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Prefrontal stimulation as a tool to disrupt hippocampal and striatal reactivations underlying fast motor memory consolidation

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ABSTRACT

Background: Recent evidence suggests that hippocampal replay in humans support rapid motor memory consolidation during epochs of wakefulness interleaved with task practice.
Objectives/Hypotheses: The goal of this study was to test whether such reactivation patterns can be modulated with experimental interventions and in turn influence fast consolidation. We hypothesized that non-invasive brain stimulation targeting hippocampal and striatal networks via the prefrontal cortex would influence brain reactivation and the rapid form of motor memory consolidation.
Methods: Theta-burst stimulation was applied to a prefrontal cluster functionally connected to both the hippocampus and striatum of young healthy participants before they learned a motor sequence task in a functional magnetic resonance imaging (fMRI) scanner. Neuroimaging data acquired during task practice and the interleaved rest epochs were analyzed to comprehensively characterize the effect of stimulation on the neural processes supporting fast motor memory consolidation.
Results: Our results collectively show that active, as compared to control, theta-burst stimulation of the prefrontal cortex hindered fast motor memory consolidation. Converging evidence from both univariate and multivariate analyses of fMRI data indicate that active stimulation disrupted hippocampal and caudate responses during inter-practice rest, presumably altering the reactivation of learning-related patterns during the micro-offline consolidation episodes. Last, stimulation altered the link between the brain and the behavioral markers of the fast consolidation process.
Conclusion: These results suggest that stimulation targeting deep brain regions via the prefrontal cortex can be used to modulate hippocampal and striatal reactivations in the human brain and influence motor memory consolidation.

1. Introduction

Motor memory consolidation is the offline (i.e., in the absence of task practice) process by which novel motor memory traces are reorganized into stabile representations [1]. Consolidation has traditionally been assessed at the macro timescale (i.e., hours to days following initial learning; e.g. [2–4]) until recent seminal research demonstrated that it can also occur on a micro timescale (i.e., seconds to minutes; e.g. [5–9]). Specifically, large gains in performance can be observed over the short rest periods interspersed with practice during initial learning. Hippocampal responses [8], and hippocampal reactivation in particular [9], are thought to support the fast motor memory consolidation process during these micro-offline intervals. Importantly, it remains unknown whether: a) similar micro-offline reactivation processes can be observed in other motor learning-related regions such as the striatum (see [10] for striatal reactivation on the macro timescale); and, b) such reactivation patterns can be modulated with experimental interventions and in turn influence the fast consolidation process.

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An intervention that has shown promise to modulate responses in deep brain regions is the application of transcranial magnetic stimulation (TMS) to cortical regions functionally connected to these deeper areas (e.g., [11–17]). Using this approach, we recently showed that dorsolateral prefrontal cortex (DLPFC) stimulation targeting striatal and hippocampal networks influenced responses in these brain areas during motor sequence learning and post-training waking rest [18,19]. Specifically, inhibitory - as compared to facilitatory - theta-burst stimulation (TBS) of the DLPFC altered functional connectivity patterns in fronto-hippocampal and striatal networks over the course of learning [18] and the reactivation of hippocampal patterns immediately following learning [19]. Importantly, no studies have investigated whether such stimulation targeted to deep brain regions can influence the behavioral and neural markers of the fast consolidation process occurring during the short rest breaks between bouts of task practice.

To address this question, we applied theta-burst stimulation targeting hippocampal and striatal networks via the prefrontal cortex of young healthy participants before they learned a new motor sequence task in a functional magnetic resonance imaging (fMRI) scanner (Fig. 1A). We combined univariate and multivariate analyses of fMRI data acquired during task practice and the interleaved rest epochs (Fig. 1B) to comprehensively characterize the effect of deep-brain-region-targeted stimulation via the prefrontal cortex on the neural processes supporting motor memory consolidation at the micro timescale. Based on our earlier work showing that inhibitory stimulation of the DLPFC altered task- and rest-related hippocampal and striatal patterns [18,19], we expected inhibitory - as compared to facilitatory or control - theta-burst stimulation to influence hippocampal and striatal responses during the micro-offline consolidation episodes. As these brain responses are linked to fast consolidation [8,9], we expected inhibitory stimulation to modulate the rapid form of motor memory consolidation.

2. Methods

This study was pre-registered in the Open Science Framework (https://osf.io/e2cnq). Data acquisition followed the pre-registered procedures. However, the primary analyses reported below were not pre-registered and are therefore considered as exploratory.

2.1. Participants

Seventy-six healthy young (age range 19–29 years, 52 females), right-handed volunteers participated in the current study. One participant withdrew before group assignment and the 75 remaining participants were distributed in 3 experimental groups in a single-blinded design (control n = 25; iTBS n = 25; cTBS n = 25). All participants were eligible for MR measurements and TMS interventions. They were free of medical, neurological, psychological or psychiatric conditions and were not taking any psychoactive or sleep-influencing medications at the time of the experiment. Participants reported no previous extensive training with a musical instrument requiring dexterous finger movements (e.g., piano, guitar) or as a professional typist. None of the participants worked nights shifts or performed trans-meridian trips within the month prior to the experiment. Of these 75 complete datasets, 6 were excluded from the final analyses: 3 participants (2 control, 1 cTBS) because they presented performance accuracy >3SD below the mean of the sample and 3 other participants (2 control, 1 iTBS) because they did not respect the regular sleep schedule. Characteristics of the 69 participants included in the analyses are presented in Supplemental Table S1. All participants gave written informed consent before participating in this study that was approved by the local Ethics Committee (UZ/KU Leuven) and was conducted according to the declaration of Helsinki (2013). All participants were compensated for their time and effort.

2.2. General experimental procedure

Participants first visited the MR unit for a baseline session including resting-state (RS), anatomical MRI measurements and baseline TMS measures (search of hotspot, resting motor threshold (rMT) and active motor threshold (aMT)). Note that RS data are not reported in the current study. At least three days after the baseline session, participants were invited for two consecutive experimental days (day 1 and day 2). This manuscript only focuses on the data collected during experimental day 1. For the three days before experimental day 1, participants were instructed to follow a regular sleep/wake schedule (according to their own schedule ±1h, no naps). They were also instructed to refrain from alcohol and nicotine during this period. Sleep diaries and wrist actigraphy (ActiGraph wGT3X-BT, Pensacola, FL) were used to assess

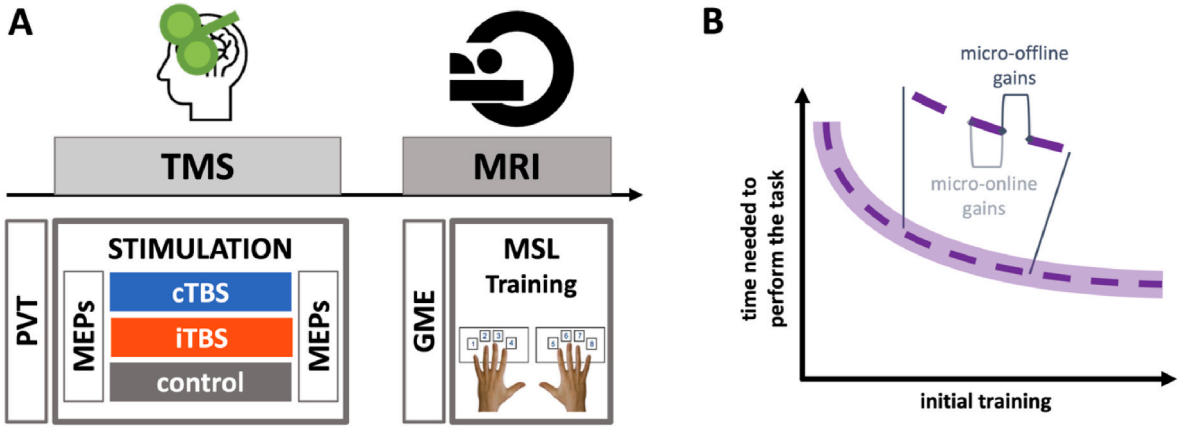

Fig. 1. (A) Experimental design. Sixty-nine young healthy participants received either inhibitory continuous (cTBS; n = 24), facilitatory intermittent (iTBS, n = 24) or control (n = 21) theta-burst stimulation (TBS) to a frontal cluster (DLPFC, -30 22 48 mm) functionally connected to the striatum and the hippocampus [18] before they learned a new motor sequence learning (MSL) task in the MRI scanner. Corticospinal excitability of the primary motor cortex was measured with motor evoked potentials (MEPs) pre- and post-TBS. Immediately following stimulation, participants were placed in the magnetic resonance imaging (MRI) scanner where general motor execution (GME) was probed with a random serial reaction time task immediately prior MSL training. Vigilance was assessed with a psychomotor vigilance test (PVT). (B) Schematic overview of practice (purple dashes) and inter-practice rest episodes during MSL. Micro-online gains in performance represent performance changes from the beginning to the end of a practice block, while micro-offline gains represent performance changes across the short rest intervals, i.e., from the end of one to the beginning of the next practice block. Note that MSL training included 20 practice blocks but only 9 are represented in this figure to increase readability. TMS: transcranial magnetic stimulation, cTBS and iTBS: continuous and intermittent TBS. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

compliance to the sleep schedule.

On experimental day 1, participants were divided in 3 groups according to whether they received continuous, intermittent or control theta-burst stimulation (TBS) of the DLPFC (cTBS, iTBS or control, as described below; see Fig. 1A). TBS was applied outside the scanner before initial MSL (between 9:30am and 5:30pm). Motor evoked potentials (MEPs; see Supplemental Methods and Results, see Supplemental Figure S1) were measured before and after TBS. Immediately following stimulation, general motor execution (GME in Fig. 1A) was measured with a random serial reaction time task (SRTT, see Supplemental Methods for a description of the task and Supplemental Results) and participants were then trained on the MSL task while brain activity was recorded with fMRI (task duration: 17.17 ± 3.96min, range 10.03–31.87min). The time between TBS offset and the start of MSL training (21.49 ± 1.71min; range 16.33–25.83min) did not differ between groups ($F_{(2,66)} = 0.967$, $\eta^2_p = 0.296$, $p = 0.385$). At the end of the experimental session on day 1, participants went home with the instructions to have a good night of sleep according to their sleep schedule, to not practice the task or consume any alcohol or drugs. Participants came back the next day (day 2) for a 24h task retest (between 9:15am and 5:15pm) that took place in the MR scanner approximately at the same time as the training session on day 1. Prior to each MSL session on both experimental days, vigilance and sleep quality from the preceding night were assessed (Supplemental Table S1).

2.3. Motor sequence learning task

Participants performed a bimanual finger-tapping task previously used in our group [20,21], and implemented in Matlab. They practiced the task in an MRI scanner during two different sessions, i.e., MSL training and retest (retest data not reported in this manuscript). During the task, participants tapped an eight-element finger sequence (8 fingers, all fingers except thumbs) as quickly and correctly as possible on a specially designed keyboard. Before initial training, participants were explicitly taught the sequence (4-7-3-8-6-2-5-1, with 1 representing the left little finger and 8 representing the right little finger) and performed a pre-training session that ended when three consecutive correct sequences were performed. Each session (MSL training and MSL retest) included 20 practice blocks followed, for the training session, by a 2min break and a post-training test including 4 practice blocks (data not reported in the current manuscript). During each practice block (48 key presses), the cross in the middle of the screen was green and the sequence of numbers corresponding to the fingers to press was displayed. During rest blocks (15s), the cross turned to red and 8 asterisks replaced the numbers on the screen.

Motor performance was measured in terms of speed (per practice block: mean time to perform a correct transition, i.e., the time between two consecutive correct key presses, see below) and accuracy (per practice block: percentage of correct transitions; results reported in the supplements). For a 4-7-3-8-6-2-5-1 sequence, the 8 possible correct transitions were 47, 73, 38, 86, 62, 25, 51 and 14. Behavioral data were analyzed with separate repeated measures ANOVAs conducted on performance speed as well as accuracy during MSL training (20 blocks) with blocks as within-subject factor and group as between-subject factor (cTBS/iTBS/control). Additionally, we examined consolidation processes on a micro timescale during MSL training (see Fig. 1B) with similar procedures as in earlier work [5,6,8,9] (but see below for additional information on the behavioral outcome). Specifically, micro-online gains in performance speed, reflecting performance changes during task practice periods, were defined as the difference between the average performance speed of the first 8 correct transitions of a block and the average speed of the last 8 correct transitions of the same block. The corresponding micro-online gains in performance extracted from the 20 practice blocks were then summed up for each participant for further statistical analyses. Micro-offline gains in performance, reflecting processes occurring during inter-practice rest periods, were computed as the difference between the average speed of the last 8 correct transitions of a block and the average speed of the first 8 correct transitions of the following block. The micro-offline gains in performance extracted from the 19 pairs of practice blocks were then summed up for each participant. ANOVAs were conducted for micro-online and -offline gains with group (3) as between-subject factor. We then followed-up with relevant two-tailed two-sample *t* tests. Note that the distribution of the different transitions used in the computations of micro-online and -offline processes is reported in Supplemental Table S2. The first/last 8 correct transitions, rather than the first/last correct sequences [6], were used for the micro timescale computations as with an 8-element sequence, the transition-level outcome allows to better reflect performance at the beginning and end of each block in the case of errors. For example, in the case of 4-7-**2**-8-6-2-5-1-4-7-3-8-**5**-2-5-1-4-7-3-8-6-2-5-1-4 …, where errors are shown in bold, the first correct sequence (underlined) is within the first 24 key presses while the first 8 correct transitions are included within the first 11 key presses.

2.4. TMS administration

Neuro-navigated TMS (BrainSight, Rogue Research Inc, Montreal, Quebec, CA) was applied with a theta-burst stimulation (TBS) procedure (a burst of 3 pulses given at 50 Hz, repeated every 200 ms; [22]) on the DLPFC MNI coordinate -30 22 48 mm using a DuoMAG XT-100 rTMS stimulator (DEYMED Diagnostics s.r.o., Hronov, Czech Republic) similar as in our earlier research [18]. Stimulation was applied with a 45° angle so that the handle of the 70mm butterfly coil pointed posteriorly. This TMS target was chosen as it has previously been shown to be functionally connected to the striatum and the hippocampus during rest and its stimulation was described to influence striatal as well as hippocampo-frontal functional connectivity during MSL [18] (and see Supplemental Methods and Supplemental Figure S2 for a map of individual DLPFC peaks of maximal connectivity with the striatal and hippocampal seeds in a 15mm sphere centered around the fixed coordinate mentioned above).

We applied intermittent (iTBS, 2s TBS trains repeated every 10s for 190s, 600 pulses) or continuous stimulation (cTBS, 40s uninterrupted train of TBS, 600 pulses) to the DLPFC at 80% of the aMT [22]. Control stimulation was applied with similar procedures as above but with a lower threshold (i.e., 40% aMT [23–27]). Supplemental Figure S3 shows a simulation of the induced electric field resulting from the active and control TBS protocols (see Supplemental Methods for details). Note that active TBS effects (inhibitory and facilitatory) have been described to outlast the stimulation itself for up to 60min [22,28] and therefore overlapped with MSL training (range MSL training: 29.23–53.33min after TBS).

2.5. Statistical analyses of non-imaging data

Statistical analyses of the behavioral data (MSL, SRTT, PVT) as well as the MEP, sleep, questionnaire and demographic data were performed in SPSS Statistics 27 (IBM), with probability levels set to $p < 0.05$. We applied Greenhouse-Geisser corrections if the sphericity assumption was violated. *T* test statistics for independent sample tests were computed with un-pooled variance and correction of the degrees of freedom in the case of non-equal variance across two groups.

2.6. fMRI data acquisition and analysis

2.6.1. Acquisition

During the baseline session, high-resolution T1-weighted structural images were acquired with a MPRAGE sequence (TR/TE = 9.6/4.6ms; voxel size = 0.98 × 0.98 × 1.2mm^3; field of view = 250 × 250 × 228mm^3; 190 coronal slices) for each participant. Additional brain images described in the Supplemental Information were acquired during

baseline but not analyzed in the presented paper.

Task-related fMRI data were acquired using an ascending gradient EPI pulse sequence for T2*-weighted images (TR = 2000ms; TE = 29.8ms; multiband factor 2; flip angle = 90°; 54 transverse slices; slice thickness = 2.5mm; interslice gap = 0.2mm; voxel size = 2.5 × 2.5 × 2.5mm^3; field of view = 210 × 210 × 145.6mm^3; matrix = 84 × 82; training: 514.23 ± 115.90, post-test: 94.49 ± 48.44, retest: 383.54 ± 88.85 dynamical scans) during each task run. After the last task run of each session, field maps were acquired (TR = 1500ms; TE = 3.5ms; flip angle = 90°; 42 transverse slices; slice thickness = 3.75mm; interslice gap = 0.2mm; voxel size = 3.75 × 3.75 × 3.75mm^3; field of view = 240 × 240 × 157.5mm^3; matrix = 64 × 64). Only MRI data related to the MSL training session are reported in the present manuscript. Note that the MRI data related to the last block of practice of one participant (cTBS group) are missing as they did not terminate the task within the allocated scanning time.

2.6.2. Univariate fMRI analyses

2.6.2.1. Spatial preprocessing. Task-based functional volumes of each participant were realigned to the first image of each session and then realigned to the mean functional image computed across sessions. The high-resolution T1-weighted anatomical image was co-registered to the realigned functional images. The structural image was segmented into 6 tissues. All functional and anatomical images were normalized to an average subject-based template created with DARTEL and registered to the Montreal Neurological Institute (MNI). Functional images were spatially smoothed using an isotropic 8 mm full-width at half-maximum (FWHM) Gaussian kernel.

None of the participants were excluded after preprocessing as movement was overall minimal during scanning. However, MSL training data of 2 participants (1 cTBS, 1 iTBS) were truncated due to movement exceeding 2 voxels (leaving 13 and 18 full MSL practice blocks for the respective participants).

2.6.2.2. Activation analyses. The task-based fMRI data analyses were based on a summary statistics approach and were conducted in 2 serial steps accounting for intra-individual (fixed effects) and inter-individual (random effects) variance, respectively. Changes in brain regional responses were estimated for each participant with a model including responses to the motor task and its linear modulation by performance speed (mean time to perform correct transitions per block; results not reported in the current manuscript) for each task run (training (TR), immediate post-test (PT) and 24h-retest (RT); results related to PT and RT are not reported in the current manuscript). The 15s inter-practice rest blocks served as the baseline condition and were only modelled implicitly (i.e., no separate rest regressor was included in the model) as they showed perfect collinearity with task blocks. These regressors consisted of box cars convolved with the canonical hemodynamic response function. Movement parameters derived from realignment as well as erroneous key presses were included as covariates of no interest. Consequently, the betas for general linear model for the first-level analyses were estimated for the practice, the modulation of the practice (using mean speed), errors (wrong button presses as well as button presses during rest) and the six movement parameters for each run (training (TR), immediate post-test (PT) and 24h-retest (RT)) as well as one constant per run:

$$Y_i = \beta_{i\_practice\text{-}TR}X_{i\_practice\text{-}TR} + \beta_{i\_modulation\text{-}TR}X_{i\_modulation\text{-}TR} + \beta_{i\_errors\text{-}TR}X_{i\_errors\text{-}TR} + \beta_{i\_movement1\text{-}TR}X_{i\_movement1\text{-}TR} + \beta_{i\_movement2\text{-}TR}X_{i\_movement2\text{-}TR} + \beta_{i\_movement3\text{-}TR}X_{i\_movement3\text{-}TR} + \beta_{i\_movement4\text{-}TR}X_{i\_movement4\text{-}TR} + \beta_{i\_movement5\_TR}X_{i\_movement5\_TR} + \beta_{i\_movement6\text{-}TR}X_{i\_movement6\text{-}TR} + \beta_{i\_practice\text{-}PT}X_{i\_practice\text{-}PT} + \beta_{i\_modulation\text{-}PT}X_{i\_modulation\text{-}PT} + \beta_{i\_errors\text{-}PT}X_{i\_errors\text{-}PT} + \beta_{i\_movement1\text{-}PT}X_{i\_movement1\text{-}PT} + \beta_{i\_movement2\text{-}PT}X_{i\_movement2\text{-}PT} + \beta_{i\_movement3\text{-}PT}X_{i\_movement3\text{-}PT} + \beta_{i\_movement4\text{-}PT}X_{i\_movement4\text{-}PT} + \beta_{i\_movement5\_PT}X_{i\_movement5\_PT} + \beta_{i\_movement6\text{-}PT}X_{i\_movement6\text{-}PT} + \beta_{i\_practice\text{-}RT}X_{i\_practice\text{-}RT} + \beta_{i\_modulation\text{-}RT}X_{i\_modulation\text{-}RT} + \beta_{i\_errors\text{-}RT}X_{i\_errors\text{-}RT} + \beta_{i\_movement1\text{-}RT}X_{i\_movement1\text{-}RT} + \beta_{i\_movement2\text{-}RT}X_{i\_movement2\text{-}RT} + \beta_{i\_movement3\text{-}RT}X_{i\_movement3\text{-}RT} + \beta_{i\_movement4\text{-}RT}X_{i\_movement4\text{-}RT} + \beta_{i\_movement5\_RT}X_{i\_movement5\_RT} + \beta_{i\_movement6\text{-}RT}X_{i\_movement6\text{-}RT} + c_{TR} + c_{PT} + c_{RT}$$

[with Y: the measured signal, i: timepoint, β: beta value, X: experimental design variable, c: constant].

High-pass filtering was applied with a cutoff period of 128s. Serial correlations in the fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood (ReML) algorithm. The linear contrast testing for the main effect of practice during MSL training (i.e., task > rest) was further spatially smoothed (Gaussian kernel 6mm FWHM) and entered in a second level analysis for statistical inference at the group level (ANOVA with group (3) as between-subject factor). Follow-up two-sample *t* tests were performed when appropriate.

2.6.2.3. Regression analyses. We regressed the individuals' contrast images from the activation-based analyses against the individuals' micro-offline performance gains (speed) in a separate second level analysis for statistical inference at the group level (ANOVA with group (3) as between-subject factor) where $Y_{ij} = \mu + \tau_j + \beta(x_{ij}\text{-}X) + \varepsilon_{ij}$ [with Y: the measured signal, i: participant, j: group, μ: grand mean of Y, τ: group effect, β: regression coefficient between Y and x, x: covariate, X: grand mean of x, ε: residual]. Follow-up analyses (*t* tests) were performed when appropriate.

2.6.2.4. Statistical inferences. The set of voxel values resulting from each second level analysis listed above constituted maps of the F statistic testing for the main effect of group [SPM(F)] thresholded at $p < 0.005$ (uncorrected for multiple comparisons). Follow-up two-sample *t* tests constituted maps of the T statistics [SPM(T)]. We used an ROI approach that included the DLPFC target defined as all the voxels in a 10 mm radius sphere around the target coordinate (-30 22 48 mm) as well as the hippocampi and the basal ganglia (putamen, caudate nucleus and globus pallidus) defined as all the voxels included within anatomical masks provided by Neuromorphometrics, Inc. (http://Neuromorphometrics.com/) under academic subscription and incorporated in SPM12. Statistical inference was conducted at a threshold of $p < 0.05$ after family-wise error (FWE) correction for multiple comparisons over small volume within the ROIs (small volume correction (SVC) approach [29,30]; see Supplemental Table S3 for the Main and Supplemental Results). This procedure was followed by Holm-Bonferroni correction [31] for multiple brain regions highlighted in each contrast ($p < 0.05$, indicated by an asterisk in the tables).

2.6.3. Multivariate fMRI analyses

To investigate the effect of prefrontal stimulation on the neural processes supporting consolidation on a micro timescale, we performed multivariate analyses of the fMRI data of the training session. The goal of these analyses was to further characterize the stimulation-induced modulation of brain activity during inter-practice rest periods (i.e., micro-offline epochs). Specifically, we investigated whether multivariate brain patterns observed during task practice persisted into the inter-practice rest periods during initial training. To do so, we computed the level of similarity (similarity index) of multi-voxel correlation structures (MVCS) between task practice and inter-practice rest periods in two ROIs and in a control region (see below). The analysis pipeline, implemented in Matlab, is summarized below and followed similar procedures as in previous work [10,19,32–34].

2.6.3.1. Preprocessing. For each participant, the structural image was reoriented and segmented. The functional volumes were slice-time corrected (reference: middle slice), realigned and co-registered to the T1-weighted anatomical image. To optimize voxel pattern analyses, functional and anatomical data remained in subject-specific (i.e., native) space, and no spatial smoothing was applied to functional images [10,

19,32]. Additional preprocessing of the time series included detrending and high-pass filtering (cutoff = 1/128). Framewise displacement of any given volume exceeding 0.5mm led to exclusion of that volume as well as the subsequent one (on average 8.65% of volumes excluded). Voxels with < 10% GM probability were excluded from the analyses at the ROI level. The following nuisance factors were regressed out from the signal: the three first principal components of the signal extracted from the white matter and cerebrospinal masks (6 regressors), the 6-dimensional head motion realignment parameters, their square, derivatives, and the squared derivatives (24 regressors). Lastly, the number of volumes was matched between each task practice block and the following inter-practice rest block (mean ± SD number of volumes for control: 122.24 ± 18.45, cTBS: 115.38 ± 20.71, iTBS: 118.67 ± 20.16; the amount of volumes did not differ between the groups: $F_{(2,66)} = 0.77$, $\eta_p^2 = 0.023$, $p = 0.467$). Importantly, volumes including a transition between states (practice or rest) were excluded from the timeseries (i.e., 2 volumes per practice block of each participant were excluded).

2.6.3.2. ROI selection and definition. The selection of ROIs for the MVCS analyses was based on the results of the univariate fMRI analyses showing stimulation-induced modulation of activity during inter-practice rest periods in the hippocampus and the caudate nucleus (see Table 1). Analyses also included a control ROI that did not show any stimulation-induced modulation of activity in the univariate analyses, even at a more permissive threshold. As signal to noise ratio and therefore similarity indices are usually lower in subcortical as compared to cortical regions [10,19], we opted to select a *subcortical* control region, i.e., the thalamus, to facilitate qualitative comparisons between ROIs. Bilateral caudate, hippocampus and thalamus ROIs were therefore created in the native space of each individual using the FMRIB's Integrated Registration Segmentation Toolkit (FSL FIRST; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST) employing boundary correction ('fast').

2.6.3.3. Multivoxel correlation structure (MVCS) analyses. For each ROI and each block state (practice or rest), multi-voxel correlation structure (MVCS) matrices were computed across all the voxels showing > 10% GM probability. Specifically, Pearson's correlations were computed between each of n BOLD-fMRI voxel time courses, yielding an n by n MVCS matrix per ROI and per state. Correlation coefficients were then Fisher Z-transformed to ensure normality. A similarity index (SI) reflecting the similarity of the multi-voxel patterns between task practice and inter-practice rest was computed as the r-to-z transformed correlation between the two MVCS matrices. Here, SI reflects the amount of persistence of task-related brain patterns into inter-practice rest periods. SI values were compared between groups using an ANOVA with group (3) as between-subject factor. Follow-up *t* tests were performed when appropriate. All *t* tests including the control group were one-sided as we expected, based on the univariate fMRI results, less persistence of task patterns into rest after active as compared to control stimulation.

Additionally, in order to test for relationships between behavioral and brain markers of micro-offline processes, we performed correlation analyses in SPSS between micro-offline gains in performance and (1) the amplitude of the BOLD response in ROIs reported in Table 1 (i.e., using parameter estimates extracted from the univariate analyses reported in Table 1); and (2) SI in all ROIs. Correlations were compared between groups using an online tool available on http://home.ubalt.edu/ntsbarsh/business-stat/otherapplets/MultiCorr.htm.

3. Results

3.1. Behavioral analyses

Behavioral results show that performance speed (mean time to perform a correct transition) significantly improved across practice blocks during the MSL training session (see Fig. 2A; main effect of block: $F_{(6.798,448.694)} = 73.471$, $\eta_p^2 = 0.527$, $p < 0.001$) similarly between groups (block by group interaction: $F_{(13.597,448.694)} = 0.933$, $\eta_p^2 = 0.028$, $p = 0.587$; group effect: $F_{(2,66)} = 0.65$, $\eta_p^2 = 0.024$, $p = 0.444$). These results suggest that prefrontal stimulation prior to MSL did not influence overall motor performance during training.

Next, we examined the effect of stimulation on the fast consolidation process occurring at the micro timescale (see Fig. 1B). Results showed a trend for a group main effect on micro-offline gains in performance ($F_{(2,66)} = 2.904$, $\eta_p^2 = 0.081$, $p = 0.062$). Inspection of the data and follow-up comparisons (Supplemental Table S4) indicated a similar pattern of results in the two active stimulation groups as compared to control. Collapsing across iTBS and cTBS groups revealed that active - as compared to control - stimulation resulted in decreased micro-offline gains in performance (active vs. control; $t_{(29.685)} = -2.05$, d = -0.606, $p = 0.049$, corrected for unequal variances; Fig. 2B). Similarly, micro-online gains in performance showed a trend for a group effect ($F_{(2,66)} = 2.786$, $\eta_p^2 = 0.078$, $p = 0.069$) with greater gains in the active as compared to the control stimulation group (active vs. control; $t_{(67)} = 2.19$, d = 0.573, $p = 0.032$, equal variances met; Fig. 2C; see Supplemental Table S4 for group pair comparisons). Altogether, these results suggest that active DLPFC stimulation applied prior to MSL enhanced and disrupted micro-online and -offline learning, respectively, as compared to control stimulation.

3.2. Functional brain imaging data analyses

3.2.1. Univariate analyses

Results showed a main effect of group on task-related activity in the hippocampus and the caudate nucleus (task vs. rest; Table 1). Follow-up two-sample *t* tests (Supplemental Table S5) and data inspection (Fig. 3A) indicated that this effect was driven by more deactivation (i.e., more activity during inter-practice rest intervals as compared to task practice) in the control group as compared to the two active stimulation groups (iTBS and cTBS groups). Analyses pooling the two active stimulation groups together confirmed this pattern of results (Table 1). Altogether, these data suggest that active, as compared to control, stimulation disrupted hippocampal and caudate activity during inter-practice rest (relative to task) intervals during motor learning.

3.2.2. Multivariate analyses

Results of the MVCS analyses showed that the similarity indices between task and rest were higher in the control as compared to the active stimulation conditions in the caudate nucleus ($t_{(67)} = 1.899$, d = -0.497, $p = 0.031$; see Supplemental Table S6 for all pair-wise comparisons; Fig. 4B). A similar trend was observed in the hippocampus ($t_{(67)} = 1.494$, d = -0.391, $p = 0.07$; Fig. 4C). Interestingly, no such effects were observed in the control subcortical region (thalamus; group effect: $F_{(2,66)} = 0.82$, $\eta_p^2 = 0.024$, $p = 0.445$; active vs. control stimulation: $t_{(67)} = 1.088$, d = 0.285, $p = 0.14$; Fig. 4D). In sum, the MVCS results indicate that active stimulation disrupted the persistence of task-related patterns into the inter-practice rest periods in the caudate nucleus and, to a lesser extent, the hippocampus. These findings suggest that DLPFC stimulation hindered the reactivation of learning-related patterns during the micro-offline rest episodes.

3.2.3. BOLD amplitude/pattern persistence relationship

We tested whether the amplitude of the BOLD response in the ROIs was related to the pattern persistence (similarity index) measured with MVCS; and whether stimulation conditions altered this relationship. Results show that there was no main effect of group ($\chi^2 = 0.33$, $p = 0.85$) or difference between active and control stimulation conditions ($\chi^2 = 0.23$, $p = 0.629$; Fig. 5A, left panel) in the relationship between activity and pattern persistence in the caudate nucleus (see Supplemental Table S7 for results in each group). However, in the hippocampus, this relationship differed among the three groups ($\chi^2 = 7.68$, $p = 0.021$, see

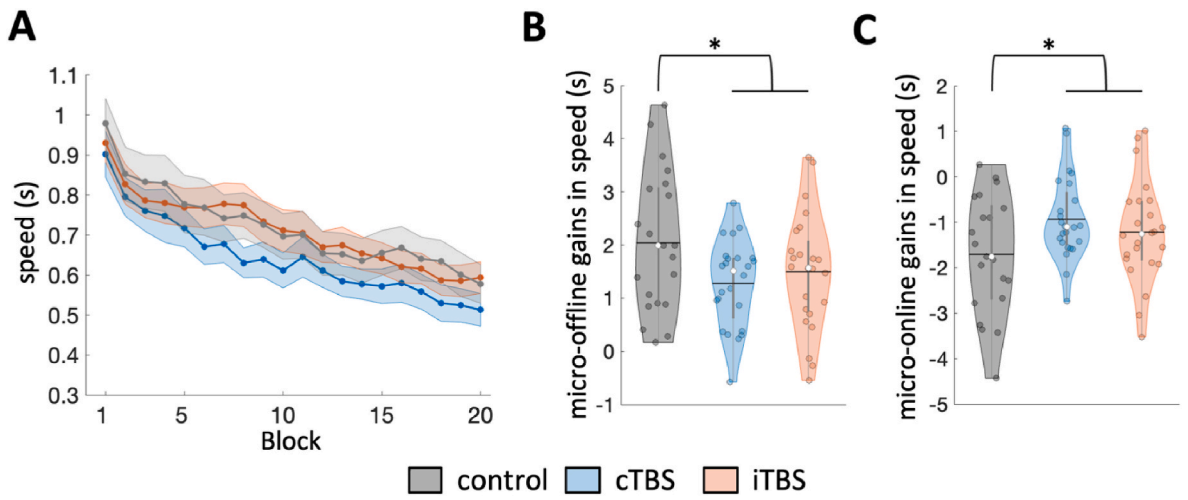

Fig. 2. Behavioral results. (A) Performance speed (mean time to perform a correct transition, in s) improved over the course of initial training similarly in the three experimental groups. Dots represent mean values; shaded areas represent standard errors of the mean. While overall learning (A) did not differ among the three groups, active (cTBS and iTBS) - as compared to control - stimulation resulted in (B) lower micro-offline and (C) higher micro-online gains in performance speed (in s). In panels B and C, colored circles represent individual data, jittered in arbitrary distances on the x-axis within the respective violin plot to increase perceptibility. Black horizontal lines represent means and white circles represent medians. The shape of the violin plots depicts the distribution of the data and grey vertical lines represent quartiles. Violin plots were created with [35]. Asterisks (*) indicate significant ($p < 0.05$) effects comparing the active stimulation (n = 48) with the control (n = 21) group. cTBS: continuous theta-burst stimulation, iTBS: intermittent theta-burst stimulation.

Table 1
Functional imaging results of activation-based contrasts (Main effect of practice).

Area	x	y	z	k	Z	p_{FWEsvc}
1. Main effect of group (F test)						
Hippocampus	-28	-10	-26	16	3.1	0.027
Caudate	-8	16	4	47	2.97	0.037
2. Main effect of active stimulation ([iTBS + cTBS] vs. control) (*t*-test)						
[control-active]						
No significant responses						
[active-control]						
Hippocampus	-28	-10	-26	55	3.67	0.0038*
Caudate	-8	16	4	47	3.58	0.0051*
Putamen/Pallidum	-10	0	6	175	2.88	0.036
Pallidum	-12	-2	-2	23	3.09	0.021
Caudate	8	14	4	31	2.83	0.041

Asterisk (*) indicates significance at $p < 0.05$ after Holm-Bonferroni correction for multiple comparison.

Supplemental Table S7 for group pair comparisons) as well as between the active and control stimulation conditions ($\chi^2 = 5.98$, $p = 0.014$; Fig. 5A, right panel). Specifically, higher hippocampal activity during inter-practice rest blocks (i.e., stronger deactivation during practice blocks) was related to higher pattern persistence in the control group as compared to the active stimulation groups. These results not only suggest that the amplitude of the BOLD signal in the hippocampus during inter-practice rest periods is related to pattern persistence (and might therefore reflect reactivation of learning-related patterns), but also that active DLPFC stimulation disrupted this relationship.

3.2.4. Brain/behavior relationships

We tested whether there was a relationship between the behavioral and brain markers of the micro-offline consolidation process and whether this relationship was influenced by stimulation. First, we examined BOLD/behavior relationships using micro-offline gains in performance as covariate in an univariate regression analyses. Results showed that this relationship differed between active and control

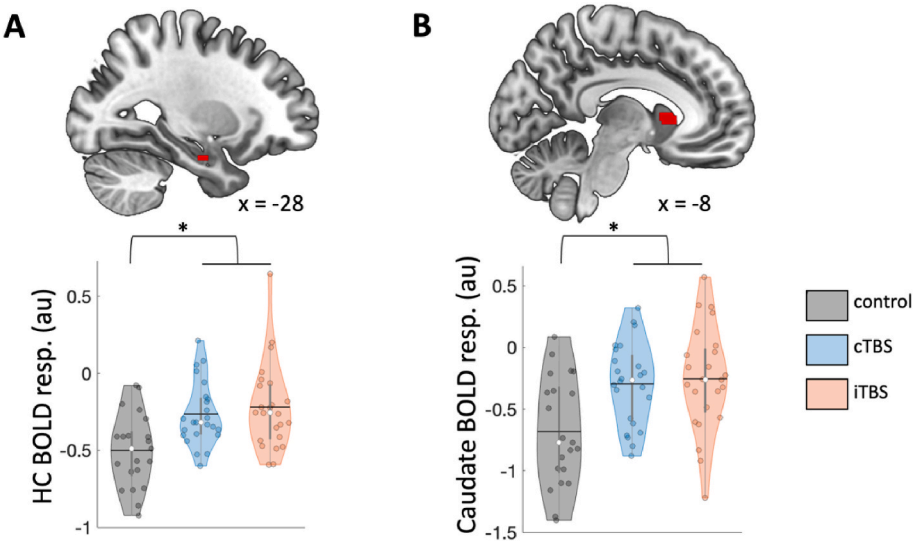

Fig. 3. Main effect of group on brain activity during MSL training (TR). The group effect observed in the hippocampus (HC; panel A) and the caudate (Panel B) was explained by greater task-related deactivation (i.e., higher activity during inter-practice rest intervals) in the control group (n = 21) compared to the two active TBS (n = 24 each) groups. Activation maps are displayed within the ROIs on a T1-weighted template image at a threshold of $p < 0.005$, uncorrected. Asterisks indicate significant group differences between group pairs ($p_{FWEsvc} < 0.05$, see Supplemental Table S4 for paired comparisons). Colored circles represent individual data, jittered in arbitrary distances on the x-axis within the respective violin plot to increase perceptibility. Black horizontal lines represent means and white circles represent medians. The shape of the violin plots depicts the distribution of the data and grey vertical lines represent quartiles. Resp.: response, au: arbitrary unit, cTBS: continuous theta-burst stimulation, iTBS: intermittent theta-burst stimulation.

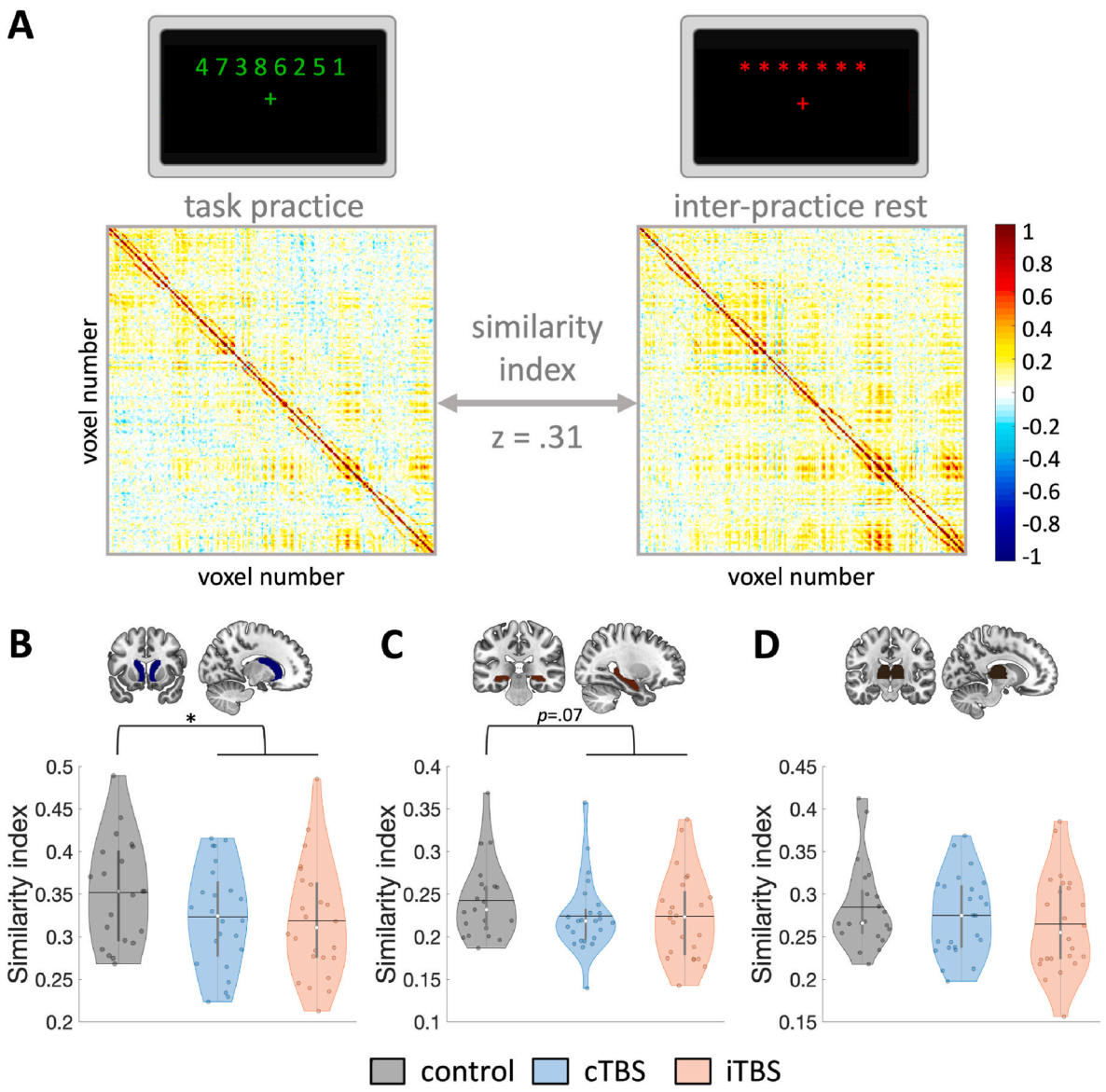

Fig. 4. Similarity index between task practice and inter-practice rest periods during MSL training. (A) Multivoxel correlation structure (MVCS) for an exemplar ROI and participant. Each matrix depicts the correlation between each of the n voxels of the ROI with all the other voxels of the ROI during task and inter-practice rest periods. The similarity between two matrices is calculated as the r-to-z transformed correlation between the two MVCS. Resulting Z scores are compared between stimulation groups. (B) The similarity index, reflecting the persistence of brain patterns from task practice into inter-practice rest periods, was lower in the active (cTBS and iTBS, n = 24 each) groups as compared to the control (n = 21) stimulation in the caudate nucleus. (C) A similar effect was trending for the hippocampus (p = 0.07), but not for (D) the thalamus. Colored circles represent individual data, jittered in arbitrary distances on the x-axis within the respective violin plot to increase perceptibility. Black horizontal lines represent means and white circles represent medians. The shape of the violin plots depicts the distribution of the data and grey vertical lines represent quartiles. ROI masks are depicted on a T1-weighted template image. cTBS: continuous theta-burst stimulation, iTBS: intermittent theta-burst stimulation.

stimulation conditions in the hippocampus (Table 2 and Supplemental Table S8; Fig. 5B). Specifically, higher hippocampal activity during inter-practice rest blocks (i.e., more negative beta weights) was related to higher micro-offline gains in performance in the control group and lower gains in the active stimulation groups. These findings suggest that active stimulation modulated the relationship between brain and behavioral markers of the micro-offline memory consolidation process. Second, we tested whether pattern persistence metrics were related to the amplitude of the micro-offline gains in performance. Results did not reveal any significant group effect or active vs. control stimulation effect in any of the ROIs (group comparison: caudate nucleus: $\chi^2 = 2.49$, $p = 0.288$; hippocampus: $\chi^2 = 0.18$, $p = 0.913$; thalamus: $\chi^2 = 2.21$, $p = 0.33$; active vs. control stimulation: caudate nucleus: $\chi^2 = 0.004$, $p = 0.948$, Fig. 5C left panel; hippocampus: $\chi^2 = 0.02$, $p = 0.88$, Fig. 5C right panel; thalamus: $\chi^2 = 0.3$, $p = 0.583$; see Supplemental Table S5 for group pair comparisons).

Altogether, the brain imaging results indicate that active prefrontal - as compared to control - stimulation disrupted (1) brain responses reflecting motor memory reactivation during the micro-offline episodes and (2) the link between the brain and behavioral markers of the micro-offline motor memory consolidation process.

4. Discussion

We investigated whether stimulation targeting hippocampal and striatal networks via the prefrontal cortex prior to initial motor sequence learning altered consolidation at the micro timescale. Our results indicated that stimulation disrupted both the behavioral and neural markers

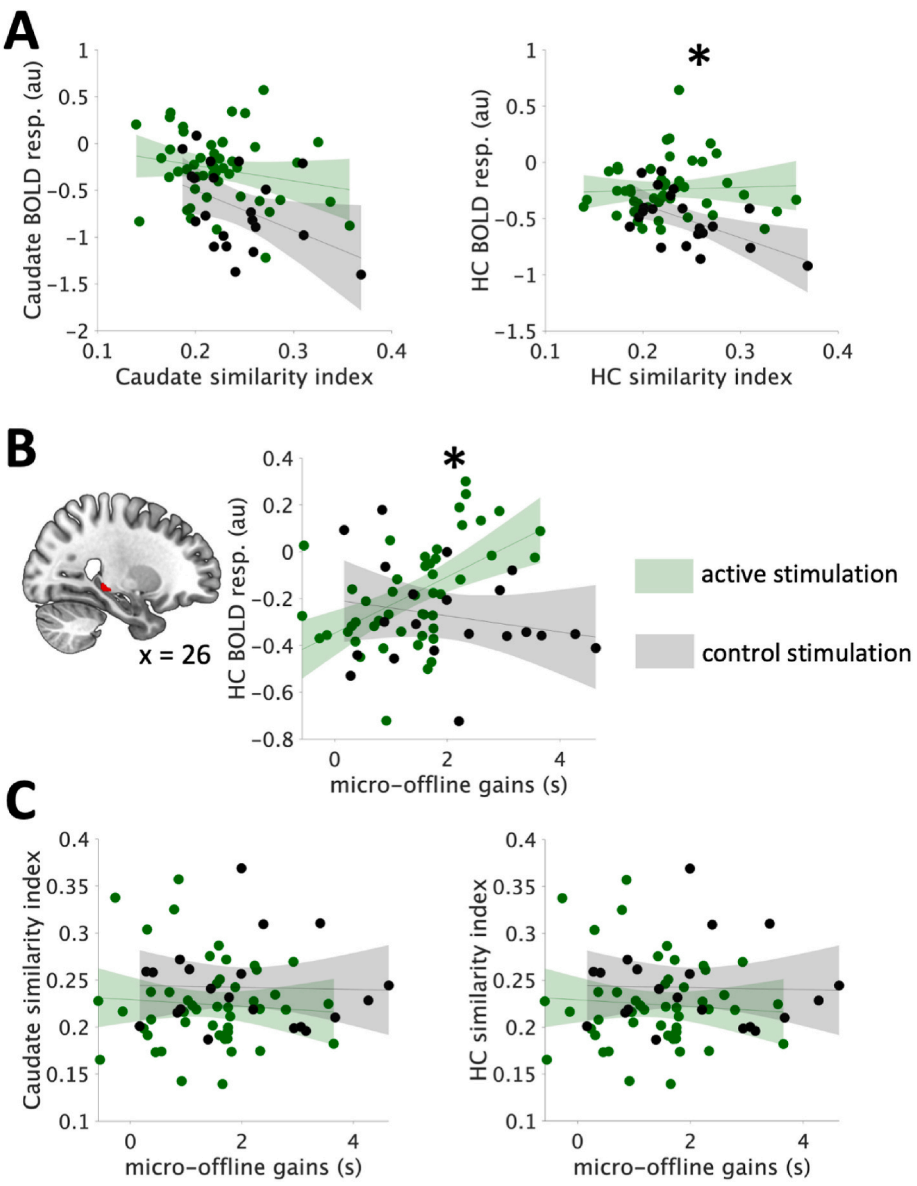

Fig. 5. (A) Left panel. Active (cTBS and iTBS, n = 24 each) vs. control (n = 21) stimulation group differences in the relationship between task-related BOLD responses (beta values extracted from the caudate coordinate reported in Table 1) and similarity of caudate patterns between task and inter-practice rest during MSL training. There was no significant difference between active and control stimulation conditions in the relationship between caudate activity during inter-practice rest intervals and the persistence of task pattern into rest in the caudate nucleus. Right panel. A significant group effect was observed in the hippocampus such that higher hippocampal activity during inter-practice rest intervals (i.e., more negative beta values) was related to higher persistence (reflected by higher similarity index) of brain patterns from task practice into rest epochs in the control group compared to the active stimulation groups (B) Regression analysis showing active vs. control stimulation group difference in the relationship between task-related responses in the hippocampus and micro-offline gains in performance speed during MSL training. Higher hippocampal activity during inter-practice rest intervals (i.e., more negative beta values) was related to greater micro-offline gains in performance in the control group and lower gains in the active stimulation groups. Regression maps are displayed in the ROIs on a T1-weighted template image at a threshold of $p < 0.005$, uncorrected. (C) The relationship between pattern persistence metrics (similarity index) and the amplitude of the micro-offline gains in performance did not differ between active and control stimulation groups in either the caudate (left panel) or the hippocampus (right panel). In all panels, circles represent individual data, solid lines represent linear regression fits, shaded areas depict 95% prediction intervals of the linear function. HC: Hippocampus, resp.: response, au: arbitrary unit. Asterisks (*) indicate a significant active vs. control stimulation group effect.

Table 2
Functional imaging results of the regression analyses between task-related activity maps (main effect of practice) and the sum of micro-offline gains during initial MSL.

Area	x	y	z	k	Z	p_{FWEsvc}
1. Main effect of group (F test)						
No significant responses						
2. Active vs control stimulation (*t* tests)						
[control-active]						
No significant responses						
[active-control]						
Hippocampus	26	-30	-6	16	3.07	0.023*

Asterisk (*) indicates significance at $p < 0.05$ after Holm-Bonferroni correction for multiple comparison. See Supplemental Table S7 for pairwise group comparisons.

of the fast consolidation process. Specifically, active stimulation resulted in a decrease in micro-offline gains in performance observed over the short inter-practice rest intervals during learning. At the brain level, stimulation disrupted activity in the caudate nucleus and the hippocampus during these micro-offline intervals. Additionally, multivariate pattern persistence from task into inter-practice rest episodes - which is thought to reflect the reactivation of learning-related patterns - was hindered by active prefrontal stimulation in the hippocampus and the caudate nucleus. Importantly, our results also show that stimulation altered the link between the behavioral and brain markers of the micro-offline consolidation process.

Earlier research has consistently shown that motor memory consolidation can occur at a fast timescale during the short micro-offline rest intervals interspersed with task practice [6–9,36]. These studies have collectively demonstrated that overall performance improvement during initial motor sequence learning is primarily driven by micro-offline gains occurring across inter-practice rest intervals, as limited performance improvements are observed during online task practice. Even though there are differences in motor learning paradigms (e.g., 5 vs. 8 elements, unimanual vs. bimanual) that prevent us from directly comparing the magnitude of the observed micro-offline gains in performance to previous literature, our behavioral data confirm these previous findings. Importantly, our analyses also showed that active stimulation modulated these micro timescale consolidation processes. Specifically, DLPFC stimulation altered the balance between micro-online and -offline gains in performance such that online and

offline learning were respectively enhanced and disrupted as compared to control stimulation. Together with the neuroimaging results demonstrating a disruption of the brain responses associated to micro-offline processes, we speculate that greater micro-online gains in performance under stimulation might compensate for the disruption of the micro-offline processes. These compensatory processes might ultimately result in similar overall performance between the active stimulation and control groups. It could be assumed that such online compensatory processes are supported by greater brain activations during task practice as compared to rest in the stimulated groups. Our data do not support this view but it is worth noting that the current design does not allow to fully disentangle brain activity patterns between online and offline periods (see limitations below). Further research is therefore warranted to characterize potential neural processes compensating for the deleterious effect of brain stimulation on micro-offline consolidation.

Recent research has associated hippocampal responses during inter-practice rest intervals to micro-offline consolidation [8,9]. Our brain imaging data analyzed with both univariate and multivariate approaches are collectively in line with these earlier observations but also suggest that active DLPFC stimulation disrupted hippocampal responses during inter-practice rest. Interestingly, similar results were observed in the caudate nucleus, a brain region which, together with the hippocampus, is part of an associative network connected to the prefrontal cortex and recruited early during training [3]. Additionally, our data indicated that stimulation altered the relationship between hippocampal activity during these inter-practice rest periods (as compared to task) and micro-offline gains in performance such that greater hippocampal activity during rest was related to higher and lower micro-offline gains in the control group and active stimulation groups, respectively. The brain-behavior relationship observed in the control group is in line with previous findings showing a positive correlation between hippocampal BOLD responses during rest and the amplitude of micro-offline gains in performance during early learning [8]. Interestingly, our data show that stimulation modulated the relationship between rest-related hippocampal activity and micro-offline gains in performance.

The multivariate analyses showed that active prefrontal stimulation disrupted the persistence of task patterns into inter-practice rest periods in the caudate nucleus and, to a lesser extent, the hippocampus. As persistence of task patterns into subsequent rest is thought to reflect memory reactivation [10,31], these data suggest that hippocampal and caudate reactivations occur during the micro-offline motor memory consolidation episode. While it cannot be ruled out that these persistence patterns are associated to mental rehearsal/imagery, we suggest that they rather reflect spontaneous reactivations of task patterns as previous MEG research has reported time-compressed hippocampal replays during these intervals [9]. Interestingly, such hippocampal and striatal reactivations have also been observed at the macro timescale, i.e., a few minutes after the end of initial motor learning [10]. It, however, remains unclear whether the same neural mechanisms underly reactivation processes over longer time scales, such as reconsolidation processes over several days following initial motor learning [38,39] and how these effects relate to processes at the micro-time scale. Nevertheless, our data suggest that micro-offline reactivation is supported by similar neural mechanisms as during macro-offline episodes (i.e., reactivation of task patterns). Importantly, our data also show that prefrontal stimulation hindered the reactivation process in these deep brain regions that are critical for learning. Additionally, our findings not only provide evidence for a link between brain activity during rest and pattern persistence but also indicate that this relationship was disrupted by the stimulation. Specifically, higher hippocampal pattern persistence was related to greater hippocampal BOLD signal during inter-practice rest in controls more than in the stimulated groups. Altogether, the results of the multivariate analyses suggest that (1) task-related hippocampal and caudate patterns are reactivated during the micro-offline episodes, (2) the amplitude of the BOLD signal in the hippocampus during inter-practice rest periods reflects hippocampal reactivation, and (3) active prefrontal stimulation disrupted these processes.

Unexpectedly, our analyses did not show a differential effect of iTBS vs. cTBS on brain responses. One might argue that the effect of continuous and intermittent TBS on the DLPFC are less dichotomic (i.e., inhibition vs. facilitation) than those observed on M1 [22]. However, evidence from earlier TMS-EEG studies does not support such view. Despite high inter-subject variability [37], plasticity processes in the DLPFC - as measured with electrophysiological responses - are described to be affected by TBS in a similar manner as in M1 [40,41]. It therefore remains unclear why the different stimulation conditions yielded similar results. It is possible that the different stimulation types show less dichotomic effects as a function of time (interval between stimulation and task was approximately 22min, ranging from 16 to 25min). This remains however speculative and additional research is warranted to better characterize the specific effect of different frontal TBS protocols on brain functioning.

5. Limitations

One limitation of the univariate analyses of the present MRI data is that they don't allow to disentangle the contribution of task vs. inter-practice rest to the pattern of observed results. Accordingly, it cannot be ruled out that the stimulation-induced decrease in sub-cortical activity during inter-practice rest episodes might be - at least in part - related to increased activation during task practice. We based our interpretations above in light of the results of the multivariate analyses and of previous literature relating hippocampal processing during rest periods to micro-offline processes [8,9].

As mentioned above, another limitation is that the task design prevents from directly comparing the present results to the previous literature. Also note that based on the length of the sequence in the current study (8-element), we elected to use a transition-level measure as outcome variable to better reflect micro-time scale processes as a sequence-level measure (as done in previous research with 5-element sequences [6]) introduced additional confounds in case of errors (see Methods). We acknowledge that the use of a transition-level measure presents the limitation of inhomogeneities in the distribution of the transitions included in the computation of the micro-online and -offline gains in case of errors. However, we argue that this limitation is unlikely to influence group comparisons as transition distribution did not differ between groups (see Supplemental Table S2). Nevertheless, we acknowledge that the results of the analyses related to micro-time scale processes are moderate in strength and should therefore be interpreted with caution. Further studies will be necessary to confirm the above described pattern of results.

6. Conclusions

In the present study, we employed cortical stimulation to target deep brain regions in order to modulate motor memory consolidation at the micro timescale. Altogether, our results indicated that stimulation hindered the micro-offline consolidation process. Specifically, we showed that prefrontal stimulation disrupted both the behavioral and brain markers of this fast plasticity processes as well as their relationship. This study provides the first evidence, to the best of our knowledge, that non-invasive-brain-stimulation of the prefrontal cortex can modulate fast motor memory consolidation through the modulation of reactivations in the hippocampus and the striatum during micro-offline episodes.

Data Availability

Source data corresponding to figures and tables in this manuscript, as well as raw behevioral and MEP data and the corresponding analysis scripts are publicly available on Zenodo at the following link: https://zenodo.org/record/8233882.

CRediT authorship contribution statement

Mareike A. Gann: Conceptualization, Resources, Data curation, Software, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Nina Dolfen:** Investigation, Methodology, Writing – review & editing. **Bradley R. King:** Conceptualization, Resources, Data curation, Software, Formal analysis, Validation, Writing – review & editing. **Edwin M. Robertson:** Conceptualization, Writing – review & editing. **Geneviève Albouy:** Conceptualization, Resources, Data curation, Software, Formal analysis, Supervision, Funding acquisition, Validation, Investigation, Writing – original draft, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.08.022.

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