateral prefrontal cortex (DLPFC) in statistical learning, which is a fundamental learning mechanism of the brain, using non-invasive brain stimulation. Participants were trained on a probabilistic sequence learning task while applying transcranial magnetic stimulation on both the left and right DLPFC in order to disrupt frontal lobe functions. This is the first time when bilateral TMS was applied in a cognitive neuroscience study. According to the results, the DLPFC disruption led to long-term enhanced performance providing causal evidence for the models of competition between DLPFC functions and procedural learning. Thus, our work supports the view that an antagonistic relationship exists between the brain networks of automatic and controlled processes.

Keywords: statistical learning, probabilistic sequence learning, implicit learning, prefrontal cortex (PFC), fronto-striatal network, memory consolidation, Transcranial Magnetic Stimulation (TMS)

Introduction

Memory systems and their underlying brain structures interact not only in a cooperative manner but can also compete with one another in optimizing performance. Such an antagonistic, competitive relationship is theorized to exist between the prefrontal cortex/medial temporal lobe-mediated hypothesis-testing, attention-dependent processes, and the basal ganglia/cerebellum-dependent procedural system (1–3). Evidence for this competition-model comes from developmental observations (4), neuropsychological studies (5), and from studies that experimentally manipulate the engagement of the two systems (6, 7). Despite the growing body of research on competition, direct evidence is still missing. The aim of our study was to fill this gap by directly manipulating the involvement of dorsolateral prefrontal cortex (DLPFC) in striatum-mediated statistical learning using transcranial magnetic stimulation (TMS).

Statistical learning is a fundamental mechanism of the brain (8, 9) that extracts and represents relationship between events of the environment based on frequency and rule-type information in order to make better predictions of future events. The competition between this type of learning and frontal lobe related processes have been supported by previous research (2, 5, 10). A widely used task for measuring statistical learning is the alternating serial reaction time task (ASRT, Fig 3A and B) (11–14). The ASRT task is a four-choice reaction time task in which predetermined stimuli alternate with random ones creating a probabilistic structure with more frequent versus less frequent stimulus triplets. It has been shown that participants are able to pick up these statistical regularities, and over time, performance differences emerge between high- and low- frequency triplets without the participants becoming aware of the underlying structure (11, 15). This statistical structure can be learnt by relying on striatum-mediated data-driven model-free processes, thus without frontal lobe-mediated hypothesis testing and model-based processes (4, 8–10).

In order to directly test the role of DLPFC in statistical learning we used 1 Hz repetitive TMS which has been shown previously to reduce blood flow in the stimulated region (16), extending beyond the termination of the stimulation (17, 18). Conclusions derived from previous investigations using external brain stimulation methods are limited by the fact that at one time, only one site can be targeted. Thus, to investigate the effects of disruption of both left and right DLPFCs during learning, the sequential use of a stimulation protocol that produces a lasting effect, was needed. We applied sequential, bilateral TMS in order to suppress the involvement of both DLPFCs during acquisition that otherwise might occur

in a purely unilateral design. To track the offline effects of the intervention, retests at 10-min, 2-hour, and 24-hour post-stimulation were implemented. We hypothesized that disrupting the DLPFC functions bilaterally would increase statistical learning performance in the ASRT task.

Results

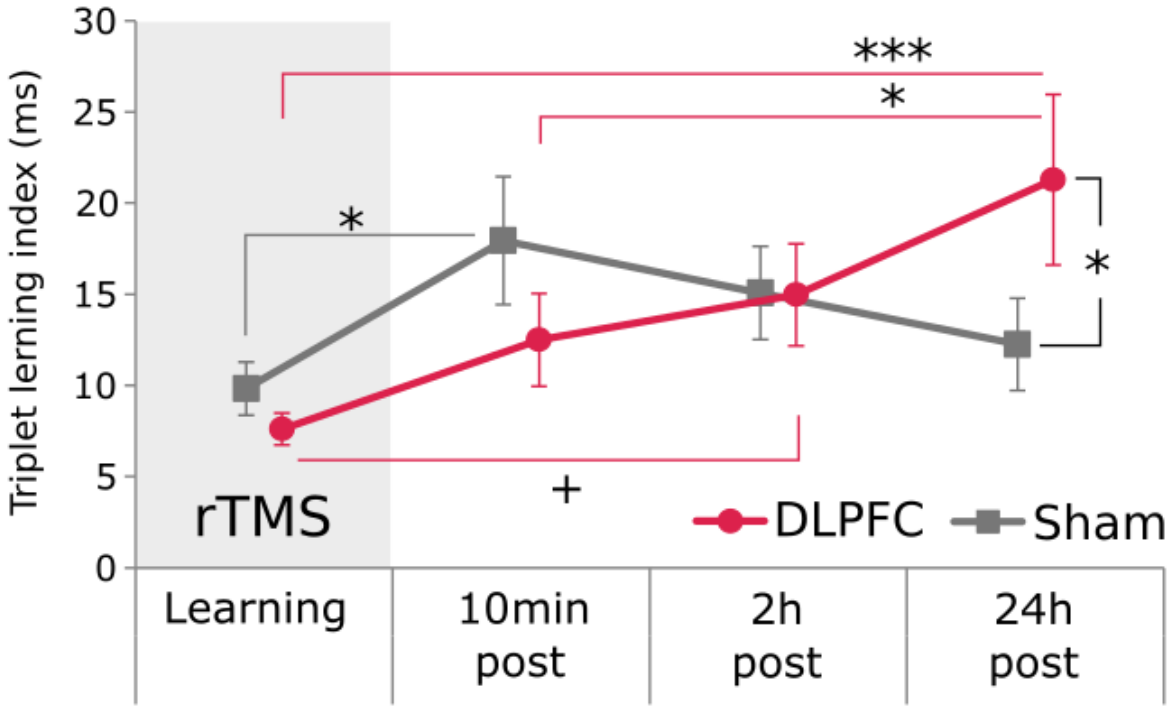

Figure 1. The triplet-learning index in the two experimental groups along the course of the experiment. We observed an increase in performance in the active DLPFC stimulation group, while performance in the sham group was only significantly better in the 10-minutes post-stimulation phase. After 24 hours, the performance of the active DLPFC stimulation group was statistically higher compared to the sham control group. Error bars denote SEM. N = 16 in both groups. $^{+}p < 0.10$, * $p < 0.05$, ***$p < 0.001$

The ANOVA conducted on the triplet learning indices (i.e., RTs for low-frequency stimulus triplets minus RTs for high-frequency stimulus triplets) revealed a significant main effect of experimental Phase ($F_{3, 90} = 4.012$, $p < 0.010$, $\eta^2_p = 0.118$), indicating an overall increase in performance when compared to the Learning/rTMS Phase (10min: $p = 0.025$, 2h: $p = 0.030$, 24h: $p = 0.006$). There was no main effect of Stimulation Group ($F_{1, 30} = 0.016$, $p = 0.902$, $\eta^2_p < 0.001$), but the interaction between experimental Phase and Stimulation Group was shown to be significant ($F_{3, 90} = 3.047$, $p = 0.045$, $\eta^2_p = 0.092$). Post-hoc comparisons revealed a significant increase in performance between the Leaning/rTMS Phase and the 10min Test Phase in the Sham stimulation group ($p = 0.045$). On the other hand, performance in the DLPFC stimulation group increased with time, with a trend towards statistical significance between the

Learning/rTMS and the 2h Phases ($p = 0.068$), and reaching the level of statistical significance at 24h post-stimulation ($p < 0.001$). It should also be noted that the DLPFC groups' performance at 24h post-stimulation was not only markedly better than that in the Learning Phase, but differed significantly from that of the 10min post-stimulation Phase ($p = 0.030$), and also moderately from that of the 2h post-stimulation Phase ($p = 0.118$). Importantly, the performance of the DLPFC stimulation group in the 24h Retest Phase was significantly higher than the Sham groups' performance ($p = 0.026$), indicating the boosting effect of bilateral rTMS on performance that was evident after a consolidation period (see Fig 1).

The observed group differences are unlikely to be due to a general effect of the stimulation on arousal level since general reaction time (Phase × Stimulation Group interaction: $F_{3,\ 90} = 0.344$, $p = 0.794$, $\eta^2_p = 0.011$) and response accuracy (Phase × Stimulation Group interaction: $F_{3,\ 90} = 0.695$, $p = 0.557$, $\eta^2_p = 0.023$) was not statistically different between the two groups. Furthermore, the level of discomfort ($p = 0.409$), tiredness ($p = 0.937$), perceived task difficulty ($p = 0.258$), assessed as a part of the post-experiment debriefing, was also not different between the DLPFC and the Sham groups (see Methods).

Moreover, the order of the hemispheres stimulated, assessed by the two-way interaction of a 3 (TMS condition: Right Start, Left Start, Sham) × 4 (Phase) mixed-design ANOVA, had no effect on statistical learning performance ($F_{6,\ 87} = 1.642$, $p = 0.164$, $\eta^2_p = 0.102$).

Discussion

To date, most of the TMS studies on learning in the procedural domain concentrated on the primary motor cortex, highlighting its importance in the acquisition of motor skills (19, 20). In contrast, the causal role of prefrontal cortex in procedural learning and its consolidation remained elusive. Here we aimed to fill in this gap by a new approach whereby bilateral rTMS of the DLPFCs was used during procedural learning of statistical regularities and performance was tested 10 minutes, 2 hours, and 24 hours post-stimulation. Our results show that the disruption of the DLPFCs bilaterally during the learning phase had a beneficial effect on the performance after the 24 hours offline period.

Our findings, as predicted, are in line with the competition model that posits an antagonistic relationship between the fronto-striatal networks that mediate executive functions, and striatum-linked implicit statistical learning. Without providing mechanistic and causal insight, previous studies have demonstrated the inverse relationship of these two systems on the behavior level. For instance, Virág et al. (5) have shown negative correlation between frontal-lobe related executive functions and implicit

statistical learning. Filoteo and colleagues found that implicit category learning improved with the addition of a secondary working memory task, reducing the contribution of the frontal lobes by overly engaging working memory processes (6). Using hypnosis, Nemeth and colleagues (7) experimentally reduced frontal-lobe connectivity, reducing competition from the attention-based frontal lobe processes, and found increased statistical learning performance compared to an alert, awake state. Janacsek and colleagues (10) examined statistical learning across the human life-span, and observed the strongest learning effect between the ages of 4 and 12 years. Supporting the competition model, the learning scores dropped sharply with the onset of adolescence, coinciding with the maturation of the frontal lobe.

With the intention of disrupting cortical processing by 5 Hz rTMS during deterministic serial reaction time task (SRTT), Pascual-Leone et al. (21) found that stimulation over contralateral DLPFC impaired on-line learning. It should be noted, however, that since the publication of this study, 5 Hz rTMS has been found to induce excitatory effects on cortical excitability (22, 23), thus the performance decrease might be better explained by the facilitation of DLPFC functions. To test the role of the DLPFC in consolidation of sequential knowledge by applying continuous theta-burst transcranial magnetic stimulation (cTBS) after the execution of deterministic SRTT, Galea et al. (24) found offline improvement following the inhibition of the right but not the left DLPFC. These studies were the only ones that used TMS to manipulate involvement of DLPFC during and after procedural learning; however, they focused on deterministic sequences instead of statistical learning. Moreover, by stimulating only the left or the right DLPFC, they could not avoid the potential involvement of the other, unstimulated DLPFC in learning. We went beyond these studies by using bilateral brain stimulation to disrupt the involvement of both DLPFCs during learning.

We found better performance in the DLPFC stimulation group compared to the controls after the 24-hour consolidation period. Why did the effect of DLPFC disruption manifest itself 24 hours later? A possible explanation – from a computational viewpoint – involves the interaction between model-free and model-based processes (9, 10, 25). When the DLPFC is fully functioning, the model-free processes extract the statistical information from the stimulus stream, and the DLPFC mediated model-based processes combine top-down information with these statistics. In the offline period, this mixed information consolidates (see Figure 2). However, the brain stimulation on the DLPFC possibly interrupts the top-down information flow and its combination with data-driven extraction of pure statistical information. This pure statistical information consolidates, which is optimal when the brain faces the challenge to learn entirely new regularities from the environment.

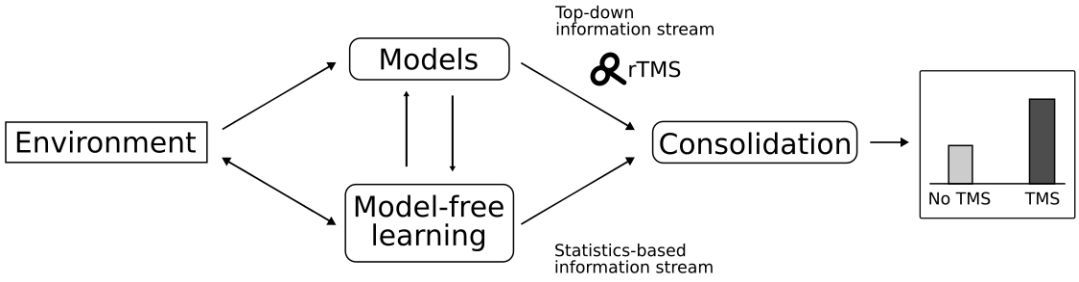

Figure 2. Internal models strongly modulate the interpretations of observed statistics of the input. This helps in extracting complex relations but relatively impairs measuring and utilizing raw probabilities in learning. rTMS disrupts the involvement of these internal models leading to an improved performance of statistical learning.

In conclusion, we observed that the bilateral disruption of the DLPFCs during the learning phase had a beneficial effect on statistical learning performance that was observable after a 24-hour offline period. This finding provides mechanistic level causal evidence for the models positing an antagonistic relationship between the frontal lobe mediated model-based and striatum mediated model-free processes. From a methodological viewpoint, previous investigations using external brain stimulation methods are limited by the fact that only one site was targeted at a time. As with brain lesion patient studies, neuroplastic processes, e.g., the taking-over of the lost function by the contralateral hemisphere, cannot be ruled out in earlier studies (26). Here we successfully overcame this limitation by the sequential application of 1 Hz rTMS before learning blocks over both hemispheres, establishing and sustaining the inhibitory effect. The finding that no effect of stimulation order was observed supports the viability and practicality of this approach, and may form the basis of future research requiring bi-hemispherical/multi-site intervention.

Methods

Participants

Thirty-two participants (16 in each TMS experimental group, 4 males, mean age, SD: 22.13 ± 2.98) took part in the experiment. All of the participants were right handed, their visual acuities were normal or corrected to normal. None of the participants reported previous history of neurological or psychological disorders, drug or alcohol abuse, had no metal implants and were not taking regular medication relevant to the study. Written informed consent has been acquired from all participants. All participants tolerated the experimental procedures, and none withdrew because of discomfort with TMS stimulation. All participants were students of the University of Jena, and participated in exchange for partial course

credits or monetary compensation. The experiment had been conducted in accordance with the guidelines of the Declaration of Helsinki, and with the approval of the ethics committee of the University of Jena.

Alternating Serial Reaction Time Task

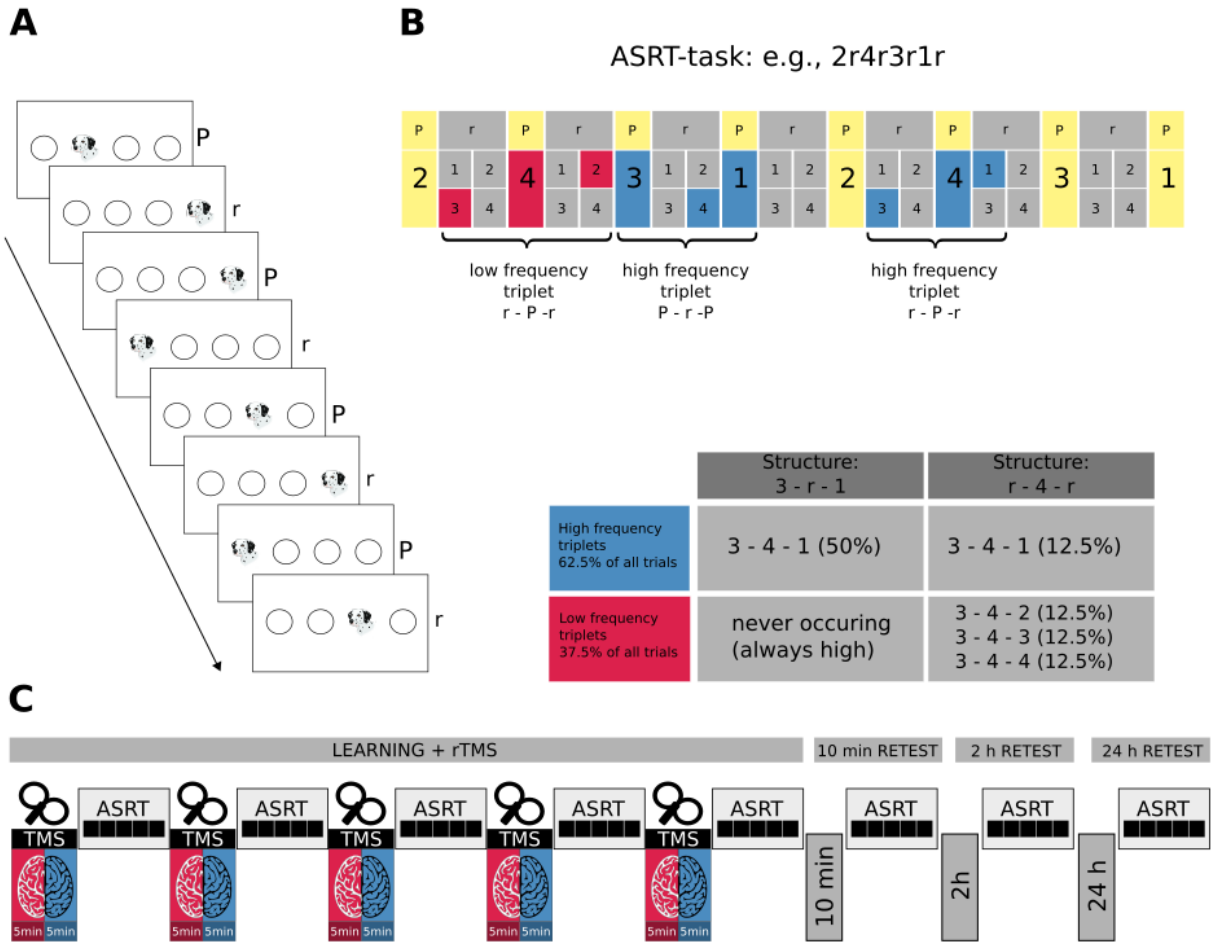

Figure 3. Experimental procedures. **A)** Stimuli of the Alternating Serial Reaction Time (ASRT) task. Repeating elements (P – pattern) alternate with random events (r – random). **B)** Due to this structure of the sequences, some triplets (i.e. three consecutive events) occur more frequently (high-frequency triplets) than others (low-frequency triplets). Implicit statistical learning is measured as the RT difference between these two triplet types. **C)** Five minutes of 1 Hz rTMS of both DLPFCs was administered before each of the five learning blocks, with the order of the stimulated hemispheres counterbalanced across participants. The volunteers performed five ASRT blocks 10 minutes, 2 hours and 24 hours post-learning, as well.

Statistical learning was measured using the Alternating Serial Reaction Time (ASRT) Task (11, 27). In this task, a stimulus (a dog's head) appeared in one of the four horizontally arranged empty circles on the screen. The participants were instructed to press the corresponding key (Z, C, B and M on a QWERTY keyboard), using both hands, as quickly and as accurately as they could (Fig. 3A). The target remained on

the screen until the participant pressed the correct button. The response to stimulus interval (RSI) was set to 120 ms. Stimuli were presented in blocks of 85 trials. The first five trials were random elements, and were for practice purposes only (not analyzed further). After these five practice trials, an eight-element alternating sequence was repeated ten times in a block (e.g., 2*r*4*r*3*r*1*r*, where 1–4 indicate the target locations from left to right, and *r* indicates a randomly selected position out of the four possible ones) (Fig. 3B). After each TMS stimulation phase, five blocks of ASRT were presented to participants which took approximately 5 minutes to complete. Similarly, five blocks of ASRT were administered after 10 minutes, 2 hours and 24 hours (Fig. 3C) to test long-term effects of stimulation on behavior.

Structural MRI and Neuronavigated TMS

Structural MRI scanning was performed in a Siemens Magnetom Trio 3T MRI scanner at the Institute for Diagnostic and Interventional Radiology, University of Jena. High-resolution sagittal T1-weighted images for the 3D head and brain meshes were acquired using a magnetization EPI sequence (MP-RAGE; TR = 2300 ms; TE = 3.03 ms; 1 mm isotropic voxel size). For the purposes of neuronavigated TMS stimulation, the 3D-head and brain models were created from the participants' individual MRI scans. Coordinates for the DLPFC were taken from a meta-analysis by Cieslik et al. (28) (MNI coordinates: x = 37, y = 33, Z = 32). For sham TMS stimulation the coil was oriented perpendicularly, facing away from the scull (29).

TMS stimulation was delivered using a PowerMag 100 Research Stimulator (MES Forschungssysteme GmbH). Neuronavigation was carried out using a PowerMag View (MES Medizintechnik GmbH) Neuronavigation system. Magnetic pulses were delivered with 1 Hz, at 55% maximum stimulator output. A single intensity was used on the basis of previous studies (30, 31). TMS was applied before each of the five learning blocks, i.e. before the first block and in the inter-block intervals (300 pulses, 5 minutes per hemisphere). The order in which the two hemispheres were stimulated was counterbalanced across participants.

Experimental procedures

Participants were seated in a dimly lit room; their heads fixed using a chinrest, 60 cm viewing distance away from the stimulus presentation monitor. After giving informed consent, the volunteers performed an ASRT practice run to familiarize themselves with the task and the keyboard layout. In the Learning/rTMS Phase, the participants received 1 Hz rTMS for both left and right hemispheres sequentially (5 minutes, 300 TMS pulses for each hemisphere, thus 5 minutes for the left and after that for the right, in a counterbalanced order per participants), then performed five blocks of the ASRT task, lasting ca. 5 minutes. This procedure was repeated five times. The order in which the two hemispheres were stimulated was assigned randomly, remained the same for each individual participant, and was

counterbalanced across the volunteers (half of them started with the left, and the other half started with the right hemisphere before each block). In the post-learning/stimulation phases the volunteers performed five blocks of ASRT task 10 minutes, 2 hours, and 24 hours after the completion of the learning phase.

To ensure that the two experimental groups did not differ in executive functions performance, the short-form of Berg Card Sorting Test (32) and the Counting Span test (33–35) were administered after the completion of the ASRT in the last session. We observed no significant differences in performance between the two experimental groups (Berg Card Sorting Test, percent correct responses: DLPFC: M = 81.06, SD = 5.90, Sham: M = 78.61, SD = 10.40, p = 0.421, percent perseverative errors: DLPFC: M = 10.15, SD = 4.56, Sham: M = 12.89, SD = 6.76, p = 0.190, percent non-perseverative errors: DLPFC: M = 8.79, SD = 5.59, Sham: M = 8.50, SD = 5.41, p = 0.880; Counting span, mean of three runs: DLPFC: M = 4.06, SD = 1.11, Sham: M = 3.60, SD = 0.83, p = 0.196)

As a part of the post-experimental debriefing, the participants filled out a questionnaire assessing their levels of discomfort, tiredness, and perceived task difficulty, measured on a ten-point scale.

The Learning Phase (with informed consent) lasted ca. 2 hours, the 10min and 2h Test Phases lasted 5 minutes each, and the 24h Retest Phase (with the control tasks) lasted ca. 30 min.

Statistical analysis

The analysis of the ASRT data followed the procedures established by previous studies (4, 7, 11, 13, 26, 27). In short: For the correct responses, we calculated the median reaction times for high- and low-frequency triplets. Stimulus repetitions (e.g. 333, 444) and trills (e.g. 313, 121) were excluded from the analysis (11, 15). Implicit statistical learning was assessed using a triplet-learning index, by subtracting the RTs for low-frequency triplets from those for high-frequency triplets. A higher score thus means faster responses for high- than for low-frequency triplets, i.e. better statistical learning performance.

The triplet-learning index was calculated in each phase of the experiment for each participant. We conducted a 2 (TMS Group: DLPFC, Sham) × 4 (Phase: Learning/rTMS, 10min Test, 2h Test, 24h Retest) mixed design ANOVA to compare statistical learning performance between the two stimulation groups along the course of the experiment. Greenhouse-Geisser corrections were applied where necessary. Significant main effects and interactions were followed up using Fisher's LSD tests.

As we aimed at investigating the effects of rTMS on both hemispheres, the possibility of the observed effect being due to the stimulation of the hemisphere before the ASRT block had to be ruled out. Thus,

we conducted a 3 (TMS condition: Right Start, Left Start, Sham) × 4 (Phase) ANOVA on the triplet learning index to ascertain if our results were due to the effect of stimulation order.

All analyses were two-tailed and were conducted with a significance level of $p < 0.05$.

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Figure legends

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Figure 2 Internal models strongly modulate the interpretations of observed statistics of the input. This helps in extracting complex relations but relatively impairs measuring and utilizing raw probabilities in learning. rTMS disrupts the involvement of these internal models leading to an improved performance of statistical learning.

Figure 3 Experimental procedures. **A)** Stimuli of the Alternating Serial Reaction Time (ASRT) task. Repeating elements (P – pattern) alternate with random events (r – random). **B)** Due to this structure of the sequences, some triplets (i.e. three consecutive events) occur more frequently (high-frequency triplets) than others (low-frequency triplets). Implicit statistical learning is measured as the RT difference between these two triplet types. **C)** Five minutes of 1 Hz rTMS of both DLPFCs was administered before each of the five learning blocks, with the order of the stimulated hemispheres counterbalanced across participants. The volunteers performed five ASRT blocks 10 minutes, 2 hours and 24 hours post-learning, as well.