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The Effects of High-Frequency rTMS Over the Left Dorsolateral Prefrontal Cortex on Reward Responsiveness

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ABSTRACT

Background: High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) over the prefrontal region has been shown to increase endogenous dopamine release in the striatum, which is closely associated with probabilistic reward learning.
Objective: We attempted to investigate whether HF-rTMS over the dorsolateral prefrontal cortex (DLPFC) would modulate reward responsiveness using a probabilistic reward task.
Methods: Eighteen healthy volunteers participated in this study using a randomized within-subject crossover design. Each participant received a single session of 10 Hz high-frequency rTMS over the left DLPFC and another session of sham stimulation, with an interval of 1 week between sessions. Nine hundred magnetic stimuli were delivered in three blocks 10 min apart, for a total duration of 30 min. After each stimulation session, participants performed a probabilistic reward task where two different stimuli were rewarded with different probabilities (i.e., rich vs. lean) to produce a response bias toward the more frequently rewarded stimulus.
Results: Participants showed faster and more accurate responses toward the rich stimulus than the lean stimulus. Participants developed a greater response bias toward the rich stimulus after HF-rTMS during the early learning trials versus after sham stimulation. No differences in response bias were observed during the later learning trials. Reaction time did not differ between the active HF-rTMS and sham stimulation conditions.
Conclusion: HF-rTMS over the left DLPFC increased responsiveness toward rewarding stimuli. This facilitation effect of HF-rTMS might be associated with changes in dopaminergic neurotransmission in the striatum. Our findings contribute to our understanding of the effects HF-rTMS can have on reward learning.

Introduction

Recently, increasing attention has been directed to the modulating roles of repetitive transcranial magnetic stimulation (rTMS) on various brain processes [1–3]. High-frequency rTMS (HF-rTMS) especially has been associated with the facilitation of various cognitive functions [1]. The underlying mechanisms of these facilitation effects were largely unknown in the past, but neuroimaging studies have found that rTMS alters neural activity in the stimulated area and in remotely connected areas [4,5]. For example, a combined PET/rTMS study revealed that 2 Hz rTMS over the left primary motor area increased regional glucose metabolism in the left and right frontal cortical regions, including the stimulation site and remote but connected cortical areas [4,5]. More interestingly, neurochemical PET imaging studies have also found that subcortical neurotransmission can be modulated by HF-rTMS over the prefrontal cortex [6–10]. Strafella and colleagues applied 10 Hz rTMS to the left prefrontal cortex of healthy individuals and assessed dopaminergic receptor availability using radiolabeled ligand C-11 raclopride and PET imaging techniques. Compared with rTMS over the control region, the authors found that HF-TMS over the left prefrontal region increased endogenous dopamine release in the striatal region [6,7]. Similar results have also been found in patients diagnosed with Parkinson's disease [9] and depression [10]. Because of increasing evidence supporting that prefrontal

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HF-rTMS increases dopaminergic neurotransmission in the striatum, one could predict that HF-rTMS may alter cognitive functions that is dependent on striatal dopaminergic neurotransmission.

The striatum and dopaminergic neurotransmission have been implicated in probabilistic reward learning, which involves gradual acquisition of stimulus-reward association with repetition and feedback [11]. Optimal behavior in a given environment is dependent on the ability to learn contingencies between antecedent events and their positive or negative outcomes. Because of the probabilistic nature of contingencies in a dynamic environment, individuals have to integrate reward history over time in order to behave advantageously. This integration is known to be dependent on non-declarative learning process, which occurs outside of the medial temporal lobes [11]. Tasks assessing probabilistic reward learning typically have participants select among two or more alternative stimuli that are differentially associated with reward [12–14]. During the tasks, healthy participants typically develop a preference for the stimulus associated with better reward outcomes. For example, in a probabilistic reward task developed by Pizzagalli and colleagues [13], participants were presented with two alternative stimuli, and correct responses to one were associated with a higher frequency of reward outcome than the other. Over time, participants developed a response bias toward the more frequently rewarded stimulus. For this task, administering drugs that facilitate or disrupt dopaminergic neurotransmission has resulted in enhanced or impaired performance, respectively [12–14]. When treated with a substance that disrupted dopaminergic neurotransmission, participants had a reduced a response bias compared to those treated with placebo [13]. On the other hand, participants receiving a substance enhancing dopaminergic neurotransmission had higher response bias than the placebo recipeints [14].

Based on these lines of evidence, we hypothesized that HF-rTMS would enhance reward responsiveness. To test this hypothesis, we used a probabilistic reward task with two alternating stimuli rewarded with different probabilities. We assessed the response shift toward the more frequently rewarded stimulus as a measure of reward responsiveness [13,14]. Healthy volunteers participated in this study in a randomized, within-subject crossover design. Each participant had two testing sessions separated by an interval of one week: once after active rTMS over the left dorsolateral prefrontal cortex, and once after sham stimulation over the same site.

Methods

Participants

Eighteen healthy college students volunteered to participate in this study. Their mean age was 23.6 years (SD = 2.09). All participants were right-handed men naïve to rTMS. They had no medical history of psychiatric illness or neurological disorders. Participants gave written informed consent prior to participation. This study was approved by the ethics committee of the Seoul National University Bundang Hospital and performed in accordance with the Declaration of Helsinki. Participants were monetarily compensated for their time (equivalent to 30 USD). All subjects were screened for medical contraindications against receiving rTMS in accordance with rTMS safety guidelines [15,16].

Repetitive transcranial magnetic stimulation (rTMS)

High-frequency rTMS was administered using a Magstim 200 magnetic stimulator (Whitland, UK) connected to a figure-of-eight-shaped coil. The stimulation site was the left dorsolateral prefrontal cortex and defined as the region 6 cm anterior in the 1 cm lateral in the parasagittal plane and 1 cm lateral from the primary motor hand area ($M1_{HAND}$). The precise location of $M1_{HAND}$ was assigned as the optimal position for stimulation of the right abductor pollicis brevis (APB) muscles by focal TMS [17]. The stimulation threshold was determined by measuring the minimum stimulus intensity necessary for a motor evoked potential to occur on the right APB muscle [18]. Stimulation was applied at 90% of the individual motor threshold and the frequency of stimulation was set at 10 Hz. The location of $M1_{HAND}$ and the motor threshold were determined one day prior to the first rTMS session. Stimulation was performed with these parameters for both active and sham stimulation sessions.

During active stimulation, participants received three consecutive blocks of stimulation: each block consisted of 15 trains of 2 s, repeated every 12 s (900 pulses total). The interval between stimulation blocks was 10 min during which participants were asked to rest with their eyes closed to avoid distractions. This particular paradigm was adopted from previous studies [4–7].

Sham stimulation was applied in the same manner except that the coil was placed at a 90° angle to the skull and only one edge of it rested on the scalp. All other parameters were applied in the same manner as in active stimulation. The study was conducted with a randomized within-subject crossover design, where each participant was tested after receiving the active rTMS and sham stimulation on two separate days, which were separated by a one-week interval. The order of stimulation was counterbalanced across participants.

Probabilistic reward task and response bias

Reward responsiveness was assessed using a probabilistic reward task that has been described in detail elsewhere [19]. The task consisted of three blocks of 100 trials. Each trial started with a fixation cross presented for 500 ms in the center of the computer screen, followed by a mouthless line drawing of a face. After 500 ms, either a short mouth (11.5 mm) or a long mouth (13 mm) was presented for 100 ms. Participants were asked to determine which type of mouth was presented by pressing either the “v” or “m” key on the keyboard. If an incorrect response was selected, no feedback was given, but if a correct response was chosen, positive feedback was displayed for 1750 ms, notifying that 500 won (equivalent to 0.45 USD) had been earned. In each block, a pseudo-random sequence of 50 long and 50 short mouths was presented and 40 correct responses were followed by reward feedback. To induce a response bias for one of the mouths, an asymmetrical reinforcer ratio of 3:1 was used. That is, correct responses for one mouth (the ‘rich’ stimulus) were associated with a reward three times more frequently (30:10) than correct responses for the other mouth (the ‘lean’ stimulus). Prior to the task, participants had been informed that only a portion of correct responses would be rewarded, but were not informed that correct identification of one of the stimuli would be disproportionally rewarded. The assignment of rich and lean stimuli was counterbalanced within subject across two test sessions. Participants were specifically instructed to try to win as much money as possible and informed of performance-based monetary incentives.

Data reduction and statistical analyses

Task performance was analyzed with respect to response bias, accuracy, and reaction time (RT). The main variable of interest was response bias. Response bias [$\text{Log}\, b = 1/2 \log(\text{Rich}_{correct} * \text{Lean}_{incorrect} / (\text{Rich}_{incorrect} * \text{Lean}_{correct}))$] assesses the systematic preference for the response paired with the rich stimulus, and increases as participants tend to correctly identify the rich stimulus, and/or misclassify the lean stimulus as the rich stimulus [13,14]. Response accuracy [= (number of hits)/(number of hits + number of misses)]