Published in final edited form as:

Cortex. 2017 December ; 97: 70–80. doi:10.1016/j.cortex.2017.10.001.

Motor cortex inhibition by TMS reduces cognitive non-motor procedural learning when immediate incentives are present

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Abstract

Inhibitory repetitive transcranial magnetic stimulation (rTMS) of the primary motor area (M1) impairs motor sequence-learning, but not basic motor function. It is unknown if this is specific for motor forms of procedural learning or a more general effect. To investigate, we tested the effect of M1-inhibition on the Weather Prediction Task, a learning task with minimal motor learning component. In the WPT, participants learn arbitrary, probabilistic, associations between sets of meaningless cues and fictional outcomes. In the standard “Feedback” (FB) condition, they receive monetary rewards/punishments during learning. In the “Paired associate” (PA) condition they learn the same information by passive observation of associations. The observational and feedback learning conditions we used were matched for their non-learning-specific motor demands.

In each of two FB or PA sessions, we delivered Real (inhibitory) or Sham continuous theta-burst (cTBS) to the left-M1, before 150 training-trials. We then tested learning with 42 trials without feedback immediately after learning and again 1-hour after cTBS. Compared to Sham, Real cTBS reduced performance during FB-learning, when learning was immediately reinforced, but not when knowledge was tested after PA learning. Furthermore, when FB memory was tested after learning without immediate incentive, there was no effect of TMS compared to post-PA test performance, showing the TMS effect operated only in the presence of incentive and feedback. We conclude that M1 is a node in a network underlying feedback-driven procedural learning and inhibitory rTMS there results in decreased network efficiency.

Keywords

Continuous theta burst stimulation; motor cortex; feedback; probabilistic classification learning and weather prediction task

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1. Introduction

Procedural (incidental/implicit/unconscious/) motor skill learning, such as occurs when people learn a sequence of button presses via repeated practice, is distinct from declarative (intentional/explicit/conscious) learning, which is involved in, for instance, memorizing a shopping list. An abundance of evidence shows these memory systems rely on different brain networks. Patients with medial temporal lobe (MTL) damage are impaired at declarative learning whereas their procedural learning remains intact (Nissen, Willingham, & Hartman, 1989; Reber & Squire, 1994, 1998). Patients with basal ganglia (BG) dysfunction, as in Parkinson disease (PD) (Pascual-Leone et al., 1993) and Huntington disease (HD) (Willingham & Koroshetz, 1993) show the opposite pattern, with impaired procedural motor learning and intact declarative memory. This double dissociation shows that the declarative and procedural systems depend on networks centered in the MTL and BG, respectively. The BG participate in functional loops with cortical regions implicated in learning (Alexander, Delong, & Strick, 1986; Rodriguez-Oroz et al., 2009) including the motor, limbic, and associative loops. Imaging and neurophysiological studies (Kantak, Sullivan, Fisher, Knowlton, & Winstein, 2010; Karni et al., 1995; Matsuzaka, Picard, & Strick, 2007) and evidence from inhibitory repetitive transcranial magnetic stimulation (rTMS) studies (Hadipour-Niktarash, Lee, Desmond, & Shadmehr, 2007; Muellbacher et al., 2002; Robertson, Press, & Pascual-Leone, 2005; Rosenthal, Roche-Kelly, Husain, & Kennard, 2009; Steel et al., 2016; Wilkinson et al., 2015; Wilkinson, Teo, Obeso, Rothwell, & Jahanshahi, 2010) show that the primary motor area (M1) is an important cortical node in the procedural motor learning network.

Inhibitory rTMS delivered to M1 during various phases of learning has implicated M1 in the acquisition, consolidation, and retention of visuo-motor knowledge (Hadipour-Niktarash et al., 2007; Muellbacher et al., 2002; Robertson et al., 2005; Rosenthal et al., 2009; Steel et al., 2016; Wilkinson et al., 2015; Wilkinson et al., 2010). In an fMRI study of visuo-motor skill learning before and after inhibitory rTMS delivered to M1, (Steel et al., 2016) we found that inhibition does not affect learning by taking M1 “offline” or creating the functional equivalent of a local, “virtual lesion.” Rather, it redistributes task-related connectivity between two learning networks less efficiently.

M1 is selectively activated during motor procedural learning and may contribute to it as part of a more general implicit learning network. Activation of M1 and the BG is also seen during probabilistic classification learning with the Weather Prediction Task (WPT; Knowlton, Squire, & Gluck, 1994), a non-motor form of procedural learning (Aron et al., 2004). In the WPT, participants learn arbitrary, probabilistic associations between meaningless stimuli and fictional outcomes. In the standard, feedback, (FB) version, they are given no information *a priori*, but receive corrective feedback after each choice. The role of feedback in WPT learning has been explored by implementing another version of the task, extensively controlled for other variables. In the “paired associate” (PA) version, designed to rely on declarative memory without feedback, participants learn the same information through passive observation and declarative memory (Poldrack et al., 2001). PD (Shohamy et al., 2004) and HD (Holl, Wilkinson, Tabrizi, Painold, & Jahanshahi, 2012) patients are

impaired on the FB, but not PA version, showing involvement of the BG-cortical reinforcement learning circuits in feedback-guided learning on this task too.

This matched pairing of tasks has also been widely used in functional imaging studies. During FB WPT learning, activity increases in the dorsolateral prefrontal cortex (DLPFC), M1, premotor cortex, caudate nucleus, and putamen, while decreasing in the MTL. In contrast, under PA conditions, where learning depends on declarative memory, MTL activity increases (Aron et al., 2004; Poldrack et al., 2001). Moreover, in a previous study by one of us, we showed that FB, but not PA, learning is associated with increased dopamine release in the ventral striatum (Wilkinson et al., 2014).

There is also some direct evidence for M1 activation during non-motor learning. Aron et al. (2004) found activation of the left M1, putamen and premotor cortex, along with the dopaminergic system during presentation of stimuli associated with rewarding feedback on the FB WPT. This suggests that M1 is a part of a network that codes or acts on prediction error in non-motor, as well as motor, learning tasks. As Aron et al. noted, their task needed a right-hand button press during stimulus presentation, so it was impossible to rule out this motor response as the explanation for left M1 activation in their study. However, it is relevant that Aron et al. found no M1, premotor, or putamen activation in a condition with the same motor demand, except that it used punishing, instead of rewarding, feedback. M1 is functionally linked to regions of the BG associated with feedback-based learning and reward and its potential involvement in motor learning, independent of movement, raises the possibility that its role in learning extends beyond coding learned motor behavior. However, this question has not been investigated. To look for involvement of M1 in non-motor procedural learning, we combined inhibitory rTMS of M1 with the WPT. We hypothesized that inhibition of M1, a node in the implicit learning network, would affect FB, relative to PA, learning.

During learning trials on the FB-based WPT, participants respond with a mouse click or key press and learning is measured by the proportion of correct responses. In the PA condition, by contrast, training is by passive observation and no measure of learning is available until after training, when learning is tested. In a previous study (Wilkinson et al., 2014) we incorporated the requirement for a mouse click on each PA training-trial in order to match the FB and PA conditions for motor demands. Here, we used the same technique.

PA and FB-based WPT learning have been compared using a variety of approaches. For instance, after several blocks of FB or PA learning, investigators (e.g., Shohamy et al., 2004), compared the last 50 FB-learning trials with performance on a test immediately after PA learning. Others (Holl et al., 2012) compared learning on the PA and FB tasks with identical, no-feedback, test blocks administered after learning under both conditions. Here, we used both approaches. Happily, this allowed us to compare the effect of M1 cTBS on learning *with* immediate incentive during the last block of the FB task, against performance on an FB test *without* immediate incentive. This approach produced some interesting and unexpected findings.

It remains an open question whether the substrata of the effects of inhibitory rTMS on learning and the motor evoked potential (MEP) are the same, or whether the MEP can serve as a biomarker of that effect. In our previous work (Wilkinson et al., 2015), we found no discernable relationship between the degree of MEP amplitude reduction and the negative effect on motor learning overall, despite the presence of a significant positive relationship between MEP reduction and learning in the presence of money reward. In this study, we again included an exploratory analysis of the effect of cTBS on the MEP from TMS.

2. Material and Methods

2.1. Participants

We recruited, 40 right-handed, healthy volunteers, all of whom met safety criteria for TMS (Keel, Smith, & Wassermann, 2001) and were free of central nervous system illness and sedating medications. We estimated intelligence with the National Adult Reading Test (NART). The study was approved by the Combined Neuroscience Institutional Review Board at the National Institutes of Health. Participants gave written consent and were paid for their participation in the study in addition to their winnings in the FB condition. Participants were randomly assigned to one of two treatment groups Real cTBS ($n = 20$, 9 women) aged 18–43 years ($M = 26.90$, $SD = 6.8$) and Sham cTBS ($n = 20$, 11 women) aged 21–51 years ($M = 26.49$, $SD = 8.1$).

2.2. Procedure

WPT: In the WPT, participants are required to predict a binary outcome; i.e., whether the weather will be rainy or fine, based on an arrangement of four cards with different patterns. Each of the cards is independently associated with the two outcomes. Participants in the Sham and Real groups completed the WPT under FB and PA conditions in separate sessions at least one week apart. The order of conditions was randomized and counterbalanced across treatment groups and participants (see Fig. 1a for experimental design). Participants performed the WPT immediately after real or sham stimulation, immediately after which they completed a WPT test (Test 1) of 42 trials without feedback. Then, 60 min after rTMS (approximately 43 min after WPT completion), participants performed a second WPT test (Test 2) also consisting of 42 trials without feedback (See Fig. 1b for timeline of the experimental session).

Stimuli were presented on a laptop computer with 19×26 cm color screen. The stimuli were one-, two-, or three-card combinations of four tarot cards, each with a different geometric pattern (i.e., triangles, circles, diamonds, and squares) in black against a white background (Fig. 2a). The position of the cards on the screen was held constant within, but counterbalanced across, participants. There were 14 possible arrangements, which occurred with equal frequency. Each arrangement was associated with one of two outcomes: “rainy” or “fine.” Each card was also independently associated with one outcome with a fixed probability. For example, the probability of rainy was 0.2 for squares, 0.4 for diamonds, 0.6 for circles, and 0.8 for triangles. The probabilities assigned to each card were counterbalanced and the probability of an outcome on a trial was based on the joint probabilities of the cards present (Table 1). Overall, participants saw identical arrangement

frequencies (order randomized for each participant), but the actual outcomes differed slightly across participants. Because each participant performed the WPT under two conditions, parallel versions of the task were employed with different types of cards and different binary outcomes (rainy and fine or cold and hot). In addition to the set of cards with triangles, circles, diamonds, and squares, three additional sets of cards were used, with 25% of participants in each group being trained on each set per condition, and with the constraint that participants were trained on a different set of cards in each condition.

2.2.1. WPT-FB condition—Participants were initially trained on two blocks of 75 trials. On each trial, participants were presented with an arrangement of cards and asked to predict the weather. After a participant responded by pointing with a mouse and clicking with the right index finger, the trial ended with feedback appearing on the screen: thumbs up and an increment of 1 dollar to money earned for a correct response, or thumbs down and a decrement of 1 dollar for an incorrect response (Fig. 2b). The next card arrangement appeared after 5 secs.

Participants were then tested with 42 trials without feedback (Test 1). Then, 60 min after stimulation, participants performed a test with 42 trials without feedback (Test 2).

2.2.2. WPT-PA condition—As in the FB condition, the training phase comprised two blocks of 75 trials. On each trial, participants were presented with an arrangement of cards, but were simultaneously shown the outcome for that arrangement. The relationship between cards and outcomes was the same as that employed during the FB condition. However, in the PA condition, no weather prediction was required. Each card arrangement appeared five secs after initial presentation of the previous one. During this time, participants were required to press a response button with their right index finger to show that they had seen the card arrangement/outcome, but this response did not influence the timing of stimulus presentation, which was fixed. Button responses were included in this condition to match the FB and PA learning tasks for motoric demand. The Test 1 and Test 2 phases were identical to those in the FB condition.

2.3. TMS

TMS was delivered with a Magstim Rapid® stimulator (Magstim Co., Dyfed, UK) connected to a figure-of-eight coil with an internal wing diameter of 70 mm, which was held tangentially to the scalp at an angle of approximately 45 degrees from the midline (Di Lazzaro et al., 1998). The electromyogram (EMG) was recorded with a belly-tendon montage from the right first dorsal interosseous (FDI) muscle.

After finding the scalp location where stimulation evoked the largest MEP from the right FDI, we determined the resting motor threshold (RMT), defined as the lowest stimulation intensity that evoked at least five MEPs $\geq 50 \mu\text{V}$ on 10 consecutive trials. We then measured the active motor threshold (AMT), defined as the minimum stimulus intensity to produce a MEP of $200 \mu\text{V}$ on five of 10 trials voluntary contraction of the right FDI at approximately 10% of maximum voluntary contraction. Effort was kept constant across participants and over time by monitoring the rectified EMG. We used MRI-guided TMS neuro navigation (Brain sight, Rogue Research Inc., Montreal, Canada) to record the optimal scalp location

for activating the FDI and this was used as the target for cTBS. cTBS was delivered according to the protocol of Huang, Edwards, Rounis, Bhatia, and Rothwell (2005). Fifty Hz bursts of three pulses were delivered every 200 msec at 80% of the AMT. The stimulation lasted 40 secs, thereby delivering 600 pulses over 200 bursts. For sham stimulation, we used a placebo coil, which was identical to the real coil in appearance, operation, and acoustic artifact but did not reproduce the physiological effect of TMS. Participants, but not experimenters, were blind to the stimulation condition.

The inhibitory effect of cTBS on the MEP lasts up to 60 min (Huang et al., 2005). As a check on the duration of the effect and an exploratory search for correlations between the MEP and learning effects, we tested MEP amplitude immediately before and after cTBS, after WPT completion (17 min after cTBS), and 45 min after cTBS. To measure MEP amplitude, we delivered 20 single pulses with an interstimulus interval of 6 secs and an intensity of 120% of the RMT (see Figure 1b). If that failed to produce MEPs ≥ 1 mV at baseline measurement before cTBS, we used the minimum intensity that produced consistent MEPs ≥ 1 mV in that individual at the baseline measurement. A 1mV test response was impossible to maintain in some participants (see Results: 3.6. Neurophysiological data).

2.4. Data analysis

Mean money earned (MME) during learning was directly related to the proportion of correct responses, and we used it as our primary measure in the FB-learning analysis (Results 3.5 & Fig. 4). Typically, the FB WPT includes 150 trials in three blocks of 50 trials and the time course of learning is measured across the early (block 1), middle (block 2), and late (block 3) blocks. Because of the time constraint imposed by the potential decay of the cTBS effect, we included two blocks of 75 trials. Nevertheless, in the feedback condition, we still wished to measure the time course of the effect of cTBS between the Real and Sham cTBS groups. Therefore, we used statistical comparison to chance to determine the onset of learning and the point at which it stabilized. To do this, we calculated the mean proportion correct (MPC) for each participant across the first 50 trials of the FB condition. It took 40 trials on average for learning to stabilize above chance (50%) in both the Real and Sham groups, so we divided the FB-learning data into early (trials 1–40), middle (trials 41–90) and late (trials 91–150) phases.

As mentioned above, in the PA condition, learning is via observation, so no behavioural data were available until participants were tested after learning. Because there was no money to be won during the tests after PA and FB-learning, we used MPC for the comparisons of overall FB-learning with: PA test data (Results 3.2. & Figs. 3b & c), FB test data (Results 3.4. & Figs. 3d & e) and between the PA and FB test data (Results 3.2. & Fig. 3a).

Responses given after more than 5 secs were scored as incorrect. To see if cTBS affected motor responses we also measured the latencies of button responses during FB-learning in the Real and Sham cTBS groups (Table 2). The latencies of button clicks during PA learning were not relevant to learning, and were only included to match the non-learning-related motor demands of each task. Data were collapsed across outcome conditions and card sets.

FB tests without immediate incentive compared to PA tests (Results 3.2., & Fig. 3a): To examine the effects of TMS and task on FB and PA test performance (both without immediate incentive) we performed a mixed ANOVA on MPC during test with test Time, (1 vs. 2, 2 levels) and Task (PA vs. FB, 2 levels) as within participant's variables and cTBS group (Real vs. Sham, 2 levels) as a between groups variable.

Overall learning with immediate incentive and overall PA test (Results 3.3., Fig. 3b & c): To compare overall performance on the FB-learning blocks to PA tests 1 and 2 in the two cTBS groups, we calculated MPC on the last 42 trials of FB-learning and compared this with MPC on PA tests 1 and 2 (42 trials each). This is a similar approach to that used previously by others (e.g., Shohamy et al., 2004) who compared performance on 42 PA test trials to the last 50 trials of FB-learning.

Here, recall FB-learning was measured at a single time point; while, PA test performance was measured at two. Therefore, and because we found no significant effect of Time in either cTBS group on PA test performance (see Section 1.3.2), we collapsed PA test performance across time so we could compare it specifically to FB-learning (during FB blocks, not test). Then we could perform a mixed ANOVA on MPC during either FB-learning or PA test with Task (PA vs. FB, 2 levels) as a within-participants' variable and cTBS group (Real vs. Sham, 2 levels) as a between-groups variable.

Early, middle, and late stage FB based learning with immediate incentive: MME (Results 3.5., Fig. 4): To investigate the effects of TMS on MME during FB-based WPT learning, we performed a mixed ANOVA on MME with Time (early vs. mid vs. late, 3 levels) as a within-participants variable and cTBS group (2 levels) as a between groups variable.

Neurophysiological data: MEP amplitudes were log-transformed for analysis (Wassermann, 2002) to correct for the skewing effect of inhibition on their distribution. In an exploratory analysis of the relationship of the effects of TMS, PA and FB-learning, and Time on the effect of cTBS on cortical excitability, we performed a mixed ANOVA on mean log transformed MEPs with MEP test Time, (baseline, immediately after cTBS/ post 1, immediately after learning/ post 2, 45 min after cTBS/ post 3, 4 levels) and Task (PA vs. FB, 2 levels) as within-participants' variables and cTBS group (Real vs. Sham, 2 levels). Eleven participants had missing data for one or more MEP measurements (Sham, $n = 3$; Real, $n = 8$) and were, therefore, excluded.

We used a significance criterion of $p = .05$. All comparisons were two-tailed apart from four comparisons in the behavioral data and one correlation in the neurophysiological data (see below). The Bonferroni correction was used to adjust the significance level for multiple comparisons. If there was a violation of the sphericity assumption, Pillai's multivariate test of significance was employed (Λ). Thus, if the Greenhouse-Geisser was less than 1.0, Pillai's exact F is reported.

3. Results

3.1. Participants

The Sham and Real cTBS TMS groups did not differ in age, sex, estimated IQ, years of education, time between sessions, time to complete tasks, mean total money won during FB-learning, and mean overall button response time across feedback learning for the two cTBS groups (Table 2). Five participants were excluded from the learning analysis because they too many missed responses at test (> 2.5 SD 's above the group mean: FB Test 1 or 2; Sham = 1, Real = 1 or PA Test 1 or 2; Sham = 2, Real = 1). Therefore, in the following analyses of FB-learning and FB and PA tests 1 and 2, (see sections 1.3.2. to 1.3.5.) we included 17 participants in the Sham group and 18 in the Real group.

3.2. FB-learning tested without immediate incentive compared to PA tests (Fig. 3a)

There was no effect of cTBS on PA or FB test performance when the FB and PA tests (all without feedback). The main effect of test Time ($F_{(1,33)} = 3.63$, $p = .07$), interaction between test Time x cTBS ($F_{(1,33)} = 1.57$, $p = .22$), the main effects of cTBS, Task, and the interactions between test Time x cTBS, Task x cTBS x test Time (all F 's < 1 , all p 's $> .05$) were not significant. As none of the main effects and interactions were significant, no further post hoc testing was justified.

3.3. Overall learning with immediate incentive and overall PA test (Figs. 3b & c)

Across cTBS groups, there was significantly better learning when participants received immediate incentive, i.e., in the FB-learning phase ($M = .72$, $SD = .1$), vs. PA learning ($M = .66$, $SD = .1$), shown by a significant main effect of Task, ($F_{(1,33)} = 11.70$, $p = .002$, Cohen's $d = 1.19$). However, the cTBS groups also differed significantly on MPC across PA and FB conditions with a significant interaction of Task x cTBS, ($F_{(1,33)} = 4.05$, $p = .05$, Cohen's $d = .70$). The main effect of cTBS was non-significant ($F_{(1,33)} = 1.71$, $p = .20$). Considering the significant Task x cTBS interaction, we compared MPC between cTBS groups and learning conditions.

First, to obtain an estimate of how much participants benefitted from FB, compared to PA learning, we calculated a Feedback difference score by taking, for each participant, the mean MPC during the last 42 trials of the FB-learning phase and subtracting from that the mean PA test score. Therefore, if the mean Feedback difference score was significantly greater than zero, this was evidence that FB was superior to PA learning (see Fig. 3c). Then, we compared the Feedback difference score for each FB and PA conditions and between cTBS groups with three, one-sample or independent t -tests. Bonferroni correction led to a significance criterion of $p = .05/3 = .02$. Furthermore, as we predicted that FB-learning would be impaired relative to PA learning by real cTBS, we used a one-tailed approach to the following comparisons where relevant. At the within-participants' level, in the Sham group, the FB difference score was significantly greater than zero ($M = .10$, $SD = .1$; $t_{(16)} = 4.05$, $p = .0005$, one-tailed, Cohen's $d = 1$) showing that FB-learning was superior to PA in that group; while in the Real group that was not the case ($M = .03$, $SD = .1$; $t_{(17)} = .96$, $p = .35$). Moreover, at the between-groups level, the FB difference score in the Sham group was

also significantly better than that of the Real group ($t_{(33)} = 2.02$, $p = .025$, one-tailed, Cohen's $d = .68$).

3.4. Overall learning with immediate incentive and overall FB test (Figs. 3d & e)

How did overall learning with feedback compare to overall FB test performance (without immediate incentive)? To address this question, we ran an identical analysis to that seen in section 3.3 but this time comparing FB-learning to FB test. As we predicted FB-learning would be impaired relative to Sham following M1 inhibition, we used a one-tailed approach to the following comparisons where relevant. At the within participants' level, interestingly, in the Sham group, the FB difference score was significantly greater than zero ($M = .09$, $SD = .2$; $t_{(16)} = 2.31$, $p = .0018$, one-tailed, Cohen's $d = .45$) showing that FB-learning was superior to FB test in that group, while in the Real group that was not true ($M = .02$, $SD = .1$; $t_{(17)} = .78$, $p = .45$). At the between groups level, in this instance, the mean Feedback difference scores did not reach significance ($t_{(33)} = 1.37$, $p = .09$, one-tailed).

3.5. Early, middle, and late stage FB-learning with immediate incentive: MME (Fig. 4)

Across cTBS groups, there was a significant increase in MME from early ($M = \$5.79$, $SD = \$5.7$) to mid ($M = \8.45, $SD = \$5.5$) to late ($M = \13.41, $SD = \$6.7$) phase learning, reflected by a significant main effect of Time, ($F_{(2,66)} = 22.63$, $p < .0005$, Cohen's $d = 1.66$). However, importantly, the groups also differed on money earned during FB-learning across time, with a significant interaction of Time x cTBS, ($F_{(2,66)} = 3.31$, $p = .04$, Cohen's $d = .63$). The main effect of cTBS was not significant ($F_{(1,33)} = 1.03$, $p = .32$). Because of the significant Time x cTBS interaction, we compared MME between groups and across time with fifteen independent or paired samples t -tests. Bonferroni correction lead to a significance criterion of $p = .05/15 = .003$.

At the within-participants' level, in the Sham group, MME increased significantly from early ($M = \$6.14$, $SD = 5.4$) to late ($M = \$15.89$, $SD = 4.7$; $t_{(16)} = -5.56$, $p < .0005$, Cohen's $d = -1.94$) and mid ($M = \$7.95$, $SD = 4.3$) to late ($t_{(16)} = -5.44$, $p < .0005$, Cohen's $d = -1.75$) learning. However, this was not true for the Real group: (early, $M = \$5.47$, $SD = 6.2$; late, $M = \$8.91$, $SD = 6.6$; $t_{(17)} = -2.82$, $p = .01$) (mid, $M = \$8.91$, $SD = 6.6$; late, $t_{(17)} = -1.49$, $p = .16$). There was no difference between MME during the early relative to mid phase in either group (Sham, $t_{(16)} = -1.25$, $p = .23$; Real, $t_{(17)} = -2.10$, $p = .05$). Thus, cTBS significantly suppressed the improvement of learning across early to late and mid to late FB training. In support of this, at the between groups level, both early ($t_{(33)} = 5.56$, $p < .0005$, Cohen's $d = 1.88$) and middle ($t_{(33)} = 3.59$, $p = .001$, Cohen's $d = 1.21$) learning in the Real group were significantly worse than late learning in the Sham group.

There were no differences in MME between: late learning in the Sham and Real groups ($t_{(28,9)} = 2.29$, $p = .03$), early learning in the Sham and Real groups ($t_{(33)} = -2.23$, $p = .03$), middle learning in the Sham group and later learning in the Real group ($t_{(27,6)} = -1.52$, $p = .14$), early learning in the Sham group and mid learning in the Real group ($t_{(33)} = -1.36$, $p = .18$), mid learning in the Sham group and early learning in the Real group ($t_{(33)} = 1.36$, $p = .15$), and both early ($t < 1$, $p > .05$) and middle ($t < 1$, $p > .05$) phase learning, in the Sham and Real groups.

3.6. Neurophysiological data

At the group level, MEPs did not differ significantly across Time, between cTBS groups or across FB and PA conditions (see Table 3 for the means and SDs). The main effect of Time ($\Lambda_{(3,25)} = 1.10, p = .37$), cTBS, Task (all F s $< 1, p$ s $> .05$ and the interactions between, Time x cTBS ($\Lambda_{(3,25)} = 1.41, p = .26$), Task x cTBS, Task x Time, Task x Time x cTBS, (all F s, Λ s $< 1, p$ s $> .05$) were not significant.

However, for the Real group in the FB condition, there was a significant association between MEP reduction immediately after learning and worse FB-learning performance. That is, MEP reduction immediately after learning was associated with less money earned during the early phase of learning ($\rho_{(17)} = .46, p = .03$, one-tailed). No such associations were found for the Sham group in the feedback condition at Test 3, or the other MEP measurement times.

4. Discussion

Basal ganglia-cortical circuits are involved in feedback-based learning on the WPT. The associative loop, including the prefrontal cortex, caudate nucleus (Poldrack et al., 2001) and limbic loop, including the ventral striatum (Wilkinson et al., 2014) are both recruited during FB, but not PA-based, learning. There is also some evidence that the motor loop, including M1, has a role in WPT learning with feedback (Aron et al., 2004). As we and others have shown, inhibitory stimulation over M1 disrupts procedural motor learning; where learning relies on error signaling (Hadipour-Niktarash et al., 2007; Muellbacher et al., 2002; Robertson et al., 2005; Rosenthal et al., 2009; Steel et al., 2016; Wilkinson et al., 2015; Wilkinson et al., 2010). However, these experiments have all used tasks with an important motor learning component. If the motor loop takes part in other forms of learning, inhibition of M1 should affect them as well.

As we hypothesized, real cTBS of M1 affected FB-learning, while there was no such effect on PA learning. In the Sham group, FB-learning produced a significant increase in MME from early to late and from mid to late phases. These effects were absent in the Real group, showing that M1 inhibition significantly suppressed FB-learning. Furthermore, in the Sham group, we found that FB-learning, when tested with ongoing feedback, was significantly greater than PA test performance. This shows that feedback with monetary incentive boosted FB-learning, compared to when the same information was learned via observation. However, in the Real group, there was no benefit of FB-learning relative to PA at any point. These findings also support our hypothesis.

Studies of FB-learning in patients with striatal motor network dysfunction from PD and HD (Holl et al., 2012; Jahanshahi, Wilkinson, Gahir, Dharmina, & Lagnado, 2010; Knowlton, Mangels, & Squire, 1996; Knowlton, Squire, et al., 1996; Shohamy et al., 2004; Wilkinson, Lagnado, Quallo, & Jahanshahi, 2008, Experiment 2; Witt, Nuhsman, & Deuschl, 2002) have found impairments similar to those produced here by M1 inhibition. In an earlier study (Holl et al., 2012) we showed that HD patients were impaired at WPT learning with immediate incentive, as well as in a subsequent test without feedback. By contrast, reduced FB-learning by M1 inhibition appears to depend on the presence of immediate incentives,

i.e., it was not seen *after* FB-learning when knowledge was tested without ongoing feedback (see Results section 1.3.2. & Fig. 3a, FB tests without immediate incentive compared to Sham tests). A key difference between this and earlier studies comparing FB and PA learning is that here we used real money incentives during FB-learning (see discussion below), which boosted the effectiveness of feedback and could explain this difference. Another possibility is that the effect of M1 inhibition on FB-learning was entirely dependent on the presence of feedback during measurement. This suggests that M1 is part of a network with a necessary role in learning under these conditions.

Functional imaging has shown that, during FB-based WPT learning, activity increases in the DLPFC and caudate nucleus, while decreasing in the MTL (Poldrack et al., 2001). In contrast, under PA conditions, where learning depends on declarative memory, MTL activity increases. Our findings support the idea that these two ways of learning the same information recruit different, potentially competitive, brain networks. This likely explains the sparing of PA learning we found. FB-learning, on the other hand, was affected by inhibition of M1, which is consistent with the involvement of M1 and its connections to the basal ganglia in procedural learning, perhaps independently of its basic motor functions.

As mentioned previously, Aron et al. (2004) found left M1 and premotor cortex activation, along with activity in the left dopaminergic midbrain nuclei and the left putamen, during presentation of stimuli associated with rewarding feedback during FB-based WPT learning. As stated above, their task required a right-hand button press during stimulus presentation, making it impossible to exclude this motor response as the cause of left M1 activation. However, they also found no left M1, premotor, or putamen activation in a similar comparison with punishing feedback, also involving a right-hand button press. This would have been expected if the M1 activation seen with reward was related to the motoric component alone.

Here, in the FB condition of the WPT, participants indicated their decisions with right-hand button responses, which could be considered a component of the learning process. However, in our adaptation of the PA condition, the button response indicated merely a request to move on to the next trial, and was included only to match the motoric demand of the FB condition. Even profound M1 inhibition produced by primed 1 Hz rTMS produces no measurable effect on simple measures of movement, such as reaction time (Iyer, Schleper, & Wassermann, 2003). Nevertheless, if there was a subtle effect on movement here, it might have influenced learning selectively in the FB condition. However, we found no evidence for this in the response time data (Table 2). These findings, with those of Aron et al. (2004), show that M1 involvement in FB WPT learning is not due simply to the motoric component of the task.

Anatomical data showing that the prefrontal cortex can influence the motor striatum (Calzavara, Mailly, & Haber, 2007), as well as computational modelling (see Frank, 2011, for a review) support the idea of cross talk, as opposed to segregation, between the motor and cognitive cortico-striatal circuits during learning and response selection. The current data are also consistent with that idea. It is possible that the disruption of FB learning we saw here following M1 inhibition was directly related to a disruption of motor loop activity,

which normally acts in concert with the associative and limbic traffic necessary for optimal learning on the FB task.

The effect of M1 inhibition on non-motor procedural learning is open to more than one interpretation. M1 could be a critical node in a procedural learning network which operates under feedback/reinforcement conditions, or it could be more of an “innocent bystander” providing access to such a network by virtue of its latent connectivity. The classical interpretation of disruptive rTMS experiments has been that the stimulation takes the targeted area “offline,” creating a “virtual lesion” analogous to pathological damage (Pascual-Leone, Walsh, & Rothwell, 2000). However, it is unlikely that M1, itself, is essential to procedural learning. An alternative explanation is provided by recent work from our laboratory (Steel et al., 2016) where cTBS of M1 caused no change in local activation during a motor procedural learning task, but disrupted connectivity in a distributed manner in a network associated with motor learning. Task-related connectivity simultaneously increased in another, previously described, learning network, which did not include M1. Therefore, M1, instead of being critical or even necessary for FB-based WPT learning, might simply provide access to the network of cortical and diencephalic regions implicated in the learning deficits in PD and HD. This is a new way to look how noninvasive brain stimulation alters behavior and suggests ways of influencing brain regions beyond the reach of direct noninvasive stimulation. Evidence for network shifting is also present in the results of an fMRI study of FB WPT learning in PD (Moody, Bookheimer, Vanek, & Knowlton, 2004). In that study, patients showed less activation in the caudate nucleus and greater activation in the anterior prefrontal cortex and MTL than controls performing the same task. This suggests that when the basal ganglia and their connections are dysfunctional, learning-related activity shifts to areas associated with declarative learning, which may be less efficient.

The addition of monetary reward and punishment to the WPT is unusual and deserves comment. Previous studies (Holl et al., 2012; Shohamy et al., 2004; Wilkinson et al., 2008; Wilkinson et al., 2014) suggest that corrective feedback alone does not improve learning on the WPT. In fact, in one of our own studies (Wilkinson et al., 2014), where healthy participants were trained on 400 trials under PA or FB conditions without monetary incentives, we found that PA was significantly better than FB-learning. However, effects involving monetary feedback have been found in other procedural learning paradigms. Adding monetary reward to visuo-motor adaptation (Galea, Mallia, Rothwell, & Diedrichsen, 2015) and force-tracking (Abe et al., 2011) tasks, improved retention of motor knowledge. Adding similar feedback and incentive improved motor sequence learning (Wachter, Lungu, Liu, Willingham, & Ashe, 2009; Wilkinson et al., 2015) and early consolidation (Wilkinson et al., 2015). We regard this as evidence that boosting the salience of feedback with monetary incentives strengthens FB-learning and provides a potentially viable strategy for training and rehabilitation and could provide a premise for future clinical trials in patient populations.

Continuous theta-burst rTMS was originally described as depressing the MEP (Huang et al., 2005), but its effects can be highly variable across participants and, possibly, sessions (Hordacre et al., 2016). In our earlier study of motor sequence learning (Wilkinson et al.,

2015) we found evidence of MEP inhibition by real M1 cTBS in the group data, although, in that study we excluded participants from the analysis who failed to produce an average baseline MEP response of 1 mV. Here, when we included all participants in the analysis, there was no overall effect of the cTBS on the MEP, even though the delivery parameter values were the same. We note, however, the negative effect of M1 cTBS on procedural learning has been found four times in similar paradigms (Rosenthal et al., 2009; Steel et al., 2016; Wilkinson et al., 2015; Wilkinson et al., 2010). Thus far, we are the only ones to have monitored the MEP.

The MEP is a compound muscle action potential and its amplitude represents the sum of cellular excitabilities and excitatory and inhibitory synaptic influences in M1 and the anterior horn of the spinal cord (Rothwell, Thompson, Day, Boyd, & Marsden, 1991; Ziemann et al., 1998). cTBS may suppress the MEP via a specific effect on the intracortical excitatory circuits, whose repetitive firing generates the efferent volleys that summate at the anterior horn to produce it (Di Lazzaro et al., 2005). While the two might share elements, this mechanism has no known relationship with the substrate of procedural learning in M1.

We did find a positive association between the effect of cTBS on the MEP and FB-learning in the Real group, suggesting some common susceptibility. It may be that cTBS depression of the MEP and procedural learning have a common mechanism or, more likely involve a synaptic change in different pathways.

5. Conclusion

Our study shows inhibition of M1 produces effects on cognitive non-motor procedural skill learning that are similar to that seen in studies of the effects of M1 inhibition on motor procedural learning, indicating M1 is involved in procedural learning even when the task involves minimal motor component. The findings we saw after M1 inhibition were almost identical to studies comparing WPT FB based and PA based learning in PD and HD patients. However, our results also show that M1 plays an important role in processing immediate incentive. We conclude M1 is a functional node in a network underlying feedback-driven procedural learning.

Acknowledgments

We thank Xiao Song and Caitlin Van-Wicklin for help with data collection and entry. We are very grateful to Irene McClain for the clinical support she provided to the study.

The authors declare no conflict of interest. Funding came from the Clinical Neuroscience Program of the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

The sponsors played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Abbreviations

AMT	active motor threshold
BG	basal ganglia

cTBS	inhibitory continuous theta burst stimulation, = a 40 secs uninterrupted train of theta burst of 600 pulses
DLPFC	dorsolateral prefrontal cortex
EMG	electromyogram
FB	feedback
FDI	first dorsal interosseous muscle
HD	Huntington's disease
fMRI	functional magnetic resonance imaging
M1	primary motor area
MEP	motor evoked potential
MME	mean money earned
MPC	mean proportion correct
MTL	medial temporal lobe
NART	National Adult Reading Test
PA	Paired associate
PD	Parkinson's disease
rTMS	repetitive transcranial magnetic stimulation
WPT	Weather Prediction Task

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Figure 1.
A. Experimental design. B. Timeline of a single experimental session.

Figure 2.

A. Probabilistic environment in the weather prediction task. B. Example of stimuli in the feedback condition. On the left is the prompt the participant is presented. On the right, after selecting “Rainy” which is the correct answer, the participant receives feedback in the form of a thumbs-up image and \$1-increase in total winnings.

Figure 3.

A. Mean proportion correct, for the FB and PA Tests 1 (T1) and 2 (T2) for the Real and Sham groups. Bars show standard error. B. Learning performance, indexed by mean proportion correct, for the last 42 trials of the feedback (FB) learning stage and observational/paired associate (PA) Tests 1 and 2; performance collapsed across time, for the Real and Sham groups. Bars show standard error. C. The benefit of learning with immediate incentive (FB-learning) compared to paired associate (PA) Test as indexed by the mean feedback difference score plotted separately for the Real and Sham groups. # = significantly different from zero after Bonferroni correction for multiple comparisons, one-tailed. * = significantly different after Bonferroni correction for multiple comparisons, one-tailed. Bars show standard error. D. Learning performance, indexed by mean proportion correct, for the last 42 trials of the feedback (FB) learning stage and feedback Tests 1 and 2; performance collapsed across time, for the Real and Sham groups. Bars show standard error. E. The benefit of learning with immediate incentive (FB-learning) compared to the feedback Test (FB) Test as indexed by the mean feedback difference score plotted separately for the Real and Sham groups. # = significantly different from zero after Bonferroni correction for multiple comparisons, one-tailed. Bars show standard error.

Figure 4. Learning performance, indexed by mean money earned, for early (trials 1–40), middle (trials 41–90) and late (91–150) feedback (FB) learning for the Real and Sham groups. * = significantly different from Sham FB late learning after Bonferroni correction for multiple comparisons, two tailed. Bars show standard error.

Learning environment for the Weather Prediction Task showing all card arrangements, their probability of occurrence across trials, and their associated probability of outcome (fine or hot) during the task. 0 = card absent, 1 = card present.

Table 1

Arrangement	Cards present				Mean total	P (arrangement)	P(fine or hot/arrangement)
	1	2	3	4			
A	0	0	0	1	15	0.095	0.895
B	0	0	1	0	7.5	0.045	0.778
C	0	0	1	1	19.5	0.13	0.923
D	0	1	0	0	7.5	0.045	0.222
E	0	1	0	1	9	0.06	0.833
F	0	1	1	0	4.5	0.03	0.5
G	0	1	1	1	15	0.095	0.895
H	1	0	0	0	15	0.095	0.105
I	1	0	0	1	4.5	0.03	0.5
J	1	0	1	0	9	0.06	0.167
K	1	0	1	1	7.5	0.045	0.556
L	1	1	0	0	19.5	0.13	0.077
M	1	1	0	1	7.5	0.045	0.444
N	1	1	1	0	15	0.095	0.105
Total					150	1.00	

Table 2

Demographics and information about task performance for the Real and Sham cTBS groups.

Group	Sham (<i>n</i> = 20)	Real (<i>n</i> = 20)	<i>t</i> or χ^2	<i>p</i>
Age	<i>M</i> = 26.49, <i>SD</i> = 8.1	<i>M</i> = 26.90, <i>SD</i> = 6.8	< 1	n.s.
Sex	11 women	9 women	.40	.53
IQ	<i>M</i> = 103.00, <i>SD</i> = 8.6	<i>M</i> = 107.56, <i>SD</i> = 6.7	−1.75	.09
Years of education	<i>M</i> = 16.23, <i>SD</i> = 2.3	<i>M</i> = 17.13, <i>SD</i> = 2.7	−1.14	.26
Time between FB and PA sessions	<i>M</i> = 13.30 days, <i>SD</i> = 8.7	<i>M</i> = 18.50 days, <i>SD</i> = 15.0	1.35	.19
Time to complete PA or FB tasks; and T1	16.96 min, <i>SD</i> = .8	17.17 min, <i>SD</i> = 8	< 1	n.s.
Total money won during FB-learning	<i>M</i> = \$60.16, <i>SD</i> = \$18.3 Range: \$20–90	Real, <i>M</i> = \$51.16, <i>SD</i> = \$28.8 Range: \$13–84	1.15	.26
Overall right hand button response time across feedback trials	<i>M</i> = 1703.73 msec., <i>SD</i> = 191.6	<i>M</i> = 1620.76.13 msec., <i>SD</i> = 278.4	1.07	.29

Table 3

MEPs for the Real and Sham cTBS groups at each time point of testing and under each learning condition (i.e. feedback (FB) or paired associate (PA)).

Group	Sham (<i>n</i> = 17)	Real (<i>n</i> = 12)
FB baseline	<i>M</i> = .01, <i>SD</i> = .3	<i>M</i> = .10, <i>SD</i> = .2
FB post 1	<i>M</i> = .01, <i>SD</i> = .3	<i>M</i> = .01, <i>SD</i> = .3
FB post 2	<i>M</i> = -.08, <i>SD</i> = .4	<i>M</i> = .13, <i>SD</i> = .2
FB post 3	<i>M</i> = -.02, <i>SD</i> = .3	<i>M</i> = .01, <i>SD</i> = .2
PA baseline	<i>M</i> = .04, <i>SD</i> = .3	<i>M</i> = .15, <i>SD</i> = .2
PA post 1	<i>M</i> = .08, <i>SD</i> = .3	<i>M</i> = .07, <i>SD</i> = .3
PA post 2	<i>M</i> = -.01, <i>SD</i> = .5	<i>M</i> = .11, <i>SD</i> = .2
PA post 3	<i>M</i> = -.05, <i>SD</i> = .5	<i>M</i> = -.02, <i>SD</i> = .6