

COGNITIVE NEUROSCIENCE

Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex decreases valuations during food choices

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Abstract

Several studies have found decision-making-related value signals in the dorsolateral prefrontal cortex (DLPFC). However, it is unknown whether the DLPFC plays a causal role in decision-making, or whether it implements computations that are correlated with valuations, but that do not participate in the valuation process itself. We addressed this question by using repetitive transcranial magnetic stimulation (rTMS) while subjects were involved in an economic valuation task involving the consumption of real foods. We found that, as compared with a control condition, application of rTMS to the right DLPFC caused a decrease in the values assigned to the stimuli. The results are consistent with the possibility that the DLPFC plays a causal role in the computation of values at the time of choice.

Introduction

Most theoretical models of goal-directed decision-making in neuroscience, psychology and economics assume that subjects make choices in two steps: first, a value is assigned to every option under consideration (often called the goal value); and then the values are compared to select one of the options. This view has motivated a search for neural correlates of valuation, which have been identified in a wide range of decision-making tasks and brain regions. For example, Sugrue *et al.* (2004) found correlates of stimulus value signals in single neurons in the macaque parietal cortex during a binary reinforcement learning choice task, and two studies found neurons encoding action-specific value signals in the striatum during a binary choice task (Samejima *et al.*, 2005; Lau & Glimcher, 2008). Dynamic encoding of other types of value-related signals has also been found in various areas of the parietal and dorsolateral prefrontal cortices, both in functional magnetic resonance imaging (fMRI) and monkey electrophysiology studies (Kim & Shadlen, 1999; Gold & Shadlen, 2007; Heekeren *et al.*, 2008; Rangel, 2008).

Of particular interest for choice, several human fMRI studies have shown that activity in the medial orbitofrontal cortex (OFC) is correlated with behavioral measures of goal values at the time of decision-making (Erk *et al.*, 2002; Paulus & Frank, 2003; Kable &

Glimcher, 2007; Plassmann *et al.*, 2007; Rolls *et al.*, 2007; Tom *et al.*, 2007; Valentin *et al.*, 2007; Hare *et al.*, 2008, 2009). Similar results have been found in monkey electrophysiology experiments (Wallis & Miller, 2003; Padoa-Schioppa & Assad, 2006, 2008). On the basis of this evidence, the anatomical connectivity of the OFC (Petrides & Pandya, 1999; Price, 2006), and studies showing impairments in simple economic choice tasks in patients with lesions to this area (Fellows & Farah, 2007), it has been suggested that the OFC might be an area where multiple sensory, affective and cognitive inputs converge and are integrated into a goal value signal for every stimulus under consideration (Wallis, 2007; Rangel, 2008; Rangel *et al.*, 2008; Padoa-Schioppa & Platt, 2009).

Another region that is thought to play an important role in decision-making is the dorsolateral prefrontal cortex (DLPFC). The evidence comes from several sources. First, fMRI (Plassmann *et al.*, 2007) and monkey electrophysiology (Pieters *et al.*, 1999; Wallis & Miller, 2003; Barraclough *et al.*, 2004; Seo *et al.*, 2007) studies have found neural activity correlated with goal values in the DLPFC at the time of decision-making. Second, many studies exploring the role of the DLPFC in working memory (Levy & Goldman-Rakic, 2000; Petrides, 2000; Curtis & D'Esposito, 2004), cognitive control (Miller, 2000; Miller & Cohen, 2001; Milham *et al.*, 2003), emotional regulation (Ochsner & Gross, 2005; Delgado *et al.*, 2008) and various aspects of decision-making (Watanabe, 1996; Barraclough *et al.*, 2004; Lee *et al.*, 2007; Sakagami & Watanabe, 2007; Seo *et al.*, 2007; Watanabe & Sakagami, 2007; Hare *et al.*, 2008) have found that it often plays an

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'executive control' role by modulating activity in other areas. Third, a recent study on the neurobiology of self-control (Hare *et al.*, 2009) has found evidence suggesting that the value signals in the OFC are modulated by areas of the DLPFC. In particular, the evidence from that study is consistent with the hypothesis that parts of the DLPFC send inputs to the OFC that are integrated, together with input from other areas, to compute the goal value signals.

All of this evidence notwithstanding, the role of the DLPFC in the computation of goal values during simple choice is still unknown. In this study, we addressed this question by combining a simple decision-making task with low-frequency repetitive transcranial magnetic stimulation (rTMS) (Pascual-Leone *et al.*, 1999; Walsh & Cowey, 2000; Hallett, 2007; Wagner *et al.*, 2007). On the basis of the previous evidence, and a large body of work showing that low-frequency rTMS often interferes with the computations performed by the targeted region, we hypothesized that stimulating the areas of the right DLPFC that were found in Plassmann *et al.* (2007) and Hare *et al.* (2009) would reduce the amount of inputs sent to the OFC, which in turn should decrease the amount that subjects are willing to pay for items.

We tested this hypothesis in a simple decision-making paradigm, adopted from Plassmann *et al.* (2007), in which subjects need to compute the goal value of one item at a time. The idea of the experiment is simple. If the DLPFC participates in the computation of goal values by supplying critical inputs to the OFC, then applying low-frequency rTMS over the DLPFC should reduce the goal values that are computed. In contrast, if the DLPFC does not participate in the computation, then applying rTMS to it should have no effect on measured goal values. The results of the experiment provide evidence in favor of the first hypothesis.

Materials and methods

Experiment 1

Subjects

Fifty-six normal-weight Caltech students (30 males; mean age, 22 years; age range, 19–26 years; body mass index, 18–25) participated in the experiment. All subjects were right-handed, healthy, had normal or corrected-to-normal vision, had no history of psychiatric diagnoses, neurological or metabolic illnesses, were not taking any psychotropic medications, had no history of eating disorders, and were screened for liking and, at least occasionally, eating the types of foods that we used. Subjects gave written informed consent before participating. The review board of the California Institute of Technology (Pasadena, CA, USA) approved the study, which was in accordance with the National Institutes of Health Guidelines. No deception was used in the experiments.

Task

Figure 1A describes the timeline of the experiment. Subjects were told that the goal of the experiment was to study food preferences, and were instructed not to eat for 3 h before the experiment. This was done to increase the value that they placed on the foods used. The experiment had three parts: (i) an initial liking-rating task; (ii) 15 min of rTMS; and (iii) a bidding task. Upon arrival at the laboratory, subjects were told that they would have to remain in the laboratory for 30 min at the conclusion of the experiment, and that the only thing that they would have to eat is whatever food they purchased from us during the bidding task.

In the liking-rating task, subjects were shown high-resolution pictures (72 dots per inch, 3 × 4 inches) of 50 different sweet and salty junk foods (e.g. chips and candy bars). They were asked to rate

them on a scale from -7 to $+7$ ('how much would they like to eat that food, and only that food, at the end of the experiment?'), with 0 denoting that they were indifferent with regard to eating that food or not eating it, $+7$ denoting that they would strongly like it, and -7 denoting that they would strongly dislike it. The stimulus presentation and response recording were controlled by E-PRIME (Psychology Software Tools, Pittsburgh, PA, USA). The pictures stayed in the screen until the subject entered a rating by clicking with a mouse on an analog scale bar shown below the food item (Fig. 1A). Liking-rating trials were separated by a 2 s intertrial interval, in which a black screen with a central fixation cross was shown.

The foods were selected on the basis of pilot data, to satisfy several criteria. First, we wanted items to be highly familiar and to be sold in local convenience stores in order to remove uncertainty considerations from the subjects' value computations. Familiarity data collected in a previous experiment (Plassmann *et al.*, 2007) show that the items were highly familiar to our subject pool [familiarity scores: mean, 3.97; standard deviation, 1.34; scale, 1 (not familiar) to 5 (very familiar)]. Second, we wanted items that most subjects found appetizing. The liking-rating data collected from every subject in the first phase of the experiment suggest that this was the case (70% of the items had non-negative scores).

At the beginning of the bidding task, subjects received three \$1 bills in 'spending money' and were allowed to purchase food from us with these funds. Whatever money they did not spend was theirs to keep. Subjects were asked to place bids for the right to eat a snack during the 30 min of wait time at the end of the experiment. The same 50 foods used in the liking-rating task were used here, and were presented using the same pictures. In each trial they were allowed to bid \$0, \$1, \$2 or \$3 for each food item. At the end of the experiment, one of those trials was randomly selected, and only the outcome of that trial was implemented using the rules described below. As a result, subjects did not have to worry about spreading their \$3 budget over the different items, and could treat each trial as if it were the only decision that counted.

The foods were sold using a Becker–DeGroot–Marschak (BDM) auction (Becker *et al.*, 1964). The rules of the auction were as follows. Let b denote the bid made by the subject for a particular item. After the bid was made, a random number n was drawn from a known distribution (in our case, \$0, \$1, \$2 and \$3 were chosen with equal probability). If $b = n$, the subject got the item and paid a price equal to n . In contrast, if $b < n$, the subject did not get the object but also did not have to pay anything.

We used this auction institution to measure goal values after the rTMS, because it has two very useful properties. First, it is characterized by a simple set of rules. Second, the optimal strategy for a buyer is to bid exactly his or her value for the item being sold. The rationale for this is as follows. There is no incentive to bid less than the true value, because the price paid is determined by the random number n , and therefore the bids do not affect the price paid. There is also no incentive to increase the bid above the true value, because this may lead to a situation in which the subject gets the item but ends up paying a price larger than his true value (for example, consider the case true value \$1, $b = \$3$, and $n = \$2$). The fact that bidding the true value is the optimal strategy was explained and emphasized extensively during the instruction and training period. In particular, the instructions emphasized that the subjects' best strategy is to look at the item, ask how much it is worth to them, and simply bid that amount.

A between-subjects design was used. Each subject performed the bidding task in one, and only one, of three conditions: (i) after stimulation of the DLPFC ($N = 32$); (ii) after stimulation of the vertex ($N = 14$); or (iii) after sham stimulation ($N = 10$). In fact, the DLPFC condition was run twice under slightly different conditions, described below.

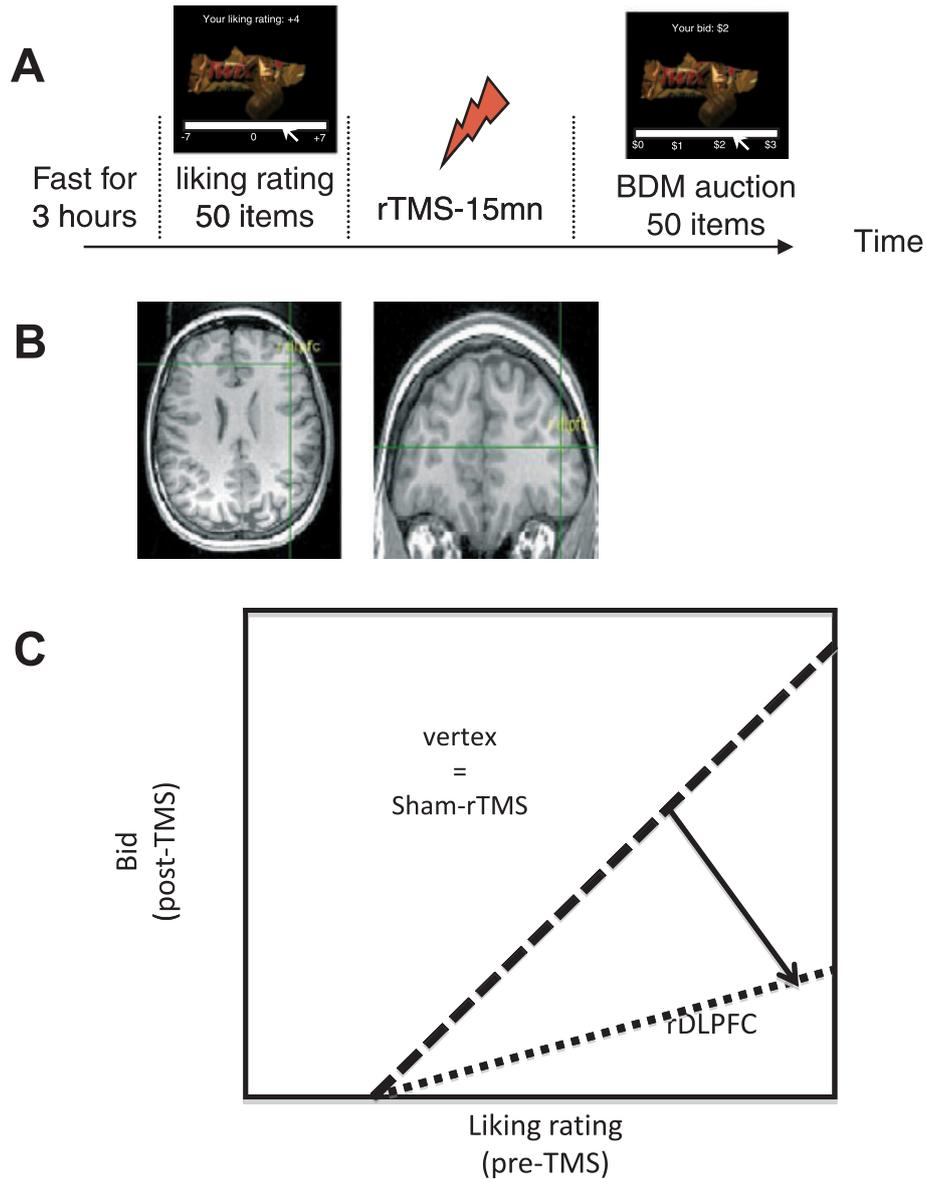


FIG. 1. Experimental design and hypotheses. (A) Timeline of Experiment 1. Subjects fasted for 3 h before the experiment. The task consisted of two parts: a liking-rating task, and a Becker–DeGroot–Marschak (BDM) auction task. Each task lasted approximately 7.5–10 min. Between the two tasks, subjects received 15 min of repetitive transcranial magnetic stimulation (rTMS) in one of four conditions: C1, right dorsolateral prefrontal cortex (rDLPFC), which was the treatment condition; C2, another DLPFC condition, which was a replication of the main treatment; C3, vertex, which was an active control condition; and C4, sham stimulation over the same area of the DLPFC, which was a second control condition. Subjects entered liking ratings in a -7 to $+7$ rating scale. They were allowed to bid between \$0 and \$3 dollars for each item. (B) Location of the target areas for rTMS in the DLPFC condition ($x = 44, y = 44, z = 18$). (C) Hypothesized results. The liking rating, depicted on the x-axis, is a measure of goal value taken prior to rTMS, and thus provides a measure of the value assigned to each food item in the absence of any stimulation effects. The bid, depicted on the y-axis, is a different measure of value taken immediately after the rTMS stimulation. The relationship between both measures is the bidding curve. Note that the pre-rTMS and post-rTMS data exhibit a spline relationship: bids are zero for items with liking ratings below a threshold liking rating, which we refer to as the kink, but linearly increase for values above that. The thick line denotes the hypothesized bidding curve for the control vertex and sham-rTMS conditions. Thus, the figure reflects the hypothesis that rTMS over the vertex has no effect on the computation of values. The thin line denotes the hypothesized effect of applying rTMS over the DLPFC. Note that, under this hypothesis, the post-rTMS bidding curve still increases in the underlying value of the items (as measured by the liking ratings), but that the rate of increase is lower. We refer to this effect as a downmodulation of the goal value signal.

In the first DLPFC ($N = 22$) and vertex conditions, subjects were only allowed to bid discrete amounts for the items (\$0, \$1, \$2, or \$3) by pressing a button. As a consequence, the bids were only approximations of the goal values computed by subjects. For example, when the true value was \$2.3, our measure was \$2. Similarly, subjects with a value larger than \$3 entered a bid of \$3. However, this approximation led to bids that were a monotonic function of the goal values and highly correlated with them. In order to improve this aspect

of the design, in the last two conditions subjects were allowed to bid any amount between \$0 and \$3 by clicking in an analog scale with a mouse (Fig. 1A).

Note that the liking ratings were a measure of the goal value that the subjects assigned to the different items at the time of decision-making in the absence of the disruptions caused by rTMS. In contrast, the bids were a measure of the goal value assigned to the items after the application of rTMS. A different method was used to measure value

pre-rTMS and post-rTMS, to minimize consistency and memory biases. The relationship between bids and liking ratings is referred to as the bidding curve. Fig. 1C depicts a hypothetical bidding curve. Note several things about the relationship. First, when the items are sufficiently negative (as measured by the liking rating), subjects bid zero for them. The true value of such items is negative, but subjects bid zero for them because they cannot bid a negative amount. Second, the bids are positive for items with a sufficiently large liking rating and increase with the liking rating. The resulting bi-linear pattern is known as a spline.

rTMS

rTMS was applied immediately after the liking-rating task, using a Magstim-200 stimulator (maximum magnetic field strength of 2.0 T; Magstim, Dyfed, UK) and a figure-of-eight coil (70-mm-diameter double circle, air cooled; Magstim). There were three different stimulation conditions.

The DLPFC group received stimulation over the right DLPFC (Fig. 1B; $x = 44$, $y = 44$, $z = 18$). This target area was selected on the basis of the work of Plassmann *et al.* (2007), who found that blood oxygen level-dependent activity in this region correlated with the goal values during decision-making in the BDM task. The peak coordinates from their group activation maps were used as the target area for rTMS. These coordinates were projected onto the subjects' anatomy using an inverse warping from the Montreal Neurological Institute standard space. The location was determined in each individual, using a frameless neuronavigation system (Brainsight; Rogue Research Inc., Montreal, Canada) that allowed us to co-register the individual anatomical magnetic resonance images with the target stimulation coordinates. The coil was positioned tangentially to the scalp, pointing in an anteromedial direction, 45° from the midsagittal plane axis of the subject's head. Stimulation intensity was set at 50% of the stimulator maximum. Subjects received a single, 15 min, 1 Hz rTMS train (900 pulses) over the target area. Note that these parameters are well within currently recommended guidelines, and are thought to result in suppression of the excitability of the targeted cortical region for several minutes after completion of the rTMS train (Phillips *et al.*, 1999; Walsh & Rushworth, 1999; Walsh & Pascual-Leone, 2003).

Two control groups were used. The first one received stimulation over the vertex, using the same parameters described above (15 min, 1 Hz rTMS train at 50% of the stimulator maximum). The coil was placed in contact with the scalp parallel to the midline, and its center was aligned anteroposteriorly against the vertex, according to the 10/20 system for electroencephalography electrode placement. The second control group received sham rTMS over the right DLPFC, using a figure-of-eight placebo-stimulator (Double 70 mm Placebo Coil System, air cooled; Magstim). The center of the coil was placed over F4 of the international 10/20 system for stimulation of the DLPFC (Jahanshahi *et al.*, 1998). No subjects had to be removed from the study because of head movement or other technical complications.

Data analysis

The data were analysed in several steps. First, for every subject, a bi-linear spline of bid on liking rating was estimated. The model assumed that bids were zero for items with liking ratings below an unknown threshold value, which we call the kink, and linear and non-negatively sloped for higher liking ratings. The justification for using this model is described in the text. The slope in the positive liking-rating range is referred to simply as the 'slope'. Second, two-sample *t*-tests of the individual slope coefficients between all of the relevant groups (Fig. 2B) and of the location of the kinks (Fig. 2C) were performed.

Third, for each individual, sum-of-square residuals were computed for the spline regression and compared across conditions using two-sample *t*-tests (Fig. 2D).

Experiment 2

Subjects

Fifteen different normal-weight subjects (eight males, mean age, 21 years; age range, 19–25 years) participated in Experiment 2. The same screening criteria as in Experiment 1 were applied to the subjects.

Task

The task was very similar to that in Experiment 1, and thus only the differences are described. Instead of valuing the foods, subjects were asked to estimate their caloric content. In the first part of the experiment, before rTMS, they were asked to 'guess the caloric content of the foods' on a numerical scale from 1 (light) to 6 (heavy). In the second part of the experiment, immediately after the application of rTMS, subjects were asked to 'guess again the caloric content of the foods, this time, using a numerical scale that goes from 100 to 600+ calories (in 100 calorie bins)'. The performances of two groups were compared: (i) subjects receiving rTMS over the right DLPFC ($N = 7$); and (ii) subjects receiving rTMS over the vertex ($N = 8$). To make the two ratings more comparable in the analyses below, they were both normalized to 0–1 within subjects. No subjects had to be removed from the study because of head movement or other technical complications.

The stimulation protocol was identical to that for Experiment 1. The data analysis was also very similar, except that a standard linear regression with the intercept restricted to zero was used, instead of a bi-linear spline, to characterize the relationship between the pre-rTMS and post-rTMS caloric ratings. The justification for doing this is described in the text.

Results

Experiment 1

The logic of the experiment is simple. In the absence of rTMS effects (e.g. in the sham stimulation condition), there should be a monotonic and ideally nearly linear relationship between the two measures of goal value for items with sufficiently liked items. In contrast, if rTMS over the DLPFC were to completely abolish the brain's ability to produce a goal value signal, the bidding curve would correspond to a flat line passing through the origin. Our hypothesis, depicted in Fig. 1C, was that rTMS over the DLPFC would downmodulate the brain's ability to separate items with different underlying goal values, which amounts to a rotation of the bidding curve through the kink. Note that such a downmodulation would lead to a reduction on the slope of the bidding curve in the positive liking-rating area, but should have no effect on the location of the kink. In the rest of the article, we refer to the slope of the positive region simply as the slope.

The bidding curve for a typical subject in the sham condition is depicted in Fig. 2A. Note several things about the bidding curve. First, the bidding curve exhibits a spline relationship, and the bids are highly linearly correlated with the liking ratings in the positive region ($R^2 = 0.91$ for a linear regression in this region). Second, there is some noise in our pre-rTMS and post-rTMS measures of goal value, but as the high R^2 demonstrates, it is relatively small. Third, the liking ratings do not capture precisely the absolute values of the items, as most

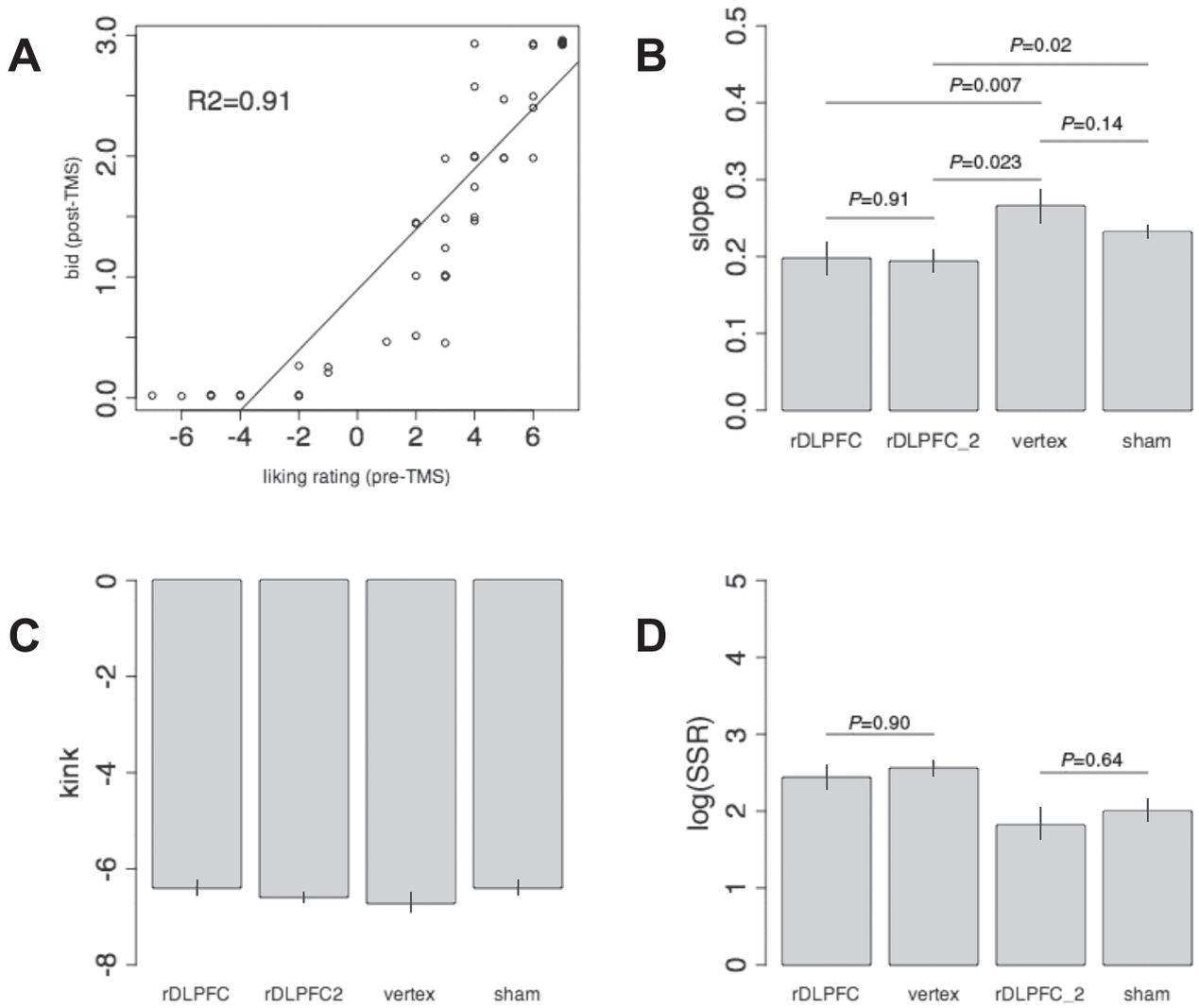


FIG. 2. Effects of repetitive transcranial magnetic stimulation (rTMS) on goal value computations. (A) Sample data for an individual in the sham condition of Experiment 1. The R^2 statistic refers to the increasing part of the spline. (B) Slope of the bidding curve in four different groups: first dorsolateral prefrontal cortex (DLPFC) group, second DLPFC group, vertex, and sham. A bi-linear regression of bid on liking rating was estimated for every subject. The slopes of the spline were then averaged across subjects in each of the groups. (C) Location of the kinks in each of the conditions. (D) Sum-of-squared residuals (SSRs) for the spline regression in the four different conditions. P -values denote the results of two-sample t -tests.

subjects, such as the one depicted in Fig. 2A, are willing to bid a positive amount for items that they rate as mildly negative. We suspect that this is due to the fact that they were asked to fast for several hours prior to the experiment, and thus were extremely hungry at the time of bidding.

A comparison of the four groups provides evidence consistent with our hypotheses. We fitted a linear spline model for every subject, and then compared differences in the slope and kink locations across the conditions. Fig. 2B shows that the slope was nearly identical in both DLPFC conditions, but there were significant differences between the slopes for the DLPFC conditions and the vertex and sham conditions. There was no significant difference between the slopes for the vertex and sham conditions. Fig. 2C shows that the average location of the kink was statistically indistinguishable among the four experiments (the lowest P -value among all possible pairwise comparisons was 0.07) and very close to the lower bound in the liking ratings. The results suggest that applying rTMS to the DLPFC downmodulates the bidding curve. The difference in the slope between the treatment and

sham conditions was 5 cents, which means that there was an average difference of 65 cents between the bids in the DLPFC and control conditions.

Figure 2D depicts the log of the sum-of-square residuals for the fitted spline model. This variable is interesting because it provides a measure of the amount of noise in the bidding process after rTMS. There were no significant differences between the first DLPFC experiment and the vertex condition, or between the second DLPFC experiment and the sham condition, but there was a significant difference between these two groups ($P < 0.01$). As described in Materials and methods, however, there was a small change in the experimental design between the first and second set of experiments: in the former case, subjects were only allowed to bid in discrete increments (\$0, \$1, \$2, and \$3), whereas in the latter case, they were allowed to bid in continuous amounts within the same range. This explains the difference in fits across the two conditions. Thus, we can conclude that there were no differences in noise between the treatment and equivalent control conditions.

Experiment 2

A potential concern with the previous experiment is that rTMS over the DLPFC might interfere with the general ability to make numerical estimates based on sensory data, and not just with the ability to compute values. The control experiment tested for this concern.

Figure 3A depicts the pre-rTMS ratings and post-rTMS ratings of a typical subject in the vertex condition. Note several things about the relationship. First, the two ratings are highly and nearly linearly correlated. Second, the relationship between the two variables is now a line instead of a spline. Third, the intersection for the linear regression of the post-rTMS rating on the pre-rTMS rating is close to the origin, as one would expect. For these reasons, a linear regression is used for the results described below (with an imposed restriction, based on the individual data, that the intercept be at zero), instead of a spline regression.

Figure 3B and C summarizes the results of the control experiment, which were analysed in a similar manner to those of the first experiment. There were no significant differences between the rTMS and control conditions in either the slope (Fig. 3B) or the amount of

noise (Fig. 3C). This suggests that the impact of applying rTMS over the right DLFC is not due to an impairment of the ability to make numerical calculations based on sensory data.

Discussion

The results of the first experiment show that applying inhibitory low-frequency rTMS over the DLPFC causes a downmodulation of the computation of goal values at the time of decision-making. The results of the second experiment suggest that the effect might be specific to the computation of goal values, and not a general decrease in the ability to make numerical estimates based on the sensory properties of stimuli.

The DLPFC is known to perform a variety of cognitive functions, including the top-down modulation of posterior brain regions (Miller, 2000; Miller & Cohen, 2001; Milham *et al.*, 2003), maintenance of information in working memory (Levy & Goldman-Rakic, 2000; Petrides, 2000; Curtis & D'Esposito, 2004), and manipulation of information in working memory (Petrides, 2000). Several studies have also shown that the activities of some parts of the DLPFC are

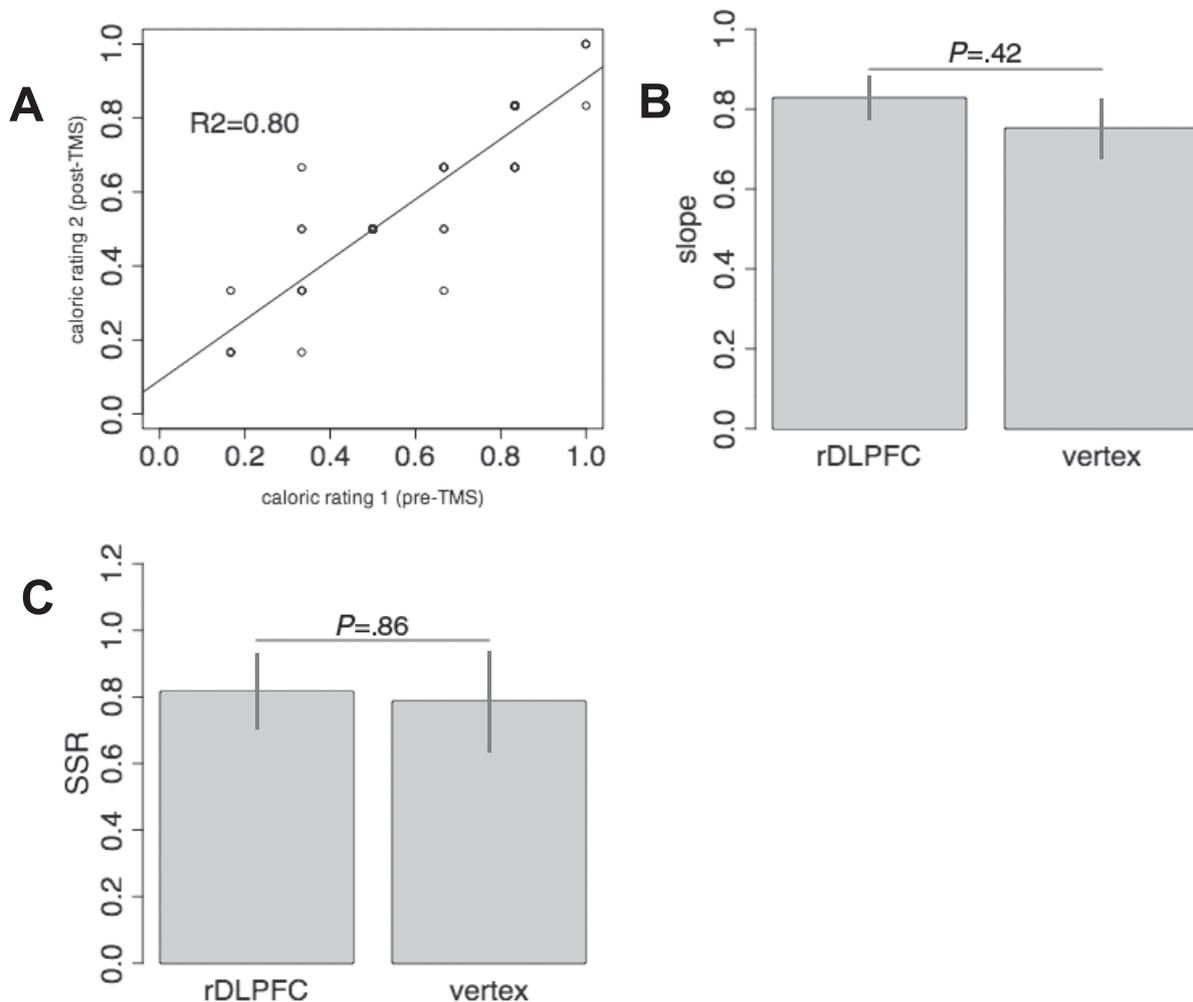


FIG. 3. Effect of repetitive transcranial magnetic stimulation (rTMS) on caloric estimates. (A) Sample data for an individual in the vertex condition of Experiment 2. Note that the pre-rTMS and post-rTMS caloric rating data exhibit a standard linear relationship and that the intercept is approximately zero. The R^2 statistic refers to the linear regression of the post-rTMS measure on the pre-rTMS measure. (B) Slope of the caloric rating curve (relating the post-rTMS caloric measure to the pre-TMS caloric measure) in the dorsolateral prefrontal cortex (DLPFC) and vertex conditions. A linear regression of the post-rTMS caloric rating on the pre-rTMS caloric rating was estimated for every subject. The slope coefficients were averaged across subjects in each of the two groups. In order to maximize the comparability of the two caloric measures, both ratings were re-scaled to 0–1. The regression imposes the restriction that the intercepts be equal to zero. (C) Sum-of-square residuals (SSRs) in the DLPFC and vertex conditions computed using the same regression analysis. P -values denote the results of two-sample t -tests.

correlated with various measures of value during perceptual and economic decision-making tasks (Kim & Shadlen, 1999; Pieters *et al.*, 1999; Wallis & Miller, 2003; Barraclough *et al.*, 2004; Plassmann *et al.*, 2007; Seo *et al.*, 2007; Delgado *et al.*, 2008). However, the exact role that these signals play in the computation of values during decision-making is not known. The results given in this article suggest that the DLPFC is causally involved in the computation of values.

There are two natural explanations for this effect. The first one is based on the widely proposed hypothesis that the OFC might be an area where multiple sensory, affective and cognitive inputs converge and are integrated into a goal value signal for every stimulus under consideration, and that the value signals computed here might be the ultimate drivers of goal-directed choices (Wallis, 2007; Rangel, 2008; Rangel *et al.*, 2008; Padoa-Schioppa & Platt, 2009). If this hypothesis is confirmed, one of the roles of the DLPFC in goal-directed choice might be to send critical inputs to the OFC that are then integrated with other sensory and memory inputs into a value signal. According to this theory, low-frequency rTMS of the DLPFC downmodulates the goal values computed in the OFC by reducing the number of such inputs. This model is consistent with our results, because fewer inputs from the DLPFC would translate into a smaller value signal in the OFC, which in our experiment would show up as a downmodulation of the bidding curve, as illustrated in Fig. 1C. A few additional pieces of evidence provide support for this interpretation. First, the hypothesized role of the DLPFC is consistent with its well-known general involvement in top-down modulation of other brain areas (Miller, 2000; Miller & Cohen, 2001; Milham *et al.*, 2003). Second, recent studies of emotional regulation (Delgado *et al.*, 2008) and self-control (Hare *et al.*, 2009) have shown that this area of the DLPFC exhibits functional connectivity with the OFC during affective and decision-making valuation tasks.

A second, and more direct, explanation of the findings is that the targeted area of the DLPFC is perhaps one of the regions where input from other areas is integrated into a goal value signal. In this case, low-frequency rTMS would make the DLPFC less sensitive to such inputs, and this should also lead to a smaller goal value signal. Although it is impossible to distinguish between the two hypotheses using only the results from this study, findings from a related study provide evidence against this second explanation. In a recent study on the neurobiology of self-control, Hare *et al.* (2009) found that a very similar area on the DLPFC, although contralateral to the region stimulated here, exhibited two key properties. First, its activity did not significantly correlate with goal values, which rules out this second explanation. Second, it exhibited positive functional connectivity with the areas of the medial OFC encoding values, which is consistent with the previous explanation.

Our results are related to several other recent studies that have used either rTMS or transcranial direct current stimulation (tDCS) to inhibit activity in the DLPFC in a decision-making context. First, consistent with our findings, Fregni *et al.* (2008b) have shown that reported food cravings and food consumption can be modulated by applying tDCS to the DLPFC. In closely related findings, several studies have shown that stimulation of the DLPFC with either rTMS (Eichhammer *et al.*, 2003; Camprodon *et al.*, 2007) or tDCS (Boggio *et al.*, 2008; Fregni *et al.*, 2008a) reduces reported cravings for the consumption of various substances. This article contributes to this literature by showing that the DLPFC can affect decision-making specifically through its role in the computation of goal values.

Second, Knoch *et al.* (2006a,b) have shown that inhibitory stimulation of the right, but not the left, DLPFC leads to a decrease in risk-taking and in subjects' willingness to reject unfair offers in the ultimatum game. A natural interpretation of these findings, consistent

with the first interpretation of our results, is that the right DLPFC exhibits a modulatory role of the goal value signal in the OFC during these two tasks by reducing the value assigned to high-risk gambles and decreasing the influence of emotions such as anger on the valuation process. Also related to this hypothesis is the involvement of the DLPFC in emotional regulation (Ochsner & Gross, 2005; Delgado *et al.*, 2008). The findings reported in this article show that the modulatory effects of the DLPFC might be important even in tasks that do not require explicit self-control or emotional control, as was the case in Experiment 1, as subjects were screened to ensure that they were non-dieters.

Several potential concerns with the rTMS protocol used need to be addressed. First, we applied rTMS at low frequencies (1 Hz or less), and, in our interpretation of the results, have assumed that this would interfere with the computations carried out by the targeted DLPFC area. This is justified on the basis of the findings of a large number of previous studies that have found such interference effects in a wide range of behavioral paradigms (Chen *et al.*, 1997; Fox *et al.*, 1997; Tergau *et al.*, 1997; Wassermann *et al.*, 1997, 1998; Boroojerdi *et al.*, 2000; Pascual-Leone *et al.*, 1998; Maeda *et al.*, 2000; Muellbacher *et al.*, 2000; Hilgetag *et al.*, 2001; Knoch *et al.*, 2005) and inhibitory effects in experiments combining positron emission tomography and rTMS (Fox *et al.*, 1997; Wassermann *et al.*, 1997). More specifically, several previous studies have found inhibitory effects of applying low-frequency rTMS to the DLPFC in a variety of tasks: working memory (Pascual-Leone & Hallett, 1994; Robertson *et al.*, 2001; Mottaghy *et al.*, 2002), random number generation (Knoch *et al.*, 2005), attention (Wagner *et al.*, 2006; Johnson *et al.*, 2007), and sequence learning (Robertson *et al.*, 2001).

A second concern is the actual duration of the modulatory effects of rTMS, which is applied 'off-line' before the actual bidding task. In this experiment, we stimulated for 15 min, and all of the subjects completed the bidding task in 10 min or less, which is within the accepted norms in the rTMS literature (Robertson *et al.*, 2003). For example, studies of this issue in the motor system found that the decrease in corticospinal excitability lasted for up to half the stimulation time in one study (Chen *et al.*, 1997) and for twice that time in another (Muellbacher *et al.*, 2000), studies in the visual cortex found that cortical excitability was decreased for 10 min after 15 min of rTMS (Boroojerdi *et al.*, 2000), one study on the effects of the DLPFC on working memory found that the inhibitory effect lasted for 5 min after 10 min of stimulation (Mottaghy *et al.*, 2002), and a positron emission tomography study of the effects of low-frequency rTMS over the DLPFC found that its neurophysiological effects lasted for over 60% of the stimulation time (Eisenegger *et al.*, 2008). This suggests that the inhibitory effects of rTMS were probably present in our experiment during the entire bidding task.

Third, an important limitation of rTMS is a lack of detailed knowledge about the spatial resolution of the technique, which makes it hard to stimulate a highly specific anatomical region. Some studies of single-pulse transcranial magnetic stimulation have argued that the spatial resolution at the scalp surface might be in the range 0.5–1 cm (Jahanshahi & Rothwell, 2000; Walsh & Cowey, 2000). However, it might be the case that prolonged stimulation during rTMS leads to less localised effects (Pascual-Leone & Hallett, 1994). In addition, several studies have shown that rTMS can induce effects at remote locations connected to the region being stimulated (Fox *et al.*, 1997; Ilmoniemi *et al.*, 1997; Paus *et al.*, 1997, 1998). An additional concern is that rTMS might also affect the excitability in fibers passing through the area. However, it is worth emphasizing that in the study of Plassmann *et al.* (2007), the only two areas where blood oxygen level-dependent activity correlated with goal values were the target location of DLPFC

stimulation and the medial OFC. Given the distance between the two structures, it is highly unlikely that the OFC was directly affected by the rTMS, although, given the high level of interconnectedness between these two areas (Barbas & Pandya, 1989), it is likely that the stimulation had an indirect effect on the OFC through changes in the levels of DLPFC activity.

To summarize, we have found that applying rTMS to the right DLPFC caused a decrease in the values assigned to food stimuli. These results are consistent with the possibility that the DLPFC plays a causal role in the computation of values at the time of choice, perhaps by sending inputs into the OFC that are integrated with other signals to compute values for stimuli at the time of decision-making.

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Abbreviations

BDM, Becker–DeGroot–Marschak; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; OFC, orbitofrontal cortex; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

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