Targeted Stimulation of Human Orbitofrontal Networks Disrupts Outcome-Guided Behavior

Highlights

- Animal orbitofrontal cortex (OFC) is critical for responding in the devaluation task
- Connectivity-guided TMS of human OFC impairs choices for devalued outcomes
- OFC-targeted TMS disrupts orbitofrontal network connectivity, predicting behavior
- OFC-targeted TMS does not impair value-based choices in general

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In Brief
Howard et al. show that indirectly targeting orbitofrontal cortex (OFC) with TMS disrupts choices that require inference without affecting value-based choices in general. Moreover, TMS reduces OFC network connectivity, and the magnitude of this effect predicts individual differences in the behavioral impairment.
Targeted Stimulation of Human Orbitofrontal Networks Disrupts Outcome-Guided Behavior

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SUMMARY

Outcome-guided behavior requires knowledge about the current value of expected outcomes. Such behavior can be isolated in the reinforcer devaluation task, which assesses the ability to infer the current value of specific rewards after devaluation. Animal lesion studies demonstrate that orbitofrontal cortex (OFC) is necessary for normal behavior in this task, but a causal role for human OFC in outcome-guided behavior has not been established. Here, we used sham-controlled, non-invasive, continuous theta-burst stimulation (cTBS) to temporarily disrupt human OFC network activity by stimulating a site in the lateral prefrontal cortex that is strongly connected to OFC prior to devaluation of food odor rewards. Subjects in the sham group appropriately avoided Pavlovian cues associated with devalued food odors. However, subjects in the stimulation group persistently chose those cues, even though devaluation of food odors themselves was unaffected by cTBS. This behavioral impairment was mirrored in changes in resting-state functional magnetic resonance imaging (rs-fMRI) activity such that subjects in the stimulation group exhibited reduced OFC network connectivity after cTBS, and the magnitude of this reduction was correlated with choices after devaluation. These findings demonstrate the feasibility of indirectly targeting the human OFC with non-invasive cTBS and indicate that OFC is specifically required for inferring the value of expected outcomes.

INTRODUCTION

To make adaptive choices, organisms must anticipate the value of expected outcomes. In the face of continually changing motivational states and external contingencies, this requires the ability to infer the current value of specific outcomes on the fly, without the need for new learning [1, 2]. For example, when perusing the menu at a new restaurant, we can readily infer how much we will like each option and make a choice without having to try each one first. Such inference, or mental simulation, is a hallmark of outcome-guided behavior, distinguishing it from behavior that can be based on first-hand experience [3, 4].

Decisions that require inference can be isolated in the reinforcer devaluation paradigm, in which responses to a predictive cue are probed after selective devaluation of an associated outcome [5]. Experiments in rodents and nonhuman primates demonstrate that inactivation of the orbitofrontal cortex (OFC) results in continued responding to Pavlovian cues predicting a devalued outcome, indicating an inability to infer its new value [6–13]. Yet, although neuroimaging studies show a correlation between human OFC activity and updated reward expectations in devaluation tasks [14–16], definitive evidence in support of a causal role for human OFC in outcome-guided behavior is lacking.

Activity in the human brain can be modulated non-invasively using transcranial magnetic stimulation (TMS) [17]. Yet, due to its anatomical location, the OFC is not directly accessible to surface stimulation techniques, such as TMS, making it difficult to test the causal role of OFC in inference-based decisions in healthy humans. However, previous studies have demonstrated that TMS can affect brain function at locations beyond the stimulation site [18–21]. Moreover, continuous theta-burst stimulation (cTBS) protocols have been shown to modulate network-level activity of regions functionally connected to the stimulation site [22–28]. Here, we adopted this approach by administering cTBS unilaterally to a right lateral prefrontal cortex (LPFC) site that is both anatomically [29–31] and functionally [32] connected with OFC.

We targeted a central/lateral section of OFC, which has previously been shown to correlate with specific outcome expectations [33–35] and inactivation of which causes deficits in the devaluation task in nonhuman primates [10, 11]. The specific LPFC coordinate of stimulation was individually determined to have maximal resting-state functional magnetic resonance imaging (rs-fMRI) connectivity with this intended OFC target. We...
hypothesized that targeting a region functionally connected to OFC would temporarily disrupt activity in the larger OFC network and thus selectively impair inference-based choices in the devaluation task.

RESULTS

Learning of Cue-Outcome Associations during Training

We administered cTBS to two groups of healthy subjects (STIM: n = 28, cTBS at 80% resting motor threshold [RMT]; SHAM: n = 28, cTBS at 5% RMT) in the context of a reinforcer devaluation task (Figure 1A). In an initial training session, hungry subjects learned associations between visual cues (i.e., conditioned stimuli) and two individually selected food odor rewards (i.e., unconditioned stimuli; Figures 1B and 1C). On the next day, preferences for the two food odors predicted by these cues were assessed in a baseline free-choice task. Subjects then received cTBS to the individually determined LPFC coordinate that was maximally connected to the intended target in central/lateral OFC (Figure 1D; STAR Methods), followed by feeding to satiety and session (baseline/probe) on pleasantness ratings (three-way ANOVA; Table 1). The effect of cTBS on choices for these food odors was then measured in a probe session (Figures 1B and 1C). On the next day, preferences for the two food odors predicted by these cues were assessed in a baseline free-choice task. Subjects then received cTBS to the individually determined LPFC coordinate that was maximally connected to the intended target in central/lateral OFC (Figure 1D; STAR Methods), followed by feeding to satiety and session (baseline/probe) on pleasantness ratings (three-way ANOVA; Table 1). The effect of cTBS on choices for these food odors was then measured in a probe session (Figures 1B and 1C).

In the training session conducted on day 1, subjects in the STIM and SHAM groups learned the cue-outcome associations equally for both the sated (SA) and non-sated (NS) choice types (three-way ANOVA with time [trial blocks] and condition [SA/NS] as within-subject factors and group [STIM/SHAM] as a between-subject factor: main effect of time: $F_{3,54} = 97.2, p = 4.97 \times 10^{-36}$; main effect of group: $F_{1,54} = 0.72, p = 0.40$; group $\times$ time interaction: $F_{3,162} = 0.58, p = 0.63$; group $\times$ time $\times$ condition interaction: $F_{3,162} = 1.42, p = 0.24$; Figure 2A). Note that the abbreviations SA and NS refer to odors that are designated to be sated and to be non-sated before the meal (i.e., in training and baseline sessions) and are sated and non-sated after the meal (i.e., in the probe session).

Selective Devaluation of Food Odors

Based on previous studies [16, 36, 37], we expected that consumption of a meal would result in devaluation of the odor related to that meal (SA) and little or no change in value to the odor unrelated to the meal (NS). To formally test this, we compared odor pleasantness ratings acquired for SA and NS at the beginning of the baseline phase to odor pleasantness ratings acquired immediately after the meal at the beginning of the probe phase. There was a significant interaction between condition (SA/NS) and session (baseline/probe) on pleasantness ratings (three-way ANOVA; $F_{1,54} = 34.6, p = 2.60 \times 10^{-7}$) but no main effect of group ($F_{1,54} = 2.36, p = 0.13$) or interaction involving group (group $\times$ condition; $F_{1,54} = 1.10, p = 0.30$; group $\times$ session; $F_{1,54} = 1.17, p = 0.28$; group $\times$ condition $\times$ session; $F_{1,54} = 0.54, p = 0.46$; Figure 2B). Follow-up two-way ANOVA revealed significant interactions between condition and session in both groups (SHAM: $F_{3,27} = 22.3, p = 6.42 \times 10^{-5}$; STIM: $F_{3,27} = 13.0, p = 0.0012$), which were driven by a decrease in pleasantness for the SA odor (SHAM: $t_{27} = 4.69, p = 7.02 \times 10^{-6}$; STIM: $t_{27} = 4.29, p = 2.02 \times 10^{-4}$, paired t tests), and no change in pleasantness for the NS odor (SHAM: $t_{27} = 0.02, p = 0.99$).
STIM: $t_{27} = 0.60$, $p = 0.55$; paired t tests). Thus, consistent with prior work, disruption of OFC activity did not affect the ability to update the value of rewards themselves [11, 12, 38].

### Indirect OFC-Targeted cTBS Disrupts Choices for Devalued Outcomes

We next tested whether targeted OFC stimulation had an effect on subjects’ ability to infer that new value to adapt their choice behavior. For this, we first calculated the percentage of choice trials in which cues predicting the SA odor were chosen over cues predicting the NS odor across the entire baseline session and then compared this to the percentage of choices for cues predicting the SA odor in the earliest trials of the probe session. If subjects are able to infer the lower value of the SA odor, they should be more likely to choose cues predicting the NS odor when first given the choice between the two after the meal. If, however, inference is impaired, subjects should continue to choose cues predicting the SA odor in probe at the same rate as in baseline. We focus on the earliest trials of probe because this session was conducted in extinction (i.e., odorless air was delivered, regardless of which cue was selected), and therefore, these trials should reflect current associations rather than newly learned associations between the cues and odorless air.

A two-way ANOVA revealed an interaction between group (SHAM/STIM) and session (baseline/probe) on percent SA-predicting cues chosen ($F_{1,54} = 8.03; p = 0.0064$; Figure 3A). This effect was driven by a significant decrease in choices for the SA cues after devaluation in the SHAM group ($t_{27} = 4.23; p = 2.37 \times 10^{-4}$; paired t test; baseline versus 1st probe block) and no change in responding in the STIM group ($t_{27} = 1.34; p = 0.19$; paired t test; baseline versus 1st probe block; Figure 3B). The percentage of SA-predicting cues chosen was different between groups in the 1st probe block ($t_{54} = 2.83; p = 0.0064$; two-sample t test) but was not different in subsequent blocks ($p > 0.57$), suggesting subjects learned that odorless air would be delivered regardless of the cue chosen.

Thus, although subjects in the SHAM group redirected choices away from cues predicting the devalued odor, subjects in the STIM group failed to show this effect of selective devaluation on choices and continued to respond at the same rate as in baseline. This group difference was also evident on the very first trial of the probe session (% SA cues chosen; SHAM versus STIM: $t_{54} = -2.44; p = 0.0176$; two-sample t test; Figure 3), further demonstrating that OFC-targeted cTBS, much like lesions to or inactivation of OFC in animal studies [5–13], impaired the ability to infer the new value of the devalued outcome.

### Indirect OFC-Targeted cTBS Reduces Global Connectedness of OFC

To characterize the effects of OFC-targeted cTBS on OFC network activity, we analyzed rs-fMRI data acquired the day before (day 1) and immediately after (day 2) stimulation. For this, we first calculated a measure of global “connectedness” for each voxel, defined as the average absolute (i.e., unsigned) correlation between each voxel’s rs-fMRI time series and that of every other voxel in the brain (STAR Methods). We then computed the change in global connectedness from day 1 to day 2 to generate subject-specific difference maps and compared these difference maps between STIM and SHAM at the group level. This analysis revealed a focal effect of stimulation on connectedness in OFC ($x = 34, y = 50, z = -8; p = 0.00036$; Figure 4A). Post hoc tests confirmed that the significant group effect in OFC was driven by reduced OFC network connectivity in the STIM group ($Z = 2.30; p = 0.021$; Wilcoxon signed rank test), whereas no changes were found in the SHAM group ($Z = 1.34; p = 0.18$; Wilcoxon signed rank test; Figure 4B). There were no differences between groups on day 1 ($Z = 1.38; p = 0.17$; Wilcoxon signed rank test).

To illustrate the brain areas that contributed to the group difference in OFC connectedness, we performed a whole-brain connectivity analysis using the OFC as a seed area. This analysis showed that the global connectedness effect in the OFC was driven by relatively widespread but weak decreases in absolute connectivity in distributed cortical areas, including cingulate cortex, lateral prefrontal cortex, posterior parietal cortex, ventrotemporal cortex, and contralateral OFC (Figure S2; STAR Methods). Follow-up analysis showed that this effect was only present in areas that are part of the central/lateral OFC network that was targeted here ($t_{54} = 2.60; p = 0.012$), as previously identified using connectivity-based parcellation of OFC [32], whereas no group differences were observed in the medial OFC network identified in the same study that was not targeted here ($t_{54} = 1.35; p = 0.18$).

We next asked whether the significant change in connectedness in the STIM group was related to the behavioral impairment observed in the choice task. We hypothesized that, if behavioral changes were related to changes in global OFC connectivity,
stronger reductions in OFC connectedness should be accompanied by a higher probability of selecting the cue associated with the devalued outcome in the probe test. In line with this prediction, we found that subjects in the STIM group with a larger reduction in OFC network connectivity (median split) were more likely to choose the cue predicting the devalued odor (Figure 1B). If OFC-targeted cTBS affects the ability to access or choose based on previously established value associations, we would expect STIM subjects to respond randomly in the probe session on these trials.

In a three-way ANOVA, there was no interaction between group, session, and condition on the percentage of trials in which cues predicting an odor were chosen (F1,54 = 0.035; p = 0.85). Follow-up tests revealed that the percentage of odor-predicting cues chosen was above chance in the baseline session for both conditions in both groups (SHAM: t27 = 6.80, p = 2.62 × 10−7; STIM: t27 = 5.56, p = 6.80 × 10−6; STIM: t27 = 7.15, p = 1.09 × 10−7; paired t tests) and remained above chance in the first trial block of the probe session (SHAM: t27 = 2.58, p = 0.016; SHAM: t27 = 6.80, p = 2.62 × 10−7; STIM: t27 = 3.10, p = 0.0045; STIM: t27 = 6.02, p = 2.01 × 10−6; paired t tests; Figure S1). These data show that subjects in the STIM group were not responding randomly, indicating that, similar to what has been shown with reversible inactivation of OFC in nonhuman primates [10], cTBS did not disrupt general perceptual or choice-related functions.

**Outcome-Guided Choices Are Not Affected by Incidental Effects of TMS**

It is possible that our results were driven by incidental effects of cTBS, such as stress or anxiety caused by stimulation of facial muscles and general discomfort associated with cTBS to frontal areas. To rule this out, we repeated the experiment in an independent sample (N = 10) using a control stimulation (CTLS) protocol, designed to induce comparable levels of facial muscle movement and general discomfort but without inducing changes in underlying neural activity (STAR Methods). Subjects in the CTLS group learned the initial cue-outcome associations (% odor-predicting cues chosen in final learning block versus chance, SA: t9 = 4.53, p = 0.0014; STIM: t9 = 12.5, p = 5.32 × 10−7; paired t tests; Figure 5A) and showed selective devaluation of the odor related to the consumed meal (two-way ANOVA, session × condition interaction: F1,9 = 17.0, p = 0.0026; driven by a change in pleasantness for the SA odor [t9 = 4.71; p = 0.0011] and no change for the NS odor [t9 = 0.50; p = 0.63; Figure 5B]). Three-way ANOVAs indicate learning and devaluation were comparable to SHAM and STIM subjects (learning, group × time × condition interaction: F9,63 = 0.92, p = 0.48; devaluation, group × session × condition interaction: F9,63 = 1.46, p = 0.24).

Most importantly, CTLS subjects showed a significant effect of devaluation on their choice behavior (% SA-predicting cues chosen, mean baseline versus 1st probe trial block: t9 = 2.63, p = 0.027, paired t test; % SA-predicting cue chosen on 1st probe trial versus chance: t9 = 4.00, p = 0.0031; one-sample t test; Figure 5C). This effect was significantly different from the STIM group (t9 = 1.89; p = 0.033; one-tailed; two-sample t test) but similar to the SHAM group (t9 = 0.48; p = 0.64; two-sample t test). Finally, we found that the CTLS stimulation had no effect on connectedness in the same OFC region observed in the STIM group (Z = 1.40; p = 0.16; Wilcoxon signed rank test; Figures 5E and 5F), and OFC connectedness was not related to choices in the probe test (X21 = 1.11; p = 0.29; chi-square test). Together, results from this control experiment suggest that unspecific effects
of stimulation are very unlikely to account for the behavioral effects observed with cTBS.

**DISCUSSION**

The primary contribution of OFC to decision making has been a matter of long-standing debate [40]. Prominent theories postulate that OFC is necessary for response inhibition [41], representing somatic markers [42], storing stimulus-outcome associations [43], prediction errors [44], credit assignment [45], signaling specific outcome expectations [46], or computing economic value [47]. This diversity of proposals is reflected in the heterogeneity of decision-related signals encoded in this region [35, 48–59], even in individual studies. For instance, a recent electrophysiological recording study in human neurosurgery patients found that a variety of choice and outcome variables, such as value, risk, and regret, were correlated with OFC activity [60].

In the face of such promiscuous neural coding in OFC, studies that use experimental lesions or reversible disruption of activity are indispensable for providing a clearer picture of its critical contribution [61]. By administering non-invasive OFC-targeted stimulation in the context of a devaluation task, here we provide evidence for a specific causal role for OFC in outcome-guided behavior in healthy humans, echoing previous work in rats [6–9], nonhuman primates [10–13, 62], and human patients with lesions encompassing this area [63]. These studies all converge on the finding that OFC is critical for flexibly linking predictive cues to expected rewards and their current value.

Our results are also compatible with previous human imaging [14–16] and animal recording studies using devaluation tasks [64, 65], indicating that OFC activity is specifically modulated in response to cues predicting devalued outcomes. Together with the lesion studies cited above, these results suggest that OFC is critical for value-based decision making but only when the value of specific outcomes has to be inferred [14, 40, 66]. It is possible that value is just one of many potentially relevant features of expected outcomes, including their timing, probability, and sensory properties, that together make up a cognitive map of task space that enables the model-based simulation or inference of future outcomes [67–69]. This theoretical framework can reconcile the multitude of decision-related signals previously found in the OFC.

In terms of anatomical connections, the OFC area targeted in the current study corresponds to the “orbital” (as opposed to the “medial”) OFC network [70]. In terms of functional connections, this region also corresponds to a “central/lateral” OFC network, which overlaps considerably with the orbital network, and was delineated according to rs-fMRI connectivity with the rest of the brain [32]. Neuroimaging studies have shown that both the anterior [33] and posterior [14, 35] portions of central/lateral
OFC represent the specific identity of expected rewards. Moreover, a recent devaluation study in macaques showed that inactivation of anterior OFC after satiation (but not before) impairs outcome-guided responses, and inactivation of posterior OFC prior to satiation (but not after) has similar behavioral effects [10]. This study suggests that anterior OFC is necessary for goal selection at the time of choice, whereas posterior OFC is necessary for associative value updating. This view is bolstered by recent work showing that specific outcomes are updated after selective devaluation in fMRI patterns of posterior OFC activity [14]. However, additional experiments that vary both the timing (e.g., after versus before devaluation) and the target of stimulation (e.g., posterior versus anterior OFC) would be necessary to dissociate the roles of anterior and posterior OFC subregions in human outcome-guided behavior.

Because the OFC is not directly accessible to TMS, we applied stimulation to a site in the LPFC that is maximally connected to the intended OFC target. This approach has previously been used to modulate activity in downstream areas connected to the stimulation site and has been shown to change behavior and functions that depend on these downstream areas [22–26]. However, on its face, it is possible that the behavioral effects observed here are due to activity changes in the LPFC rather than the OFC. We believe this is unlikely for several reasons. First, the connectedness analysis only identified effects of cTBS in the OFC, but not in the LPFC. Second, the behavioral effects of cTBS were directly related to effects of cTBS on OFC network connectivity, but not on LPFC connectivity. Finally, although multiple animal studies across different species have shown that OFC is necessary for responding in the reinforcer devaluation task [6–13], we are not aware of comparable positive findings in the LPFC. Taken together, although we cannot rule out the possibility that effects of cTBS on LPFC activity also contributed to the observed behavioral impairment in a way that was not measured here, we are confident that cTBS-induced modulation of OFC network connectivity was a significant factor.

It is important to note that our results provide evidence for the feasibility of targeting human OFC with non-invasive stimulation, thereby highlighting the potential of this technique to study the role of OFC in health and to modulate its function in disease. Disruption in OFC function is implicated in a variety of neurological and neuropsychiatric conditions, including depression [71, 72], obsessive compulsive disorder [73, 74], and substance abuse [75–77], and microstimulation of these networks has been shown to restore drug-induced behavioral deficits in animal models of addiction [78, 79]. Our results thus provide the basis for the development of novel stimulation protocols targeting OFC networks in humans to treat such disorders [17].

**STAR METHODS**

Detailed methods are provided in the online version of this paper and include the following:

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Supplemental Information can be found online at https://doi.org/10.1016/j.cub.2019.12.007.

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AUTHOR CONTRIBUTIONS

J.D.H. and T.K. conceived the study and designed the experiments with input from J.L.V. and G.S. J.D.H., D.E.S., and R.R. collected the data. J.D.H. analyzed the data. T.K. supervised the project. J.D.H., J.L.V., G.S., and T.K. wrote and revised the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR METHODS

KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---------------------|--------|------------|
| Deposited Data      |        |            |
| Whole-brain connectedness map | https://neurovault.org/collections/MARJGPJY/ | |
| Software and Algorithms |        |            |
| MATLAB              | https://www.mathworks.com/products/matlab.html | RRID:SCR_001622 |
| Statistical Parametric Mapping 12 | https://www.fil.ion.ucl.ac.uk/spm/ | RRID:SCR_007037 |
| BrainNet Viewer      | https://www.nitrc.org/projects/bnv/ | RRID:SCR_009446 |

LEAD CONTACT AND MATERIALS AVAILABILITY

Further information and requests should be directed to and will be fulfilled by the Lead Contact, Thorsten Kahnt (thorsten.kahnt@northwestern.edu). This study did not generate new unique reagents.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

A total of 89 subjects participated in the initial screening session (see Experimental design below). Of these, 56 subjects further participated in the main experiment and were randomly assigned to either the SHAM (n = 28, 16 female) or STIM (n = 28, 16 female) group. After the main experiment was conducted, an independent group of these subjects participated in the control experiment (CTLS, n = 10, 6 female). For demographic and other behavioral information by group, see Table 1. All subjects provided written consent to participate, reported no neurological or psychiatric disorders, no history of seizures, and were not currently taking psychotropic drugs. Eligibility for transcranial magnetic stimulation (TMS) was determined based on standardized safety guidelines [80]. Subjects were compensated with $20 per h for behavioral testing, and $40 per h for MRI scanning and TMS. The study was approved by the Northwestern University Institutional Review Board.

METHOD DETAILS

Odor stimuli and presentation
Eight food odors, including four sweet (pineapple cake, caramel, strawberry, gingerbread) and four savory (potato chips, pot roast, pizza, garlic), were provided by International Flavors and Fragrances (New York, NY) and Kerry (Melrose Park, IL). For all tasks, odors were delivered to participants’ noses using a custom-built computer-controlled olfactometer capable of redirecting medical grade air with precise timing at a constant flow rate of 3.2 L/min through the headspace of amber bottles containing liquid solutions of the food odors. The olfactometer is equipped with two independent mass flow controllers (Alicat, Tucson, AZ), allowing for dilution of odorants with odorless air. There was a constant stream of odorless air delivered throughout the experiment, and odorized air was mixed into this airstream at specific time points, with no change in the overall flow rate. Thus, odor presentation did not involve a change in somatosensory stimulation.

Food items
For the meal phase of the main experiment, food items with a dominant flavor note corresponding to one of the two odors selected for each participant were provided for consumption. These food items were as follows: pineapple cake odor: pineapple flavored cakes; caramel odor: caramel sauce on biscuits; strawberry odor: strawberry wafers; gingerbread odor: gingersnap cookies; potato chip odor: potato chips; pot roast odor: pot roast; pizza odor: cheese pizza; garlic odor: garlic bread. All food items were procured from Whole Foods, Trader Joe’s, H Mart, or Jewel Osco.

Experimental design
The experiment consisted of an initial screening session conducted in a behavioral testing room adjacent to the main lab space, followed by two consecutive days of experimental sessions (Day 1 and Day 2) conducted at a later date in rooms available at the MRI scanning facility. The Day 1 session of the main experiment was conducted on average 18.4 days (±1.77 days, s.e.m.) after the screening session. For all sessions, subjects were instructed to arrive in a hungry state, having fasted for at least 4-6 h prior to testing. Odor pleasantness ratings were made on a visual analog scale using a scroll wheel and mouse button press. Pleasantness rating anchors were “most liked sensation imaginable” and “most disliked sensation imaginable.”

Screening session
Subjects first rated the pleasantness of the 8 food odors. Based on visual inspection of these ratings by the experimenter, one sweet odor and one savory odor were selected such that they were both rated as pleasant (i.e., above the “neutral” line on pleasantness
scale), and matched as closely as possible in their rating. These 2 selected odors were then used as unconditioned stimuli for that individual subject for the remainder of the experiment. If these criteria were not met (e.g., if none of the 4 savory odors were rated above neutral in pleasantness), the subject was excluded from further participation in the experiment. Combined with subjects who “passed” the screening but were not available for scheduling of the main experiment at a later date, a total of 23 of the 89 subjects who participated in the screening session did not further participate in the Day 1 and Day 2 sessions described below.

**Day 1**

In a behavioral testing room adjacent to the MRI scanner, subjects first completed a training choice task to learn associations between abstract visual symbols and odor outcomes. This task consisted of 12 unique pairs of visual cues, randomly chosen for each subject independently. Within each pair, one cue was associated with an odor outcome, and one was associated with odorless air. Six pairs were associated with the sweet odor, and the other 6 were associated with the savory odor. On each trial of the task, the two cues in a given pair were presented on the screen simultaneously to the left and right of a white center crosshair. Subjects had 3 s to make a left or right mouse button click to choose the corresponding cue. The chosen cue was then highlighted, and after a 2 s delay the center crosshair turned blue, indicating that the outcome associated with the chosen symbol was present and they should make a sniff. The training task consisted of 4 blocks of 24 trials each, with each pair presented twice per block (left/right position of cue pairs counterbalanced). Prior to the training task, subjects were instructed to learn which of the two cues in each pair led to an odor outcome, and to choose those symbols.

After the training task, we acquired a structural T1-weighted MRI scan to aid in anatomical guidance of TMS. We also acquired an 8.5-minute baseline resting state rs-fMRI scan, which was used to identify the specific coordinate at which to apply cTBS on the following day (see TMS target coordinate selection below). In a room dedicated for TMS adjacent to the MRI scanner, we then determined resting motor threshold (RMT) (see Transcranial Magnetic Stimulation below).

**Day 2**

Subjects first completed a Baseline behavioral session consisting of pleasantness ratings of the food odors and a choice task. The choice task consisted of 48 consecutive choice trials using the same trial timing described above for the training task. Twenty-four trials in this task were the original odor/odorless pairs learned on the previous day, and the remaining 24 trials were new pairs consisting of one cue associated with the sweet odor and one cue associated with the savory odor. The trial order was pseudorandomized such that 12 original (6 sweet/odorless, 6 savory/odorless) and 12 new (sweet/savory) trials were presented in random order within each half of the task. Subjects were instructed that this was a free choice task, and they should choose whichever of the two symbols they wanted based on the odor outcome they expected to receive.

After the Baseline session, subjects received cTBS (STIM group: 80% RMT; SHAM group: 5% RMT). Immediately after the stimulation, we acquired another 8.5-minute baseline rs-fMRI scan. In a separate testing room adjacent to the scanner, subjects were then given a meal with a dominant flavor note corresponding to one of the two food odors used in the experiment (pseudorandomized). For this meal, subjects were instructed to eat as much as they wanted within a 15-minute time period. Hunger ratings between 0 and 10 (0 = “not at all hungry,” 10 = “extremely hungry”) were acquired before and after the meal.

After the meal, subjects completed a Probe behavioral testing session consisting first of odor pleasantness ratings, and then 48 choice trials in extinction (i.e., odorless air was delivered regardless of the choice). The same pseudo-randomization of choice trials was used as described above for the Baseline task, except that the first 3 trials were always sweet/savory pairs. Subjects were not debriefed about their choices after the experiment. Source data for all figures are included in Data S1.

**Transcranial Magnetic Stimulation**

We used a MagPro X100 stimulator connected to a MagPro Cool-B65 butterfly coil (MagVenture A/S, Farum, Denmark) to deliver TMS guided anatomically by the individual T1-weighted anatomical scans acquired on Day 1. Stimulation was administered in a room designated for TMS adjacent to the MRI scanner. For determination of RMT, we delivered single pulses starting at 50% of maximum stimulator output over left motor cortex, and adjusted stimulation strength as necessary to locate a site that evoked isolated movements of the right thumb. At this location, RMT was determined as the minimum percentage of stimulator output necessary to evoke 5 visible thumb movements in 10 stimulations.

The cTBS protocol on Day 2 lasted 40 s and consisted of 600 total pulses delivered at either 80% RMT (STIM group) or 5% RMT (SHAM group). Each burst in this sequence included 3 pulses delivered at 50 Hz, and bursts occurred every 200 ms (5 Hz) [81]. Previous studies demonstrate that 40 s of cTBS applied to motor cortex reduces motor-evoked potentials for up to one hour [81, 82]. We therefore designed the experiment such that all post-cTBS experimental phases took place within the putative 1 hour window of effect. The precise neural mechanisms by which cTBS changes or disrupts functional connectivity in prefrontal networks are not known.

The control stimulation (CTLS) lasted 7.5 m and consisted of a total of 600 pulses delivered at 20 Hz in 2 s trains, with 28 s of no stimulation between pulse trains. CTLS stimulation was delivered at approximately 50% RMT, which was the limit of tolerability as determined by 2 s test trains delivered to the stimulation site prior to administration of the full 7.5 m stimulation sequence. Because of the length of the pulse trains in the CTLS sequence, these pulses caused comparably more facial muscle movement and discomfort than the cTBS sequence, and therefore made it necessary to decrease the stimulation intensity. However, even at approximately 50% RMT, the CTLS sequence still caused levels of facial muscle movement comparable to cTBS at 80% RMT. This stimulation is thus an appropriate control for the possible effects of stress or discomfort on subsequent task performance.
Both cTBS and CTLS were applied at the coordinate in lateral prefrontal cortex (LPFC) determined individually to have maximal functional connectivity with the orbitofrontal cortex (OFC) seed coordinate (see TMS target coordinate selection below). The position of the coil was oriented such that the long axis of the figure-of-eight coil was approximately parallel to the long axis of the middle frontal gyrus (along which the stimulation coordinate was generally located). All subjects were informed that stimulation might cause muscle twitches in the forehead, eye area, and jaw. To demonstrate this potential movement and test for tolerability of stimulation at this location, we administered two test pulses. One subject originally designated to be in the STIM group did not tolerate the test pulses, and was thus administered sham stimulation and moved to the SHAM group (all results reported here remain significant even if this subject is excluded). Immediately after the last pulse the time was noted, and starting times of subsequent experimental phases were calculated in reference to this time. All subsequent phases took place within 50 minutes of the end of stimulation (Figure S3).

MRI data acquisition
MRI data were acquired on a Siemens 3T PRISMA system equipped with a 64-channel head-neck coil. For resting state fMRI, echo-planar imaging (EPI) volumes were acquired with a parallel imaging sequence with the following parameters: repetition time, 2 s; echo time, 22 ms; flip angle, 80°; multi-band acceleration factor, 2; slice thickness, 2 mm, no gap; number of slices, 58; interleaved slice acquisition order; matrix size, 104 x 96 voxels; field of view 208 mm x 192 mm. The functional scanning window was tilted ~30° from axial to minimize susceptibility artifacts in OFC [34, 83]. Each fMRI session (Day 1 and Day 2) consisted of 250 EPI volumes covering all but the most dorsal portion of the parietal lobes. On Day 1, a 1 mm isotropic T1-weighted structural scan was also acquired for navigation of stimulation and to aid in spatial normalization.

Image preprocessing was performed using SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/). To correct for head motion during scanning, images acquired in the Day 1 and Day 2 rs-fMRI session were aligned to the first acquired image in each session. The mean realigned images for each session were then co-registered to the T1 scan, and the resulting registration parameters were applied to the realigned EPI's. The T1 image was normalized to Montreal Neurological Institute (MNI) space using the 6-tissue probability map provided by SPM12 to generate forward and inverse deformation fields. For TMS target coordinate selection, the co-registered EPI's corresponding to the Day 1 session were smoothed with a 6 x 6 x 6 mm Gaussian kernel. For the group-level connectedness analysis described below, the realigned and co-registered Day 1 and Day 2 scans were normalized to MNI space using the forward deformation fields generated by normalization of the T1 image. The normalized Day 1 and Day 2 scans were smoothed using a 6 x 6 x 6 mm Gaussian kernel.

TMS target coordinate selection
We used the Neurosynth (https://www.neurosynth.org) database of rs-fMRI scans to select a coordinate that is both in the vicinity of the central/lateral portion of OFC that has been previously implicated in outcome-guided behavior [10–12, 14], and has high functional connectivity to a surface location that is directly accessible to TMS. This resulted in identification of a coordinate in the right central/lateral OFC (x = 28, y = 38, z = –16, corresponding to Brodmann area 11 and “Cluster 2” identified in the 2-cluster solution of a connectivity-based parcellation of OFC [32]) that is connected with a coordinate in the right middle frontal gyrus (x = 48, y = 38, z = 20, corresponding to Brodmann area 45) with a correlation of r = 0.26.

For determination of individual stimulation coordinates in LPFC, we first generated spherical masks of 8-mm radius around these two coordinates in MNI space, both inclusively masked by the gray matter tissue probability map provided by SPM12 (thresholded at > 0.1). These masks were un-normalized to each subject’s native space using the inverse deformation field generated by the normalization of the T1 scans. We then specified a general linear model for each subject with the mean Day 1 rs-fMRI activity in the un-normalized OFC sphere as the regressor of interest (i.e., the seed region), and realignment parameters as regressors-of-no-interest. The stimulation coordinate was calculated as the voxel in the un-normalized LPFC mask that had the highest beta value (i.e., highest functional connectivity with the OFC seed region) estimated from this GLM.

quantification and Statistical analysis
Global connectedness analysis
For each subject and scanning session (i.e., Day 1 and Day 2), we computed voxel-wise maps of “global connectedness,” reflecting the average connectivity between a given voxel’s time course of rs-fMRI activity and all other gray matter voxels. This was done by first extracting the time course of activity for each voxel in the gray matter tissue probability map mask (threshold at > 0.1). These time courses were then adjusted for head motion by regressing out nuisance parameters, which included: the 6 realignment parameters (3 translations, 3 rotations) calculated for each volume during motion correction; the derivative, square, and the square of the derivative of each realignment parameter; the absolute signal difference between even and odd slices in each volume and the variance across slices in each volume (to account for fMRI signal fluctuation caused by within-scan head motion); additional regressors as needed to model out individual volumes in which particularly strong head motion occurred; the mean global signal in all white matter voxels specified by exclusively masking the white matter tissue probability map with the gray matter tissue probability map. We then calculated the absolute Pearson correlation (Fisher’s Z transformed) between each voxel’s time series and every other voxel,
resulting in a voxel-by-voxel connectivity matrix. We then averaged across the rows of this matrix, resulting in a measure of global connectedness for each voxel. These whole-brain maps of global connectedness were then compared between days (Day 2 – Day 1) for each subject. Voxels with negative difference values indicate locations in which global connectivity decreased from the Day 1 baseline scan to the Day 2 scan acquired immediately after stimulation. In contrast, values close to zero indicate no change in global connectivity. To confirm that cTBS decreased global connectivity of the OFC, we compared these difference maps between groups (median SHAM > STIM) using a permutation test with 100,000 random group assignments.

To illustrate regions showing a change in connectivity with OFC, we calculated the absolute correlation between the mean time course of activity in the region of OFC identified by the previous analysis (masked at p < 0.01) and every other gray matter voxel in the brain. These connectivity values were then averaged across voxels in regions identified in a previous study [32] as functionally connected with two distinct OFC sub-regions: a central/lateral OFC network and a medial OFC network. The masks corresponding to voxels in each network were made by thresholding the statistical maps generated in that previous study at p < 0.05, whole-brain corrected for family-wise error.

Statistics
For testing effects across groups we used ANOVA’s with group as a between-subjects factor and condition, testing session, and trial blocks as within-subjects factors. For post hoc testing of effects within groups we used either repeated-measures ANOVA or paired t tests. Significance threshold was set to p = 0.05, two-tailed, unless otherwise noted.

DATA AND CODE AVAILABILITY

Whole-brain connectedness map can be viewed at https://neurovault.org/collections/MARJGPJY/ Source data for all figures are included in the published article [Data S1].