Human orbitofrontal cortex is necessary for behavior based on inferred, not experienced outcomes

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SUMMARY

Decisions are typically guided by what we have experienced in the past. However, when direct experience is unavailable, animals and humans can imagine or infer the future to make choices. Outcome expectations that are based on direct experience and inference may compete for guiding behavior [1, 2], and they may recruit distinct but overlapping brain circuits [3-5]. In rodents, the orbitofrontal cortex (OFC) contains neural signatures of inferred outcomes and is necessary for behavior that requires inference, but it is not necessary when responding can be based on direct experience [6-10]. In humans, OFC activity is also correlated with inferred outcome expectations [11, 12], but it is unclear whether the human OFC is selectively required for inference-based behavior. To test this, here we used non-invasive targeted continuous theta burst stimulation (cTBS) [13] to inactivate the human OFC in a sensory preconditioning task designed to isolate inference-based behavior from responding that can be based on direct experience [6, 12, 14]. We show that OFC-targeted cTBS disrupts reward-related behavior only in conditions in which outcome expectations have to be mentally inferred, but that it does not impair behavior that can be based on stimulus-outcome associations that were directly experienced. These findings suggest that OFC is necessary for decision making when outcomes have to be mentally simulated, providing converging cross-species evidence for a critical role of OFC in model-based but not model-free behavior.

Keywords: Orbitofrontal cortex, reward, inference, decision-making, transcranial magnetic stimulation, human, sensory preconditioning, model-based, model-free.
RESULTS AND DISCUSSION

Our experiment probed the effects of OFC-targeted cTBS [13] on the ability of human subjects (SHAM, n=23; STIM, n=24) to infer outcomes in a sensory preconditioning task (Fig. 1a). The task consists of three phases. During preconditioning, pairs of sensory cues are repeatedly presented (A→B, C→D). During conditioning, the second cue of each pair is associated with reward and no reward, respectively (B→reward, D→no reward). During the final probe test, reward-related responding to each cue (A, B, C, and D) is probed under extinction conditions (i.e., no outcomes are presented). Reward expectations in response to cue A indicate that subjects use the associations A→B and B→reward to infer A→reward. This behavior must rely on a mental simulation and cannot reflect direct experience because the reward was never directly paired with A. In contrast, reward expectations to cue B do not require outcome inference because direct experience with the cue-outcome pairings is available. Based on previous findings in rats [6], we hypothesized that the human OFC would be critical for inference-based responding to cue A, but not for responding to cue B, which could be based on direct experience.

Hungry subjects (fasted >4 hours) first learned associations between pairs of abstract visual cues during preconditioning. Next, they learned that a pleasant food odor (Fig. 1b) followed cues B, whereas cues D were always followed by odorless air. Participants indicated whether they expected an odor reward in response to each cue via button press. The percentage of trials in which an odor reward was expected after cue B increased across time relative to cue D (3-way [group x time x cue] ANOVA; main effect of cue, F(1,46)=693.94, p<0.0001; main effect of time, F(1.29,59.49)=0.510, p=0.524; cue by time interaction, F(1.53,70.44)=167.38, p<0.0001; Fig. 1c) and there were no group differences (main effect of group, F(1,45)=0.798, p=0.377; cue by group interaction, F(1,45)=0.452, p=0.505; time by group interaction, F(2,90)=3.44, p=0.057; cue by
time by group interaction, $F(2,90)=0.896$, $p=0.399$). This shows that subjects in both groups learned the associations between these cues and their predicted outcomes equally well.

Figure 1. Experimental design and learning during conditioning. (a) Participants learned cue pairs during preconditioning (A→B, C→D). During conditioning, they learned associations between the second cue in each pair and an outcome (B→odor reward, D→odorless air). Continuous theta burst stimulation (cTBS) was administered at 80% and 5% resting motor threshold in the STIM and SHAM group, respectively. During the probe test, participants were asked to make outcome predictions to all cues, but no outcomes were provided. (b) Participants rated the pleasantness (left) and intensity (right) of food odors and odorless air, which did not differ between groups ($p$'s>0.14). (c) The percentage of trials in which an odor reward was expected after cue B increased across time during conditioning, and there were no group differences. Error bars depict SEM (n=23 SHAM, n=24 STIM).

Critically, after conditioning and immediately prior to the probe test, we applied 40 seconds of cTBS to a site in lateral prefrontal cortex (LPFC) that was individually selected to have maximal resting-state fMRI connectivity with the OFC, following previously established procedures [13]. Stimulation was administered in the STIM group at a high intensity that we have previously shown
affects OFC-dependent behavior and OFC connectivity, and in the SHAM group at a low intensity that was not expected to produce any impact on neural function [13].

We hypothesized that OFC-targeted stimulation would selectively disrupt reward expectations based on inference, but not direct experience. In line with this, we found significantly reduced responses to cue A in the STIM relative to the SHAM group (t(45)=2.36, p=0.023, Fig. 2a) but no group difference in responding to cue B (t(45)=1.16, p=0.253, Fig. 2b). To examine the effects of OFC-targeted TMS on inference-based behavior independent of potential effects on direct experience, we normalized responses to cue A by responses to cue B. The resulting ratio (i.e., A/B), reflects the ability to infer outcomes beyond the ability to respond based on directly experienced stimulus-reward associations, and was significantly larger in the SHAM compared to STIM group (t(45)=2.29, p=0.027, Fig. 2c). Taken together, these findings demonstrate that OFC-targeted TMS selectively disrupts behavior based on inferred, but not directly experienced outcome expectations.

Figure 2. Responses based on inferred outcomes are disrupted by OFC-targeted brain stimulation. (a) The percentage of reward predictions in response to cue A (p=0.023) but not cue C (p=0.642) was significantly larger in the SHAM compared to the STIM group. (b) There was no group difference in responding to cue B (p=0.253) or D (p=0.740). (c) Responses to cue A relative to cue B (A/B) were significantly stronger in the SHAM compared to the STIM group (p=0.027). Error bars depict SEM (n=23 SHAM, n=24 STIM) and * depicts p<0.05.
Inference requires memory of cue-cue associations, and it is therefore possible that the findings reported above reflect a failure of memory rather than inference. To rule out this potential explanation, we measured recognition memory for cue-cue associations after the probe test, and compared it between groups. Recognition memory was significantly above chance in both groups (SHAM: \(t(21)=5.01, p=0.00006\); STIM: \(t(20)=2.70, p=0.013\)), and there was no group difference (\(t(41)=1.34, p=0.188\)). This indicates that OFC was not necessary for remembering the cue-cue associations required for outcome inference.

Our results show that OFC in humans is necessary for behavior when outcome expectations need to be mentally simulated, but that it is not required for similar behavior when expectations can be based on direct experience. This closely parallels previous findings from rats [6], providing converging cross-species evidence for a critical role of OFC in model-based but not model-free behavior. By extension, this finding implies that the value correlates previously observed in OFC across different species [15-19] may only be required for choice when these values have to be mentally inferred, but not when they can be based on direct experience. This suggests that the contribution of OFC to decision making is much more specific than previously thought, and that choices based on direct experience may rely on computations in areas other than OFC, such as the striatum [20].

Our results also demonstrate a contribution of human OFC to model-based behavior that occurs, at least in part, at the time of decision making. This effect rules out the possibility that inference-based behavior depends exclusively on memory integration or other replay-like mechanisms that occur during learning [21]. While such so-called rehearsal or mediated learning may also contribute to adapting behavior when direct experience is not available, perhaps via recruitment
of areas such as hippocampus [14, 22, 23] and medial temporal lobe [24], the susceptibility of inference-based responding to OFC-inactivation both here and in rats indicates that a substantial amount of behavior in even this simple task is based on real-time computations.

Deficits in decision making are a hallmark of many neuropsychiatric disorders, including substance use disorder (SUD) [25] and obsessive compulsive disorder (OCD) [26]. Our findings may offer a conceptual framework for how OFC dysfunction may disrupt behavior in these conditions. For instance, an impaired ability to imagine unobservable states may reinforce checking behaviors in OCD, and a failure to simulate the consequences of long-term drug-use may bias drug-taking decisions in SUD. The possibility to non-invasively manipulate human OFC highlights exciting new opportunities for novel treatments.

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AUTHOR CONTRIBUTIONS
F.W., G.S., J.L.V, and T.K. designed the experiment. F.W. and J.D.H. collected the data. F.W. analyzed the data. F.W., G.S. and T.K. interpreted the results and wrote the manuscript.
MATERIALS AND METHODS

Subjects

In total, 71 healthy adults participated in a screening session. Of these, 52 passed screening, were randomly assigned to sham (SHAM: N=25, 13 female) or stimulation group (STIM: N=27, 15 female), and participated in the experiment. All participants provided written informed consent to participate and they were compensated with $20 per hour for behavioral testing and $40 per hour for TMS and MRI scanning. The study protocol was approved by the Northwestern University Institutional Review Board. One participant in the STIM group withdrew during the experiment. Data from four participants (two per group) were excluded from all analyses because their performance in the last run of conditioning was not significantly (p=0.05) above chance. This left a total of 47 participants (SHAM: N=23, 12 female, mean age=25.24 years +/- 0.86 SEM; STIM: N=24, 13 female, age=25.30 years +/- 0.70) from whom data was analyzed. Of those, data from four participants (one SHAM, three STIM) from the recognition test of the experiment was not recorded due to technical reasons.

Stimuli and Odor Delivery

Visual cues consisted of 14 abstract symbols and 12 of them were randomly grouped into six pairs for each participant, of which two served as A1–B1 pairs, two served as A2–B2 pairs, and two served as C–D pairs. The two remaining symbols were used to form two catch-trial pairs (E–E) in which the same symbols were presented twice in a row (i.e., E1–E1, E2–E2). The two symbols constituting a pair were presented in different colors (e.g., first symbol blue, second symbol green; counterbalanced across participants).

Eight food odors (four sweet: strawberry, caramel, gingerbread, and yellow cake; four savory: potato chip, pot roast, garlic, and pizza) were provided by Kerry (Melrose Park, IL) and International Flavors and Fragrances (New York, NY). Odors were delivered to participants’ nose
using a custom-built and computer-controlled olfactometer [12, 13]. The olfactometer was equipped with two independent mass flow controllers (Alicat, Tucson, AZ), which allow dilution of any given odorant with odorless air. Odorless air was delivered constantly during the experiment and odorized air was mixed into the airstream at specific time points. The overall flow rate was kept constant at 3.2 L/min throughout the task, such that odor deliver did not involve a change in overall airflow or somatosensory stimulation.

Experimental Procedures

The study consisted of three visits: a screening session, a MRI and TMS motor threshold session, and a main task session. The MRI and TMS motor threshold session was conducted on average 18 days (SEM=4.16) after the screening session. And the average delay between motor threshold and main task sessions was 4 days (SEM=0.94). Participants were instructed to arrive in a hungry state (fast for at least 4–6 hours) for screening and main task sessions.

Screening Session

In each trial, participants were presented with one of eight food odors in a randomized order and each odor was delivered for 2 seconds. Participants were instructed to make a medium sniff and then rate the pleasantness of the delivered odor on a scale from “Most disliked sensation” to “Most liked sensation”. We then selected one sweet and one savory odor that were both rated as pleasant (i.e. pleasantness above neutral) and as closely matched as possible. The two selected odors were then used as reward for that individual participant in the main task session. If no such two odors were found, participants were excluded from further participation in the study. Next, participants rated the intensity and pleasantness of the two odors as well as odorless air. The scale of the intensity rating was from “Undetectable” to “Strongest sensation imaginable”.
Pleasantness ratings were significantly higher for food vs. no odor trials (SHAM: \( t(22)=11.62, p=7.38 \times 10^{-11}; \) STIM: \( t(23)=12.97, p=4.59 \times 10^{-12} \)), but did not differ between groups (2-way ANOVA, main effect of group, \( F(1,45)=2.29, p=0.137 \); odor by group interaction, \( F(1,45)=0.37, p=0.544 \)). In addition, rated intensity was significantly higher for food odors vs. odorless air (SHAM, \( t(22)=11.62, p=7.38 \times 10^{-11}; \) STIM, \( t(23)=12.97, p=4.59 \times 10^{-12} \)), but did not differ between groups (2-way ANOVA, main effect of group \( F(1,45)=0.11, p=0.744 \); odor by group interaction \( F(1,45)=0.11, p=0.747 \)).

**MRI and TMS Motor Threshold Session**

We first acquired a T1-weighted structural MRI scan for the purpose of TMS neuronavigation and an 8.5 minutes resting state fMRI (rs-fMRI) scan for individually defining OFC-targeted stimulation coordinates. Immediately after the scan, we measured resting motor threshold (RMT) by delivering single pulses at left motor cortex. RMT was defined as the minimum percentage of stimulator output necessary to evoke 5 visible thumb movements in 10 stimulations.

**Main Task Session**

The main task session consisted of preconditioning, conditioning, TMS, probe test, and cue-cue pair recognition test. In four preconditioning runs, participants were instructed to learn the associations between the two cues in each pair (\( A \rightarrow B \) \( [A_1 \rightarrow B_1, A_2 \rightarrow B_2] \), \( C \rightarrow D \) \( [C_1 \rightarrow D_1, C_2 \rightarrow D_2] \), \( E \rightarrow E \)). The cues in a pair were presented one after another for 3 s each, separated by a delay of 300 ms. A fixation cross appeared between trials for a variable duration between 3 and 11 s. To ensure attention to the cue pairs, participants were instructed to memorize the cue pairs, press a button if the second cue was different from the first, and withhold a response if the two cues were identical. To facilitate learning, in the first two runs of preconditioning, each cue pair was repeated three times in a row. In the remaining preconditioning runs, the order of cue pairs was randomized.
Next, participants performed three runs of conditioning, during which the second cue of each pair (cues B \{B1, B2\} and D \{D1, D2\}) was presented individually for 3,000 ms. Participants were instructed to indicate by button press which outcome (e.g. strawberry \[SB\], garlic \[GA\], or no odor \[NO\]) they expected following the cue. If they expected strawberry, they were asked to select “SB”;
if they expected garlic, they were asked to select “GA”; If they expected no odor, they were asked to select “NO”. Participants made their prediction by pressing a button with the index, middle or ring fingers of their right hand corresponding to the positions of “SB”, “GA” and “NO” on the screen. The positions of abbreviated names were randomized across trials to dissociate specific motor responses from outcome predictions. Irrespective of their selection, the outcome was always presented for 2,000 ms immediately after the cue. However, “too slow” was displayed if participants failed to respond within 3,000 ms. Each cue-outcome association was repeated four times in each run in pseudorandomized order, resulting in 12 repetitions total.

After the conditioning phase, participants received cTBS over the individually selected LPFC coordinate (see details below). The probe test followed immediately after the stimulation. In the probe test, cues A \{A1, A2\}, B \{B1, B2\}, C \{C1, C2\}, D \{D1, D2\} were presented individually in extinction conditions (odorless air was delivered throughout). Each cue was presented four times in pseudorandomized order. Participants were instructed to predict the outcome after each cue, as they did during the conditioning phase. They were further instructed to use the cue-cue associations to infer the outcomes associated with the preconditioned cues [12]. The durations of cue and the interval between trials were exactly the same during the conditioning phase.

Following the probe test, participants were tested for their memory of the cue-cue associations in a recognition task. Participants were presented with the original cue pairs as well as recombined pairs consisting of cues belonging to different pairs. Pairs were presented sequentially as during
preconditioning, and participants were asked to indicate whether a pair was old or recombined after the second cue was presented using a button press.

**Transcranial Magnetic Stimulation**

TMS was delivered using a MagPro X100 stimulator connected to a MagPro Cool-B65 butterfly coil (MagVenture A/S, Farum, Denmark). We used a cTBS protocol involving a 40 second train of 3-pulse 50 Hz bursts delivered every 200 ms [5 Hz], totaling 600 pulses [27]. Stimulation was delivered at an intensity of 80% MT in the STIM group and 5% MT in the SHAM group. The target coordinate was defined as a location in the lateral prefrontal cortex (LPFC) that showed maximal functional connectivity with the orbitofrontal cortex (OFC) seed coordinate (see details below). The orientation of the coil was tilted such that the long axis of the figure-of-eight coil was approximately parallel to the long axis of the middle frontal gyrus. All participants were informed that they may experience muscle twitches in the forehead, eye area, and jaw during stimulation. We delivered two single test pulses to demonstrate the potential muscle twitches and test for tolerability before cTBS was delivered. Immediately after the last pulse of cTBS, the time was noted. All subsequent tests took place within 30 minutes of the end of stimulation.

**MRI data acquisition**

The MRI data were acquired at the Northwestern University Center for Translational Imaging (CTI) using a Siemens 3T PRISMA system equipped with a 64-channel head coil. rs-fMRI scans were acquired with an echoplanar imaging (EPI) sequences with the following parameters: repetition time(TR), 2 s; echo time (TE), 22 ms; flip angle, 90°; slice thickness, 2mm, no gap; number of slices, 58; interleaved slice acquisition order; matrix size, 104 x 96 voxels; field of view, 208 mm x 192 mm; multiband factor, 2. To minimize susceptibility artifacts in the OFC, the acquisition plane was tilted approximately 25° from anterior commissure (AC)–posterior commissure (PC)
The rs-fMRI scan consisted of 250 EPI volumes covering all but the most dorsal portion of the parietal lobes. In addition, a 1 mm isotropic T1-weighted structural scan was collected.

**fMRI data preprocessing**

Functional image preprocessing was performed using Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/). To correct for head motion during scanning, all rs-fMRI images were aligned to the first acquired image. The mean realigned images were then co-registered to the anatomical image, and the resulting registration parameters were applied to all realigned EPI images. Finally, co-registered EPI images were smoothed with a 6 x 6 x 6 mm Gaussian kernel.

To generate forward and inverse deformation fields, the anatomical image was normalized to Montreal Neurological Institute (MNI) space using the 6-tissue probability map.

**Coordinate selection for OFC-targeted TMS**

Individualized stimulation coordinates on the right LPFC were determined based on rs-fMRI connectivity with a right central/lateral OFC seed region using a procedure described previously [13]. Briefly, we first created two spherical masks of 8-mm radius around a LPFC target coordinate (x=48, y=38, z=20) and a OFC seed coordinate (x=28, y=38, z=-16) in MNI space, both inclusively masked by the gray matter tissue probability map provided by SPM12 (thresholded at >0.1). These masks were then un-normalized to each participant’s native space using the inverse deformation field generated by the normalization of the anatomical images. We then estimated a general linear model with the rs-fMRI time series in the inverse-normalized OFC sphere as the regressor of interest and realignment parameters as regressors of no interest. The voxel in the inverse-normalized LPFC mask that had highest functional connectivity with the OFC seed was defined as stimulation coordinate.
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