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Single pulse TMS differentially modulates reward behavior

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ABSTRACT

Greater knowledge of cortical brain regions in reward processing may set the stage for using transcranial magnetic stimulation (TMS) as a treatment in patients with avolition, apathy or other drive-related symptoms. This study examined the effects of single pulse (sp) TMS to two reward circuit targets on drive in healthy subjects. Fifteen healthy subjects performed the monetary incentive delay task (MID) while receiving fMRI-guided spTMS to either inferior parietal lobe (IPL) or supplemental motor area (SMA). The study demonstrated decreasing reaction times (RT) for increasing reward. It also showed significant differences in RT modulation for TMS pulses to the IPL versus the SMA. TMS pulses during the delay period produced significantly more RT slowing when targeting the IPL than those to the SMA. This RT slowing carried over into subsequent trials without TMS stimulation, with significantly slower RTs in sessions that had targeted the IPL compared to those targeting SMA. The results of this study suggest that both SMA and IPL are involved in reward processing, with opposite effects on RT in response to TMS stimulation. TMS to these target cortical regions may be useful in modulating reward circuit deficits in psychiatric populations.

1. Introduction

Motivated behavior is controlled by our reward system. In fact, all behaviors can be considered to lead to a reward, whether internal or external, achievement of something pleasant or the avoidance of something unpleasant. We act faster or slower, work harder or slack off, based on the salience of the outcome of our actions. These processes guiding our behavior can be divided into three components: anticipation, motor expectancy and consumption. Each of these behavioral components is related to each other as they push one towards repeated (or avoided) motivated behavior: anticipation *drives* one to *plan* and *perform* a rewarded action. Once rewarded, the individual *experiences* success (or failure). The experience of the reward feeds back and modulates subsequent anticipation/drive. To gain a better understanding of the interplay between these processes, we can modulate the circuits underlying them with transcranial magnetic stimulation (TMS).

TMS can modulate cognition in a spatially and temporally precise fashion. For example, single pulse TMS (spTMS) to the pre-SMA has successfully altered intention perception in healthy individuals (Lau & Passingham, 2007) and spTMS to the inferior parietal lobe (IPL) altered word matching (Stoeckel, Gough, Watkins, & Devlin, 2009). These effects of spTMS either disrupted (Stoeckel et al., 2009) or enhanced (Lau & Passingham, 2007) underlying neuronal activity on a millisecond scale in a reliably measurable fashion.

The first step in reward modulation with TMS is to identify cortical targets in the reward circuit associated with task performance. Brain activity associated with reward anticipation has been found in ventral striatum (VS), IPL, and anterior cingulate cortex. Similarly, brain activity during reward consumption has been shown in insula, orbitofrontal cortex (OFC), and ventromedial PFC (vmPFC) (Knutson, Adams, Fong, & Hommer, 2001a; Knutson, Fong, Adams, Varner, & Hommer, 2001b). The neural correlates of motor expectancy include supplemental motor area (SMA), cerebellum, and basal ganglia (Knutson et al., 2001a). Cortical regions in these networks (e.g. SMA, IPL) are within effective reach of the magnetic field of the TMS coil. Thus, these areas are good candidates as targets for TMS modulation. Indeed, a few studies have combined TMS with reward tasks.

TMS studies in reward circuitry have examined the effects of reward processing on motor cortex excitability. Using TMS, Kapogiannis, Campion, Grafman, and Wassermann (2008) found that reward expectation increased cortical inhibition in primary

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motor cortex using a slot machine simulation (Kapogiannis et al., 2008). Gupta and Aron found that excitability of motor cortex was modulated by reward only when action was required (Gupta & Aron, 2011). Other work has shown that the enhancement of cortical inhibition of motor cortex also occurs during reward feedback/consumption (Thabit et al., 2011). Changes in excitability in motor cortex by reward value may explain the link between drive and action, i.e. if a behavior is rewarded, changes in excitability of the motor cortex may prepare the brain to initiate action. Changes in cortical inhibition are particularly relevant for psychiatric disorders in which both deficits in motivation and in cortical inhibition are present (e.g. schizophrenia, (Daskalakis et al., 2002)). These TMS studies in reward processing only measured physiological changes in motor cortex, and did not explore the ability of TMS to directly modulate reward pathways as measured by task performance. To assess the role of different cortical regions in interfacing with reward circuits, we targeted two brain regions outside of motor cortex with TMS while subjects performed MID.

The monetary incentive delay task (MID, Fig. 1) (Knutson et al., 2001a) effectively engages reward processing and has been applied to the study of diverse psychiatric populations (Nestor, Hester, & Garavan, 2010; Pizzagalli et al., 2009). During a trial of MID, subjects see a cue which alerts them to a potential reward thus activating anticipation. To win the cue associated reward (money in this case) they have to respond to the target, activating motor expectancy. When subjects receive feedback, they "consume" a hedonic response.

The purpose of this study was to assess whether fMRI guided spTMS during MID task performance in healthy subjects could modulate drive as assessed by reward behavior, i.e. task performance. TMS location and phase specific effects of TMS would represent effects on different components and timing of reward processing. We targeted two brain regions each with a different role in reward processing to determine spatial specificity of effects: IPL for its role in reward evaluation and action planning in uncertain conditions (Vickery & Jiang, 2009) and SMA for motor expectancy and selection of motor movements (Tanji, Shima, & Matsuzaka, 2002). TMS pulses were administered at different latencies to determine temporal specificity. We hypothesized that effects of targeting IPL would be found during reward dependent decision making (i.e. during the Delay period of the MID task) (Gottlieb & Snyder, 2010) and effects when targeting SMA would be found during motor action selection (during the Cue period) (Hartstra, Oldenburg, Van Leijenhorst, Rombouts, & Crone, 2010; Mann, Thau, & Schiller, 1988). Latency and task phase dependence would reflect temporal dynamics of task-relevant processing of that brain region within the trial.

Our primary outcome measure was reaction time (RT), which consistently decreases with increasing reward magnitude in the motor tasks across subjects (Milstein & Dorris, 2007). Secondary outcome included disruption of reward effects with spTMS on error rates. This is the first study we know of to assess whether reward dependent behavior can be modified with TMS.

2. Materials and methods

2.1. Subjects

Sixteen right handed, English speaking subjects (8 women) ages 18–45 (32.3, S. D. 7.12), were recruited from the local community through print and online advertisements and from a database of healthy volunteers, built from previous studies. Subjects were paid for participation in addition to money earned during the monetary incentive delay task. The study was approved by the NYSPI/Columbia University institutional review board and written informed consent was obtained from all subjects after the study had been fully explained.

Subjects were excluded if they had current or past history of substance abuse or dependence, history of any Axis I DSM-IV disorder (as ascertained by the SCID-NP (First, 2002)), current serious medical illness, bodily metal implants (e.g., pacemaker, cochlear implant,) or other devices or factors that may be affected by fMRI or TMS, severe brain disorder, pregnancy, breast-feeding, or current use of psychotropic medications.

Of the sixteen subjects enrolled in this study, one subject was omitted from the analysis as this subject did not complete both TMS sessions. Another subject who received spTMS to Left IPL, remained in the analyses after initial analysis without that subject's data showed the same effect.

2.2. Task

Monetary incentive delay task (Knutson et al., 2001a). MID consists of five phases (see Fig. 1 for durations of each task phase): (1) a Cue period during which a visual cue stimulus appeared, signifying the amount of award possible to win; (2) a variable delay (Delay 1) during which a fixation cross was shown; (3) a Target period in which an "X" appeared, indicating the need to respond; (4) a second variable delay period with a fixation cross (Delay 2); and (5) a Feedback period in which the subject is informed about the outcome of their response (the amount indicated by the cue for correct responses or $0 for incorrect responses), as well as their running monetary total. Trials were marked incorrect if the subject responded too early or too late (before Target onset or in less than 175 ms or longer than 1000 ms after Target onset). The cue was a circle with 0, 1, 2 or 3 lines drawn across it representing the amount of reward ($0, $0.05, $.25, $1.00). The choice of a given cue varied pseudorandomly from trial to trial, with an equal number of trials of each type over each block of trials. Subjects were told that the different cues were associated with specific monetary rewards and that to win the associated amount they should respond as quickly as possible when the target was presented. The target disappeared when subjects responded. The chance of successful feedback reported to the subject in a given trial was probabilistic with an 80% chance of winning on each of the rewarded trials ($0.05, $.25, $1.00). Reward outcome was not deterministic as our pilot experiments showed that probabilistic rewards resulted in faster RTs. Subjects practiced on a laptop computer to a criterion 95% hit rate (continuously computed over the previous 40 trials) to avoid learning effects during TMS sessions.

2.3. TMS

Monophasic spTMS was administered with a Magstim 200 (Magstim Company, Limited, Dyfed, United Kingdom) was used for motor threshold (MT) determination and during experiments. TMS pulses were delivered from a figure of eight coil (9 cm diameter) tangential to the scalp at 100% motor threshold, coil pointing

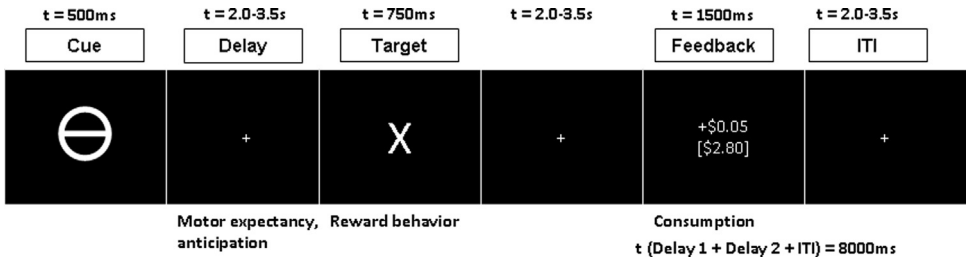

Fig. 1. MID sequence for one possible trial. Subjects saw one of four possible cues (circles with 0–3 lines corresponding to increasing reward value; 500 ms). The cue was followed by a variable delay (2000–3500 ms), after which the target was presented for a fixed length of time (750 ms). Subjects were instructed to press the space bar of a laptop as fast as possible once the target was visible to win the reward. The chance of winning was 80%. Feedback (1500 ms) appeared after a second variable delay following the target, indicating either gain or neutral, and displaying the cumulative amount of points earned. The sum of time for delay 1, delay 2 and the inter-trial interval was 8000 ms. The trial types were presented randomly within each block, to include ten trials of each of the four possible cue values.