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Reward-related activity in the human motor cortex

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Abstract

The human primary motor cortex (M1) participates in motor learning and response selection, functions that rely on feedback on the success of behavior (i.e. reward). To investigate the possibility that behavioral contingencies alter M1 activity in humans, we tested intracortical inhibition with single and paired (subthreshold/suprathreshold) transcranial magnetic stimulation during a slot machine simulation that delivered variable money rewards for three-way matches and required no movement. A two-way match before the third barrel had stopped (increased reward expectation) was associated with more paired-pulse inhibition than no match. Receiving a large reward on the preceding trial augmented this effect. A control task that manipulated attention to the same stimuli produced no changes in excitability. The origin of this reward-related activity is not clear, although dopaminergic ventral tegmental area neurons project to M1, where they are thought to inhibit output neurons and could be the source of the finding. Transcranial magnetic stimulation of M1 may be useful as a quantitative measure of reward-related activity.

Keywords

motor cortex; reward; stimulation; VTA

Introduction

Rewarding and punishing events are processed by brain regions that decode their salience, predictability and comparability to prior events, thereby modifying emotional and motivational states, autonomic responses and behavior (Schultz & Dickinson, 2000; Schultz, 2000; Pessiglione *et al.*, 2007). Studies in animals (Schultz, 2000, 2001, 2002, 2004; Fiorillo *et al.*, 2003) and humans (Schultz, 2000; Pochon *et al.*, 2002; Skolnick & Davidson, 2002; Knutson & Cooper, 2005; Oya *et al.*, 2005; Hampton & O'Doherty, 2007; Van der Linden *et al.*, 2007) have identified nodes comprising the 'decoding arm' of the network that analyses and stores the informational content of rewards: the orbitofrontal (O'Doherty *et al.*, 2001; Gottfried *et al.*, 2003) and medial pre-frontal (PFC)/anterior cingulate cortices (Williams *et al.*, 2004; Oya *et al.*, 2005), hippocampus (Chau *et al.*, 2004; Wittmann *et al.*, 2005), striatum (Haruno *et al.*, 2004; Tanaka *et al.*, 2004; Abler *et al.*, 2006; Haruno & Kawato,

2006; O'Doherty *et al.*, 2006; Rodriguez *et al.*, 2006), amygdala (Gottfried *et al.*, 2003) and ventral tegmental area (VTA) where the mesolimbic and mesocortical dopamine (DA) pathways arise (Schultz, 2000, 2004; Fiorillo *et al.*, 2003; Chau *et al.*, 2004). An 'executive arm' of the network links reward to future behavior and is thought to include the VTA (Schultz, 2004), striatum (Schultz & Dickinson, 2000; Morris *et al.*, 2006), nucleus accumbens (Chau *et al.*, 2004; Williams *et al.*, 2004), PFC (Gaspar *et al.*, 1992; Schultz & Dickinson, 2000; Frankle *et al.*, 2006) and dorsal anterior cingulate cortex (Williams *et al.*, 2004; Oya *et al.*, 2005).

Generally, it is assumed that rewards influence behavior through their effects on PFC activity and that downstream motor areas are concerned only with execution (Carmichael & Price, 1996; Ongur & Price, 2000; Schultz & Dickinson, 2000; Haber, 2003; Frankle *et al.*, 2006). However, the role of the primary motor cortex (M1) in learning, selecting and planning behavior may be broader than conventionally thought (Graziano, 2006).

Among the areas potentially influencing M1 through direct or indirect connections (Haber, 2003; Schmahmann & Pandya, 2006), many are involved in reward processing, e.g. the striatum (Schultz, 2000; Knutson *et al.*, 2001; Haber, 2003), orbitofrontal cortex and amygdala (Schultz, 2000; Gottfried *et al.*, 2003), anterior cingulate cortex (Williams *et al.*, 2004), and supplementary motor area (Campos *et al.*, 2005). However, VTA dopaminergic neurons also project directly to M1 in roughly equal numbers as to the ventral striatum and other frontal areas (Gaspar *et al.*, 1992, 1995; Williams & Goldman-Rakic, 1993). Cortical DA projections synapse on both pyramidal cells and GABAergic interneurons (Sesack *et al.*, 1998; Tseng *et al.*, 2006) and, through these inputs, reward-related behavioral contingencies may modulate M1 activity, along with other frontal areas.

Transcranial magnetic stimulation (TMS) has been used extensively to study the physiology of M1. The amplitude of the motor evoked potential (MEP) to TMS reflects the integration of excitatory and inhibitory inputs to cortical and spinal motoneurons, also referred to as their 'excitability'. However, the status of cortical circuits can be probed with little or no spinal outflow (Kujirai *et al.*, 1993; Nakamura *et al.*, 1997; Hanajima *et al.*, 1998; Sanger *et al.*, 2001; Matsunaga *et al.*, 2002). Paired-pulse TMS can measure the inhibitory or facilitatory effect of a 'conditioning' pulse, too weak to evoke spinal cord activity, on the MEP from a suprathreshold 'test' pulse delivered a few milliseconds later. The effect is expressed as the ratio of the conditioned to the unconditioned (or 'test') MEP, evoked with no preceding pulse. The conditioning pulse inhibits the MEP when it is delivered about 1–4 ms before the test pulse and facilitates it at interstimulus intervals (ISIs) of about 6–20 ms (Ziemann *et al.*, 1996a). Enhancers of GABA_A receptor-mediated inhibition, such as benzodiazepines (Ziemann *et al.*, 1996c) and neurosteroids (Smith *et al.*, 2002b) as well as DA agonists (Ziemann *et al.*, 1997), enhance intracortical inhibition during both the inhibitory and facilitatory phases (Di Lazzaro *et al.*, 2006). This is consistent with the time course of the GABA_A-mediated inhibitory post-synaptic potential (McCormick, 1989). The response to paired-pulse TMS is affected by a wide range of drugs (Ziemann *et al.*, 1995, 1996d, 1997) as well as hormones (Smith *et al.*, 1999, 2002b) and can serve as a marker for behavioral disorders (Greenberg *et al.*, 2000; Gilbert *et al.*, 2005) and individual differences (Wassermann *et al.*, 2001).

In this study, we delivered single and paired TMS to M1 before and during a slot machine simulation that manipulated reward expectation, in order to look for evidence of reward-related input.

Materials and methods

Experimental design

In order to manipulate behavioral states, we used a computer simulation of a three-barrel slot machine that delivered intermittent money rewards on trials resulting in a three-way match, i.e. when all three barrels showed matching items (cartoons of fruits). Subjects were familiarized with the task in a brief practice session with neither rewards nor TMS. Subjects started each trial by pressing the space bar with the non-dominant hand; the experiments required no other motor response. The dominant (tested) hand remained at rest throughout the experiment. At the beginning of each trial, the barrels began spinning and stopped one-by-one at 2-s intervals. We delivered TMS, time-locked to the phases of the game (Fig. 1), and recorded MEPs from the finger flexors or wrist extensor of the dominant hand.

Experiment 1 (N = 26)—This experiment contained 225 trials, randomized between behavioral conditions. A total of 180 trials resulted in a two-way match when two barrels had stopped and 90 of those in a three-way match after all three had stopped. Three-way matches were rewarded with \$0.25 (45 trials), \$1 (39 trials) or \$5 (six trials). When two barrels had stopped, a two-way match indicated a 50% probability of a three-way match and produced an increased expectation of reward relative to the no-match condition. Feedback on the size of the reward was provided after all three barrels had stopped (Fig. 1). We delivered paired and single-pulse TMS at 1 s after the second barrel had stopped. We recorded MEPs from either the finger flexors (16 subjects) or the wrist extensors (10 subjects).

Experiment 2 (N = 15)—In naive subjects, we used the same slot machine simulation without rewards. In order to manipulate attention, we instructed subjects to keep track of the number of trials where a two-way match was followed by a three-way match. Thus, after a two-way match, they had to attend to the outcome of the trial, whereas, after no match, the outcome could be ignored. In this experiment, we recorded MEPs only from the finger flexors.

Study population—Forty-one healthy men (mean age 30.7 ± 9.3 years), drawn from the population in the NIH Clinical Research Volunteer Program, were enrolled. We included only men, as ovarian hormones affect paired-pulse TMS measures in women (Smith *et al.*, 1999, 2002b,c, 2003). They underwent a neurological examination and were interviewed to exclude habitual gambling, alcoholism and illicit drug use. The experiments were undertaken with the written consent of each subject. The study conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the *British Medical Journal* (18 July, 1964). Moreover, the study was approved by the Neuroscience Institutional Review Board of the National Institutes of Health.

Methods

The stimuli were programmed in Presentation® (Version 10.0, Neurobehavioral Systems, Albany, CA, USA) and presented on a computer that triggered and sent trial condition information to another computer. This computer, interfaced with a Micro 1401 processor (CED, Cambridge, UK), controlled the TMS, recorded the electromyogram and performed conditional averaging with Signal® software (Version 3.08, CED).

Surface electrodes were applied to the skin of the dominant hand over the long finger flexors (flexor digitorum profundus and superficialis; 16 subjects) or the wrist extensors (extensor carpi radialis longus and brevis; 10 subjects). The electromyogram was recorded and displayed online. Subjects were instructed to keep the recorded muscles relaxed at all times. TMS was delivered from two Magstim 200 stimulators connected via a Bistim® module, through a round coil placed in the optimal position and orientation for producing an MEP in the target muscle. Before each experiment, the resting motor threshold in the target muscle was determined, defined as the maximum stimulus intensity that did not produce an MEP > 50 µV in the targeted muscle (Ziemann *et al.*, 1997). Mean resting motor threshold (both experiments) was $46.59 \pm 6.2\%$ of maximum stimulator output. For paired TMS, the intensity of the conditioning stimulus was set at 65% and the test stimulus intensity at 120% of resting motor threshold (Ziemann *et al.*, 1996a; MacKinnon *et al.*, 2005). The conditioning stimulus preceded the test stimulus by either 2 or 10 ms.

Before each experiment, we measured the subject's baseline response to paired-pulse stimulation with 15 trials of the test stimulus alone, 15 pairs with a 2-ms ISI and 15 pairs with a 10-ms ISI. Subjects sat with eyes open, not conversing or performing any task. During each experiment, three different TMS conditions (the test stimulus given alone and pulse pairs at 2- and 10-ms ISI) were intermixed randomly. The interval between trials varied randomly by 0–20% around a mean of 6 s. In both experiments, each one of the three TMS conditions occurred in 15 no-match trials and 60 two-(or three-)way match trials. In Experiment 1, for each TMS condition, 30 of the two-way match trials were followed by no reward, 15 by \$0.25 (small reward), 13 by \$1 and 2 by \$5 (large reward). In Experiment 2, for each TMS condition, 30 of the two-way match trials were followed by a three-way match and 30 by no three-way match.

Analysis

Trials contaminated by background electromyography (< 2% of all trials) were excluded from the analysis. Peak-to-peak MEP amplitudes were measured automatically.

The effect of the conditioning pulse was expressed as the ratio of conditioned MEP to unconditioned MEP. Ratios from individual trials were calculated by dividing the MEP from each pair by the mean MEP from the test pulse alone for the same experimental condition in each subject.

The conditioned MEP ratio was the dependent variable for all analyses. A decrease in the ratio signified an increase in inhibition. The independent variables in Experiment 1 were ISI (2 vs. 10 ms), match condition (two-way vs. no match), preceding trial reward (small or no reward vs. large reward), task condition (pre-task baseline vs. during task) and muscle

(finger flexors vs. wrist extensors). The \$5 rewards (two per TMS condition), which were included in order to increase the reward range, were grouped with the \$1 reward trials (13 per condition) as 'large' rewards. In Experiment 2, the independent variables were ISI, match condition and task condition. Experiment was introduced as a variable in order to compare the results of Experiments 1 and 2.

All statistical analyses were performed with SPSS 15[®] software, based on a mixed linear model for fixed effects, a method of analysis similar to the general linear model but which makes fewer assumptions for the data. In all analyses, all models of Covariance Structure available in SPSS 15[®] were applied to the data and the best-fitting model was determined based on two criteria of fit, the Akaike's Information Criterion and the Schwarz's Bayesian Criterion. The best-fitting model proved to be the First Order Autoregressive Moving Average, which is typical for repeated measures analyses. This model does not assume constant variance for the different independent variable levels. Restricted maximum likelihood estimation was used to analyse incomplete data. Reported denominator degrees of freedom were calculated by SPSS 15[®] based on this estimation. The Bonferroni adjustment for multiple comparisons was applied by SPSS 15[®] in all post-hoc comparisons.

Results

Conditioned MEP ratios for the 2-ms ISI were significantly smaller than for the 10-ms ISI for both experiments (d.f. = 2179.825; $F_{1,2179.8} = 429.6$; $P < 0.001$). Conditioned MEP ratios for both ISIs were larger during the tasks compared with the pre-task baseline in Experiment 1 (both muscles pooled; $F_{1,941.3} = 9.9$; $P = 0.002$) and Experiment 2 ($F_{1,198.9} = 7.9$; $P = 0.005$; Figs 2 and 3). This decrease in inhibition was similar in the two experiments (interaction of experiment type and effect of task; $F_{1,1366.6} = 1.0$; $P = 322$).

In Experiment 1, two-way matches caused a significant decrease in the conditioned MEP ratio relative to no match in the finger flexors ($F_{1,535.5} = 8.8$; $P = 0.003$; Fig. 2) and wrist extensors ($F_{1,159.2} = 10.4$; $P = 0.002$; Fig. 2). This decrease effect was seen for both 2-ms ($F_{1,820.8} = 5.2$, $P = 0.023$) and 10-ms ($F_{1,821.7} = 25.5$, $P < 0.001$) ISI. Two-way matches produced significantly more inhibition when they followed large rewards than after small or no rewards ($F_{1,273.0} = 6.6$, $P = 0.011$; Fig. 4). When the no-reward condition was excluded, the effect of the preceding trial was still significant ($F_{1,254.8} = 4.2$, $P = 0.017$), suggesting possible scaling of the response with reward value. A comparison between the \$1 and \$5 rewards was not possible because of the small number of \$5 rewards.

In Experiment 2, there was no significant difference in the conditioned MEP ratio between the two-way match and no-match conditions ($F_{1,184.9} = 1$, $P = 0.283$; Fig. 3). Notably, the estimated mean conditioned MEP ratio was higher for two-way match than for no match. Moreover, when we compared Experiment 2 with Experiment 1 directly, the interaction of experiment type with match condition was significant ($F_{1,1403.5} = 6.8$, $P = 0.009$). All subjects reported the correct number of three-way matches.

Discussion

In this study, we found an excitability change in M1 that was associated with the expectation of reward and modified by prior experience. Specifically, the inhibition produced by the conditioning pulse increased with reward expectation and this effect was greater when subjects had recently received a large reward. We regard this as evidence that M1 receives reward-related information similar to that reported for the PFC and striatum (Schultz *et al.*, 1993; Schultz & Dickinson, 2000; Schultz, 2000; Haber, 2003; Oya *et al.*, 2005).

Outcome uncertainty is coded by various brain areas, such as the VTA, following reward-predicting stimuli (Critchley *et al.*, 2001; Fiorillo *et al.*, 2003; Shizgal & Arvanitogiannis, 2003; Tobler *et al.*, 2007) but also independent of reward (Critchley *et al.*, 2001; Aron *et al.*, 2004). In this study, both reward uncertainty and likelihood were maximal following a two-way match (i.e. 50% probability of any reward), posing a confound. The fact that large rewards preceding two-way matches resulted in more inhibition than equally probable small rewards indicates that reward value modulated the response, at least on successive trials. However, the present study was not designed to distinguish between reward value and probability.

The possibility that aspects of the stimuli, other than their reward significance but specific to the two-way match condition, caused the increase in inhibition was addressed in Experiment 2 where the subject's attention was drawn to the two-way match condition but the stimuli had no reward-related significance. This was not a perfect control for attention to the two-way match condition, which may have been greater during Experiment 1. However, we do not believe that it would have been possible to match the degree of attention in Experiment 1 without involving the reward system in some way (Maunsell, 2004; Schultz, 2006). Although disentangling the effects of attention and reward can be challenging, we doubt that the increase in ICI observed in Experiment 1 was due to attention alone. Attention/arousal appears to decrease rather than increase ICI (Rosenkranz & Rothwell, 2004; Thomson *et al.*, 2008), which is what we observed in the comparison between pre-task baseline and task in both experiments.

To address the focality of the increase in ICI associated with two-way matches and the possibility that it was related to the covert preparation of a latent motor response, we tested a flexor and an extensor muscle acting across two different joints. Outputs to both muscles changed similarly with reward likelihood. Although this could still represent stereotyped activity related to movement preparation, we note that movement preparation, *per se*, is associated with increased, rather than decreased, M1 excitability (Alexander & Crutcher, 1990). Moreover, paired-pulse inhibition in M1 decreases during response preparation (Leocani *et al.*, 2000).

Reward-related activity has been observed in M1 in functional neuroimaging studies, when (unlike our paradigm) the task included a motor response (Pessiglione *et al.*, 2007) or when ventral pre-motor areas were also activated (Ponseti *et al.*, 2006). In tasks not requiring motor responses, net inhibitory inputs, such as we measured, would probably not produce

regional blood flow changes large enough to be captured by functional neuroimaging (Waldvogel *et al.*, 2000; Smith *et al.*, 2002a).

Where does the M1 reward expectation signal come from? Among the possible direct and indirect sources [striatum, orbitofrontal cortex and amygdala, anterior cingulate cortex and supplementary motor area, VTA (Schmahmann & Pandya, 2006)], circumstantial evidence suggests direct or indirect input from the VTA as a likely source. In Experiment 1, the task parameters and reward schedule (intermittent, variable reward and 0.5 reward probability after a two-way match) paralleled the values shown to maximize tonic VTA DA neuron activity in primates (Fiorillo *et al.*, 2003) and TMS delivery was timed to coincide with our estimate of peak VTA pre-reward activity (Fiorillo *et al.*, 2003). In addition, the increment in the response to a two-way match following large rewards is consistent with the observation that large rewards seem to ‘reset’ the tonic VTA activity at a higher level (Fiorillo *et al.*, 2003).

The data are also consistent with a direct effect of DA in M1 via the known VTA–M1 pathway (Gaspar *et al.*, 1992, 1995; Williams & Goldman-Rakic, 1993). Increased M1 inhibition is physiologically similar to the action of exogenous DA agonists (Ziemann *et al.*, 1996b, 1997). VTA cells are thought to fire *en masse* in response to reward-related stimuli (Schultz, 2001; Fiorillo *et al.*, 2003) and VTA projections to M1 and PFC are thought to act in parallel (Berger *et al.*, 1988; Gaspar *et al.*, 1992). VTA DA projections terminate on inhibitory cortical interneurons (Gao *et al.*, 2003; Tseng *et al.*, 2006) and pyramidal (including corticospinal) cells (Sesack *et al.*, 1998; Huda *et al.*, 2001; Awenowicz & Porter, 2002), modulating their excitability, spatial tuning and temporal dynamics (Fellous *et al.*, 2001; Gao *et al.*, 2003; Markram *et al.*, 2004). Tonic DA release (as in reward expectation) acts mostly on D2 and D4 receptors on interneurons (Huda *et al.*, 2001; Awenowicz & Porter, 2002; Gao *et al.*, 2003; Onn *et al.*, 2006; Tseng *et al.*, 2006), suppressing recurrent pyramidal cell excitation (Onn *et al.*, 2006). Recurrent excitation within the motor cortex is thought to be the basis of the repeated spinal volleys, or ‘I waves’ (Amassian *et al.*, 1987), that summate at the spinal segment to produce the MEP. Human spinal recordings show that I wave suppression is the mechanism by which the conditioning pulse inhibits the MEP (Nakamura *et al.*, 1997; Di Lazzaro *et al.*, 1998).

What is the role of a reward-related signal to M1 in shaping behavior? The current concept of M1 is no longer that of a low-level output stage (Penfield & Boldrey, 1937; Penfield & Jasper, 1954; Graziano, 2006) but a highly plastic processor, able to resolve response conflicts (Praamstra & Seiss, 2005) and learn. M1 maps are continually reshaped by information from multiple sources (Graziano, 2006). Reward signals are thought to drive the plastic changes that underlie learning (Waelti *et al.*, 2001; Schultz, 2004) in cortical (Ueki *et al.*, 2006) and striatal (Haruno *et al.*, 2004; Tanaka *et al.*, 2004; Rodriguez *et al.*, 2006) neurons. Learning in M1 alters movement representations (Karni *et al.*, 1995, 1998; Cohen *et al.*, 2005; Robertson *et al.*, 2005; Graziano, 2006; Richardson *et al.*, 2006) and probably depends, in part, on DA signals (Ueki *et al.*, 2006) to indicate behavioral salience, guide plasticity and optimize motor/pre-motor interactions (Mir *et al.*, 2005). Other cortical areas in the executive chain, medial PFC (response selection) and pre-motor areas (motor preparation) also receive VTA input (Berger *et al.*, 1988; Gaspar *et al.*, 1992). Therefore, it is

consistent that M1 (motor learning and sequence execution) should receive analogous information. Simultaneous input to all of these structures could enhance coordination between the stages of the executive arm of the reward network.

In addition to implicating M1 in reward processing, TMS may open a physiological window into the human reward system and provide a new level of ease and precision for measuring the neural coding of reward value.

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Abbreviations

DA	dopamine
ICI	intracortical inhibition
ISI	interstimulus interval
M1	primary motor cortex
MEP	motor evoked potential
PFC	pre-frontal cortex
TMS	transcranial magnetic stimulation
VTa	ventral tegmental area

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Fig. 1.
Experimental design for Experiments 1 and 2.

Fig. 2.

In Experiment 1, the condition of two-way match associated with reward expectation significantly decreased the conditioned MEP ratio, both when the finger flexors ($F=8.8$, $P=0.003$) and the wrist extensor ($F=10.4$, $P=0.002$) were tested. Conditioned MEP ratios were larger during the experimental tasks compared with the pre-task baseline (for both muscles combined, $F=1.0$, $P=0.002$; for the flexors, $F=11.3$, $P=0.001$; for the extensor, $F=1.8$, $P=0.178$). Left panel: Conditioned MEP ratio by match condition and pre-task baseline for finger flexors. Right panel: Conditioned MEP ratio by match condition and pre-task baseline for wrist extensors. The columns represent means and the error bars their SEs.

Fig. 3.

In Experiment 2, attention engagement to the two-way match condition without association with reward expectation does not change the conditioned MEP ratio ($F = 1.157$, $P = 0.283$). Conditioned MEP ratio by match condition and pre-task baseline. The columns represent means and the error bars their SEs.

Fig. 4.

In Experiment 1 for finger flexors, the condition of two-way match associated with reward expectation decreased the conditioned MEP ratio for 2- and 10-ms ISI following large (\$1 or \$5) but not small (\$0.25 or no reward) rewards. Two-way matches produced significantly more inhibition when they followed large (\$1 or \$5) compared with small (\$0.25 or no reward) rewards (for large rewards, two-way matches vs. no matches, $F = 8.0$, $P = 0.005$; for small rewards, two-way matches vs. no matches, $F = 2.0$, $P = 0.159$; for two-way matches, large rewards vs. small rewards; $F = 6.6$, $P = 0.011$). The columns represent means and the error bars their SEs.