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Values Encoded in Orbitofrontal Cortex Are Causal to Economic Choices

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In the 18th century, Daniel Bernoulli, Adam Smith and Jeremy Bentham proposed that economic choices rely on the computation and comparison of subjective values[1]. This hypothesis continues to inform modern economic theory[2] and research in behavioral economics[3], but behavioral measures are ultimately not sufficient to prove the proposal[4]. Consistent with the hypothesis, when agents make choices, neurons in the orbitofrontal cortex (OFC) encode the subjective value of offered and chosen goods[5]. Value encoding cells integrate multiple dimensions[6–9]. Furthermore, variability in the activity of each cell group correlates with variability in choices[10,11], and the population dynamics suggests the formation of a decision[12]. However, it is unclear whether these neural processes are causally related to choices. More generally, the evidence linking economic choices to value signals in the brain[13–15] remains correlational[16]. Here we show that neuronal activity in OFC is causal to economic choices. We conducted two experiments using electrical stimulation in rhesus monkeys. Low-current stimulation increased the subjective value of individual offers and thus predictably biased choices. Conversely, high-current stimulation disrupted both the computation and the comparison of subjective values, and thus increased choice variability. These results demonstrate a causal chain linking subjective values encoded in OFC to valuation and choice.

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In principle, causal links between a neuronal population and a decision process are demonstrated if one can predictably bias choices using electrical stimulation[17,18]. Thus classic work established the causal role of the middle temporal (MT) area in motion perception by showing that low-current stimulation biases[19] while high-current stimulation disrupts[20] perceptual decisions. One challenge in using this approach for economic choices is the lack of columnar organization in OFC. Since neurons associated with different goods available for choice are physically intermixed[11], one cannot selectively activate neurons associated with one particular good using electrical stimulation. We developed two experimental paradigms to circumvent this challenge.

Exp.1 examined whether perturbing OFC disrupts choices. Monkeys chose between two juices labeled A and B (with A preferred) offered in variable amounts. The two offers were presented sequentially in the center of a computer monitor (Fig.1A). Trials in which juice A was offered first and trials in which juice B was offered first were referred to as “AB trials” and “BA trials”, respectively. The terms “offer1” and “offer2” referred to the first and second offer, independent of the juice type and amount. For each pair of juice quantities, the sequential order of the two offers varied pseudo-randomly. On roughly half of the trials, high-current stimulation (≥100 μA) was delivered in OFC during offer1 or during offer2 presentation (in separate sessions). In each session, trials with and without stimulation were pseudo-randomly interleaved (see Methods).

For each group of trials (stimON, stimOFF), choice patterns were analyzed with a probit regression:

$$\begin{aligned} &choice\ B = \Phi(\mathrm{X}) \\ &\mathrm{X} = a_0 + a_1 \log(q_B/q_A) + a_2(\delta_{order,AB} - \delta_{order,BA}) \end{aligned} \quad (1)$$

where $choice\ B = 1$ if the animal chose juice B and 0 otherwise, Φ was the cumulative function of the standard normal distribution, q_A and q_B were the quantities of juices A and B offered, $\delta_{order,AB} = 1$ in AB trials and 0 in BA trials, and $\delta_{order,BA} = 1-\delta_{order,AB}$. From the fitted parameters, we derived measures for the relative value $\rho=\exp(-a_0/a_1)$, the sigmoid steepness $\eta=a_1$, and the order bias $\varepsilon=a_2$. Intuitively, ρ was the quantity that made the animal indifferent between 1A and ρB, η was inversely related to choice variability, and ε was a bias favoring the first or second offer. Specifically, $\varepsilon<0$ ($\varepsilon>0$) indicated a bias in favor of offer1 (offer2).

In one representative session, electric current was delivered during offer1. The stimulation induced a choice bias in favor of offer2 (Fig.1B). This effect was consistent across N=29 sessions: high-current stimulation during offer1 did not systematically alter the relative value or the sigmoid steepness, but it induced a systematic bias in favor of offer2 (Fig.1CDE). In a different set of N=25 sessions, we delivered ≥100 μA during offer2. In this case, stimulation induced a systematic bias in favor of offer1 (Fig.1FI). These complementary effects are interpreted as high-current stimulation interfering with or disrupting the ongoing computation of the offer value, resulting in a choice bias for the other offer (see Methods). In addition, stimulation during offer2, but not during offer1, significantly increased choice variability (Fig.1FH). This effect may be interpreted as high-current stimulation disrupting

value comparison (i.e., the decision), which took place upon presentation of offer2. A similar effect was observed in mice when OFC was inactivated using optogenetics[21].

We also examined the effects of stimulation at lower currents. In essence, the effects observed at ≥100 μA diminished and gradually vanished when the electric current was reduced to 50 μA and 25 μA (Fig.2). In summary, high-current stimulation of OFC disrupted the neural processes underlying economic choice, namely value computation during offer1, and value computation and value comparison during offer2.

The results described so far showed that OFC perturbation can disrupt valuation and choice. We next examined whether subjective values may be increased through physiological facilitation[22]. In Exp.2, we took advantage of the fact that neurons in OFC undergo range adaptation[23,24]. Fig.3 illustrates our rationale. In this experiment, monkeys chose between two juices offered simultaneously (Fig.3A). In these conditions, two groups of cells in OFC encode the offer values of juices A and B[5,10]. Importantly, their tuning curves are quasi-linear and the gain is inversely proportional to the value range (range adaptation)[23,25]. Moreover, cells in each group adapt to their own value range. The effect of low-current stimulation is to increase the firing rate of neurons in proximity of the electrode[19,26]. In turn, this increase in firing rate is equivalent to a small increase in the offer values. By virtue of range adaptation, for a given current, the increase in value is proportional to the value range (Fig.3BC). If an equal number of offer value A cells and offer value B cells are close to the electrode tip, then the effect of the electric current is equivalent to increasing both offer values. Crucially, if the two value ranges are unequal, the increases in offer value are also unequal. More specifically, the offer value of the juice with the larger range increases more. Hence, the net effect on choices is expected as follows: Low-current electrical stimulation should bias choices in favor of the juice offered with the larger value range (Fig.3D; Methods).

We tested this prediction in two animals. In each session, we selected juice types and quantity ranges such that value ranges (ΔV_A, ΔV_B) would differ. Electrical stimulation (50 μA) was delivered in OFC for 1 s during offer presentation. Trials with and without stimulation were pseudo-randomly interleaved. In each session, choice patterns were analyzed with a probit regression:

$$\begin{aligned} &choice\,\boldsymbol{B} = \boldsymbol{\Phi}(\mathrm{X}) \\ &\mathrm{X} = \mathrm{a}_0 + \mathrm{a}_1 \log(q_B/q_A) + \mathrm{a}_2(\delta_{stim,ON} - \delta_{stim,OFF}) \end{aligned} \tag{2}$$

where $\delta_{stim,ON} = 1$ in stimulation trials and 0 otherwise, and $\delta_{stim,OFF} = 1 - \delta_{stim,ON}$. We computed the relative value for each group of trials and we defined the change in relative value induced by the stimulation as $\delta\rho = \rho_{stimON} - \rho_{stimOFF}$.

In one representative session, value ranges were such that $\Delta V_A < \Delta V_B$. Consistent with our prediction, electrical stimulation induced a bias in favor of juice B ($\delta\rho < 0$, Fig.4A). In another session, where $\Delta V_A > \Delta V_B$, we measured $\delta\rho > 0$ (Fig.4B). A population analysis found that the choice bias $\delta\rho$ and the difference in value range $\Delta V_A - \Delta V_B$ were strongly correlated across sessions. This result held true in each monkey (Fig.4CD). Control analyses confirmed that range-dependent biases did not reflect simple heuristics (Extended Data

Fig.1) and were not dictated by the juice types or the electrode position (Extended Data Fig.2).

The rationale of Exp.2 rests on the assumption that low-current stimulation increases the value of the two offers (Fig.3). An analysis of response times (RTs) supported this point. Under normal conditions (stimOFF), RTs decreased as a function of the chosen value. Electrical stimulation generally reduced RTs. Furthermore, linear regressions of RTs onto the chosen value showed that this reduction was driven by lower offsets as opposed to steeper slopes (Extended Data Fig.3). These changes in RTs are as predicted if stimulation increases the subjective value of the chosen goods.

The results of Exp.2 were replicated in a secondary analysis of data from Exp.1. For this analysis, we pooled all trials (AB and BA) and all sessions (stimulation during offer1 or offer2), and we repeated the analysis conducted for Exp.2 (Eq.2). We found a significant correlation between the choice bias ($\delta\rho$) and the difference in value range ($\Delta V_A - \Delta V_B$) when stimulation was delivered at 25 μA or 50 μA, but not when it was delivered at ≥100 μA (Extended Data Fig.4). The last observation indicated that the mechanism inducing the range-dependent bias (Fig.3) was fundamentally different from those inducing the order bias. Interestingly, stimulation at 50 μA induced both biases (see Methods).

In the conditions examined here, different groups of neurons in OFC represent individual offer values, the binary choice outcome and the chosen value[10,27]. Importantly, neurons encoding the binary choice outcome do not adapt to the value range, while chosen value cells adapt to the maximum range independent of the juice type[28]. Hence, physiological facilitation of these two cell groups should not induce any range-dependent choice bias. Thus range-dependent biases induced by stimulation are mediated by offer value cells (Fig.3). The order bias observed in Exp.1 is also understood as an effect on offer value cells. Conversely, the increase in choice variability observed in Exp.1 upon stimulation during offer2 suggests that stimulation currents interfered with value comparison. More work is necessary to ascertain the organization of the decision circuit, including the role of different brain regions[29,30]. If values are compared within OFC, the increase in choice variability could be due to the effects of stimulation on the other cell groups. For example, in a neural network model[31], increasing reverberation increases choice variability[32].

In conclusion, we have shown that offer values encoded in OFC are causal to economic choices. This result demonstrates a long-held hypothesis and opens new avenues to investigate disorders affecting choices.

Methods

All experimental procedures conformed to the NIH *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee (IACUC) at Washington University.

The study was conducted on three male rhesus monkeys (*Macaca mulatta*): G (age 8, 9.1 kg), J (age 7, 10.0 kg), and D (age 8, 11.5 kg). Before training, we implanted in each monkey a head-restraining device and an oval recording chamber under general anesthesia.

The chamber (main axes, 50×30 mm) was centered on stereotaxic coordinates (AP 30, ML 0), with the longer axis parallel to a coronal plane. During the experiments, the animals sat in an electrically insulated enclosure with their head restrained. A computer monitor was placed 57 cm in front the animal. Behavioral tasks were controlled through custom-written software (http://www.monkeylogic.net/). The gaze direction was monitored by an infrared video camera (Eyelink; SR Research) at 1 kHz.

Choice tasks

In Experiment 1 (Exp.1; monkeys G and J), animals chose between two juices labeled A and B, (with A preferred) offered in variable amounts. The two offers were presented sequentially in the center of a computer monitor (Fig.1A). Each trial began with the animal fixating a dot (0.35° of visual angle) in the center of the monitor. After 0.5 s, two offers appeared in sequence. Each offer was represented by a set of colored squares (side = 1° of visual angle), where the color indicated the juice type and the number of squares indicated the juice amount. Along with the offer, a small colored circle (0.75° of visual angle) appeared around the fixation dot. The circle indicated to the animal the juice identity in the case of null offer (0 drops; forced choices). The animal maintained center fixation throughout the initial fixation (0.5 s), offer1 time (0.5 s), inter-offer time (0.5 s), offer2 time (0.5 s), wait time (0.5 s), and delay time (0.5–1 s). At the end of the delay, the fixation point was extinguished and the animal indicated its choice with a saccade. It then maintained peripheral fixation for 0.6 s before juice delivery. Center fixation was imposed within 3°. Trials in which juice A was offered first and trials in which juice B was offered first were referred to as “AB trials” and “BA trials”, respectively. The terms “offer1” and “offer2” referred to the first and second offer, independent of the juice type and amount. For each pair of juice quantities, the presentation order (AB, BA) and the spatial location of the saccade targets varied pseudo-randomly and were counterbalanced across trials. We designed offer types such that for most values of offer1 the animal split choices between the two offers[27]. Thus the monkey was discouraged from making a decision before offer2. Sessions typically included ~400 trials and offered quantities varied from trial to trial pseudo-randomly. An “offer type” was defined by two juice quantities in given order (e.g., [1A:3B] or [3B:1A]). Stimulation was delivered in half of non-forced choice trials, pseudo-randomly selected.

In Experiment 2 (Exp.2; monkeys D and G), animals performed a similar task, except that the two juices were offered simultaneously (Fig.3A). After initial fixation (0.5 s), two offers appeared on the two sides of the fixation point. Offers remained on the monitor for 1 s and then disappeared. After a brief delay (0–0.5 s), the fixation point was extinguished and the animal indicated its choice with a saccade. The chosen juice was delivered after 0.75 s of peripheral fixation. Sessions typically included ~500 trials. Offered quantities and the spatial disposition varied from trial to trial pseudo-randomly. Previous work showed that in very similar conditions offer value cells in OFC undergo range adaptation[23]. Stimulation was delivered in roughly half of the trials, pseudo-randomly selected. We always tried to set the quantity ranges for the two juices such that the two value ranges would differ appreciably. However, we could not fully control the difference in value ranges, because the relative value of the two juices (ρ) ultimately depended on the animal’s choices. In some instances, we ran two paired sessions back-to-back. In these cases, we left the stimulating electrode in

place and we used the same two juices in both sessions, but we varied the quantity ranges such that the difference in value range $\Delta V_A - \Delta V_B$ would be >0 in one session and <0 in the other session.

The quantity of juice associated with each square (quantum) was set equal to 70–100 μl in Exp.1, and to 75 μl in Exp.2 (the quantum always remained constant within a session). Across sessions, we used a variety of different juices associated with different colors, including lemon Kool-Aid (bright yellow), grape (bright green), cherry (red), peach (rose), fruit punch (magenta), apple (dark green), cranberry (pink), peppermint tea (bright blue), kiwi punch (dark blue), watermelon (lime) and 0.65 g/L salted water (light gray). This resulted in a large number of juice pairs.

Electrical stimulation

The chamber provided bilateral access to OFC. Structural MRIs (1 mm sections) performed before and after surgery were used to guide electrode penetrations. Prior to the electrical stimulation experiments, we performed extensive neuronal recordings in each monkey using standard procedures[27]. Recordings and stimulation focused on the central orbital gyrus, in a region corresponding to area 13/11. The analysis of neuronal data confirmed that stimulation experiments focused on the same region examined in previous studies[5,27].

During stimulation sessions, low-impedance (100–500 kΩ) tungsten electrodes (100 μm shank diameter; FHC) were advanced using a custom-built motorized micro-drive (step size 2.5 μm) driven remotely. Stimulation trains were generated by a programmable analog output (Power 1401, Cambridge Electronic Design) and triggered through a TTL by the computer running the behavioral task. Monopolar electric currents were generated by an analog stimulus isolator (Model 2200, A-M Systems). The parameters used for electrical stimulation were as follows.

In Exp.1, electric current was delivered during offer1 or during offer2 (in separate sessions). Stimulation started 0–100 ms after offer onset and lasted 300–600 ms. The stimulation train was constituted of biphasic pulses (200 μs each pulse, 100 μs separation between pulses) delivered at 100–333 Hz frequency[19,20,33,34]. Variability in these parameters was mostly from early sessions in monkey 1, when we were experimenting with different stimulation protocols. Parameters were not titrated within any session. In different sessions, current amplitudes varied between 25 and 150 μA (in 1 session, 200 μA). Stimulation was performed in both hemispheres of monkey G (left: AP 31:36, ML −7:−12; right: AP 31:36, ML 4:9) and in both hemispheres of monkey J (left: AP 31:35, ML −8:−10; right AP 31:35, ML 6:10). Our data set included a total 144 stimulation sessions and 50 control sessions (see Extended Data Table 2). Electric current was delivered either unilaterally or bilaterally, in separate sessions. For each current level, the two groups of sessions were combined in the analysis. Analysis of the condition for which we had two sizeable data sets (namely, offer1 stimulation) indicated that unilateral and bilateral stimulation had similar effects on choices.

In Exp.2, the stimulation train (biphasic pulses, 200 Hz frequency) was delivered throughout offer presentation, for 1 s. Stimulation was always unilateral, and current amplitude was always set at 50 μA. Stimulation was performed in the left hemisphere of monkey D (AP

31:36, ML −6:−10) and in the left hemisphere of monkey G (AP 31:36, ML −7:−11). Trials with stimulation (stimON) and without stimulation (stimOFF) were pseudo-randomly interleaved. Our data set included 97 sessions.

Electrical stimulation did not systematically alter error rates in either experiment. Errors were always defined as fixation breaks occurring any time prior to trial completion. In Exp.1, error rates were not affected by stimulation in any of the experimental conditions (25 μA, offer1, p = 0.10; 25 μA, offer2, p = 0.68; 50 μA, offer1, p = 0.15; 50 μA, offer2, p = 0.88; ≥100 μA, offer1, p = 0.20; ≥100 μA, offer2, p = 0.46; Wilcoxon test, two animals combined). Similarly, stimulation did not alter error rates in Exp.2 (p = 0.87; Wilcoxon test, two animals combined).

Data analysis

All analyses were conducted in Matlab (MathWorks Inc). For the primary analysis of data from Exp.1, choice patterns were analyzed with probit regressions, separately for stimOFF trials and stimON trials (Eq.1). For each group of trials, we derived measures for the relative value of the juices (ρ), the sigmoid steepness (η) and the order bias (ε). The effects of electrical stimulation on each parameter were assessed using Wilcoxon signed-rank tests and paired t tests (Fig.1, Fig.2). Very similar results were obtained using alternative definitions of the order bias (referring to Eq.1, we tested $\varepsilon = a_2/a_1$ and $\varepsilon = 2\ \rho\ a_2/a_1$).

For data from Exp.2, we first ran two independent probit regressions for stimON trials and stimOFF trials. We found that electrical stimulation did not systematically alter the sigmoid steepness (Extended Data Fig.5). Thus we ran a probit regression assuming equal steepness for the two groups of trials (Eq.2). Except for Extended Data Fig.5, all the results presented here were obtained from the latter fit. Referring to Eq.2, we defined $\rho_{stimON} = \exp(-(a_0+a_2)/a_1)$ and $\rho_{stimOFF} = \exp(-(a_0-a_2)/a_1)$.

At the time of Exp.1, we had not planned to examine range-dependent biases. To examine these effects, we pooled sessions in which stimulation was delivered during offer1 or offer2, and we re-analyzed data using the same procedures used for Exp.2.

In all the analyses, we identified as outliers data points that differed from the mean by >3 STD on either axis, and we removed them from the data set. In the primary analyses of Exp.1, there were no outliers. In the analyses of range-dependent biases, the criterion excluded 1/97 session from Exp.2 and 6/144 sessions from Exp.1. Including these sessions in the analyses did not substantially alter the results.

Predicting the range-dependent bias

Here we formalize the prediction illustrated in Fig.3. As a premise, previous work found that the tuning curves of offer value cells in OFC are quasi-linear[25] and the proportion of neurons presenting positive versus negative encoding is roughly 3:1[10,27]. Importantly, cells in each group adapt to their own range, not to the maximum range[28]. Neurons associated with the two juices (A and B) are physically intermixed[11].

For given offers q_A and q_B, r_A and r_B indicate the average firing rates for the two pools of offer value cells. The effect of stimulation (facilitation) is a small increase in these firing rates, such that $r_A \rightarrow r_A + \delta r_A$ and $r_B \rightarrow r_B + \delta r_B$. Since the two neuronal populations are physically intermixed, electrical stimulation affects both of them equally. In other words, $\delta r_A = \delta r_B = \delta r$.

For each population, and for each juice type, a small increase in firing rate (δr) is equivalent to a small increase of offered value (δV_A, δV_B). Since offer value cells undergo range adaptation,

$$\begin{aligned} \delta V_A &= (\delta r/\Delta r)\Delta V_A \\ \delta V_B &= (\delta r/\Delta r)\Delta V_B \end{aligned} \tag{3}$$

where Δr is the range of firing rates (which is the same for both juices), and ΔV_A and ΔV_B are the ranges of offered values[23].

We aim to understand how electrical stimulation will affect choices – that is, how the relative value ρ will change under electrical stimulation. To do so, we write the conditions of choice indifference. We assume linear indifference curves and we indicate with V(J) = uJ the value of one unit (one quantum) of juice J. In the absence of stimulation:

$$\begin{aligned} V(A) &= V(\rho_{stimOFF}\, B) \\ &= \rho_{stimOFF}\, V(B) \end{aligned} \tag{4}$$

In the presence of stimulation:

$$V(A) + \delta V_A = V(\rho_{stimON}\, B) + \delta V_B \tag{5}$$

$$= \rho_{stimON}\, V(B) + \delta V_B \tag{6}$$

$$= (\rho_{stimOFF} + \delta\rho)V(B) + \delta V_B \tag{7}$$

In the last passage, we defined $\delta\rho = \rho_{stimON} - \rho_{stimOFF}$. Now we substitute Eq.4 in Eq7 and we re-arrange:

$$\delta V_A = \delta\rho\, uB + \delta V_B \tag{8}$$

$$\delta\rho = (\delta V_A - \delta V_B)/uB \tag{9}$$

Finally, we substitute Eq.3 in Eq.9:

$$\delta\rho = \delta r/\Delta r(\Delta V_A - \Delta V_B)/uB \tag{10}$$

Eq.10 captures the key prediction: If decisions are primarily based on the activity of offer value cells, the net effect of electrical stimulation is to change the relative value of the juices by a quantity proportional to the difference in value ranges. Notably, by pooling sessions in Fig.4 we effectively assumed that $\delta r/\Delta r$ and uB remain constant across sessions. In practice, this might not be true because of variability in stimulation efficacy and because the subjective value of juice B might vary from session to session. These sources of variability effectively add noise to our measurements. However, the prediction that $\delta\rho$ and ($\Delta V_A - \Delta V_B$) should have the same sign is not affected by these factors.

Interpretation of the order bias

Here we discuss how high-current stimulation in Exp.1 might induce the order bias. We generally assume that electrical stimulation increases neuronal spiking. In Exp.1, currents varied between 25 μA and 150 μA. Previous studies indicate that when currents increase in this range, the effects of stimulation change in several ways. First, for any given cell and for equal number of pulses, the number of emitted spikes increases with the current[35,36]. Second, as the current increases, the stimulation affects a larger number of cells[26,37,38]. Third, a regime transition takes place around 50 μA. At lower currents, electrical stimulation induces spiking only through synaptic transmission; at higher currents, stimulation also induces spiking directly through depolarization of the membrane[36]. In Exp.1, the animal is presented offers sequentially. Under normal conditions (stimOFF), only one juice is offered in each time window. However, the effect of stimulation is equivalent to presenting offers for both juices in one time window (because cells associated with the two juices are physically intermixed). We assume that for each juice (A and B) the values presented in the two time windows (1 and 2) are added. The order bias is a bias favoring the juice not present on the monitor during the stimulation. With these premises, high currents may induce the order bias for two reasons.

First, decelerating response functions. During electrical stimulation, the total synaptic current entering an offer value cell (i.e., the cell's input) has two components – the current induced by the offer on the monitor (I_O) and the current induced by the electrical stimulation (I_S). For neurons in cortex, we can assume that the number of spikes emitted in a given time window increases with the total synaptic current entering the cell, and that the response function relating these quantities is decelerating (Extended Data Fig.6A)[39,40]. If so, the increase in firing rate due to I_S decreases as a function of I_O. In other words, other things equal, if the cell's firing rate is already high, the stimulation is less effective. Now consider the two groups of cells associated with the two juices. The effect of stimulation is equivalent to adding value to both juices. However, if tuning curves are linear, the stimulation adds more value to the juice that is not currently offered on the monitor, because I_O for cells associated with this juice is lower. Hence, the stimulation induces an order bias, and this effect is stronger at higher currents.

Second, neural hijacking. Experiments in motor cortex suggest that electrical stimulation at low versus high currents has qualitatively different effects on the neuronal output. At low currents, simultaneous stimulation of two cortical locations has additive effects on the EMG activity[41]. In contrast, high-current stimulation cancels and replaces the normal EMG

activity – a phenomenon termed neural hijacking[42,43]. This effect is understood based on the idea that high current stimulation induces both orthodromic and antidromic spikes, and that antidromic spikes collide with and cancel natural spikes[42]. Other work suggests that neural hijacking reflects a regime transition taking place around 50 μA, with higher current stimulating cells directly through the membrane[36]. In Exp.1, offer value cells subject to neural hijacking would have the same output independent of the juice they encode (A or B) and independent of the offer present on the monitor. It is not clear how hijacked neurons are read out by the decision circuit, but we can assume that the read-out value is equivalent for cells in the two groups.

To illustrate why this phenomenon induces an order bias, we consider the case in which stimulation is delivered (or not delivered) when juice A is offered on the monitor. We examine trials in which the two offer values are V_A and V_B. We indicate with ξ the fraction of offer value cells hijacked by the stimulation (same for the two groups), and V_H is the corresponding read-out value. If the total value of each juice is the sum of the values offered in the two time windows, we can compute the total offer values in each condition:

$$\begin{array}{lll} \text{stimOFF:} & V_A \quad \text{vs.} \quad V_B \\ \text{stimON:} & V_A\,(1-\xi) + \xi V_H \quad \text{vs.} \quad V_B + \xi V_H \end{array}$$

Under stimON, values induced by the stimulation cancel each other, and a bias favoring juice B ensues.

Decelerating response functions and neural hijacking interfere with the computation of value. Of note, these phenomena differ from that underlying the disruption of motion perception upon high-current stimulation of area MT, which presumably was due the stimulation activating cells in other mini-columns and opposite preferred direction[20].

Interestingly, 50 μA stimulation in Exp.1 induced both the order bias (Fig.2) and the range-dependent bias (Extended Data Fig.4). The concurrent presence of these effects is consistent with either mechanism discussed above. For example, the order bias induced by decelerating response functions would be independent of the value ranges, and thus take place in addition to the range-dependent bias. Also, 50 μA currents might hijack only a subset of cells, and simply increase the firing rate of other cells. That said, one might wonder how stimulation in any given session can induce both the order bias and the range-dependent bias. In fact, the two biases affect choices in very different ways (Extended Data Fig.6B). The range-dependent bias shifts the total sigmoid (obtained by pooling AB and BA trials) in the direction of the larger value range. Conversely, the order bias separates the two sigmoids for AB trials and BA trials in the positive or negative direction depending on whether the current is delivered during offer1 or offer2. Referring to Eq.1, the range-dependent bias is an effect on ρ; the order bias is an effect on ε.

Notably, 50 μA stimulation in Exp.1 induced range-dependent biases, but it did not alter relative values on average across the population (Fig.2). This is because sessions with $\Delta V_A > \Delta V_B$ and sessions with $\Delta V_A < \Delta V_B$ were pooled in Fig.2, and changes in relative value averaged out.

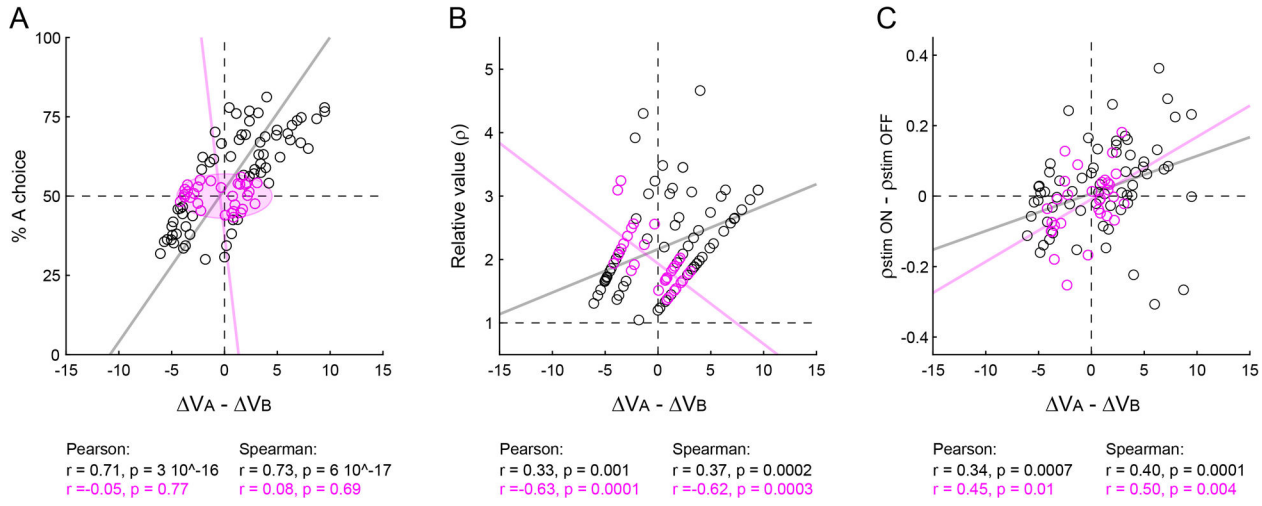
In Exp.1, ≥100 μA stimulation during offer2 also increased choice variability. In principle, high-current stimulation may increase variability in two ways: it may add noise to valuation, or it may add noise to the decision. The fact that choice variability increased only when stimulation was delivered during offer2 (and not during offer1) argued against the former and for the latter. Thus we interpret the effect shown in Fig.1H as electrical stimulation affecting value comparison.

The fact that we measured the order bias upon stimulation during offer2 (and not only during offer1) might seem in contrast with the hypothesis that values are compared within OFC. If so, the increase in choice variability could be mediated by downstream areas. However, neuronal recordings[27] revealed that when offers are presented sequentially, working memory of the first offer value is not instantiated by sustained activity in offer value cells, and might rely on synaptic mechanisms or other brain regions. At the same time, the first offer value affects the baseline activity of chosen juice cells upon presentation of offer2, as if setting the initial conditions of the decision circuit[27]. Thus stimulation during offer2 may not affect the two offer values equally. Hence, the order bias is consistent with decisions taking place in OFC.

Data and code availability

The complete data set and the Matlab code used for the analysis are available at: https://github.com/PadoaSchioppaLab/2020_Ballesta_etal_Nature

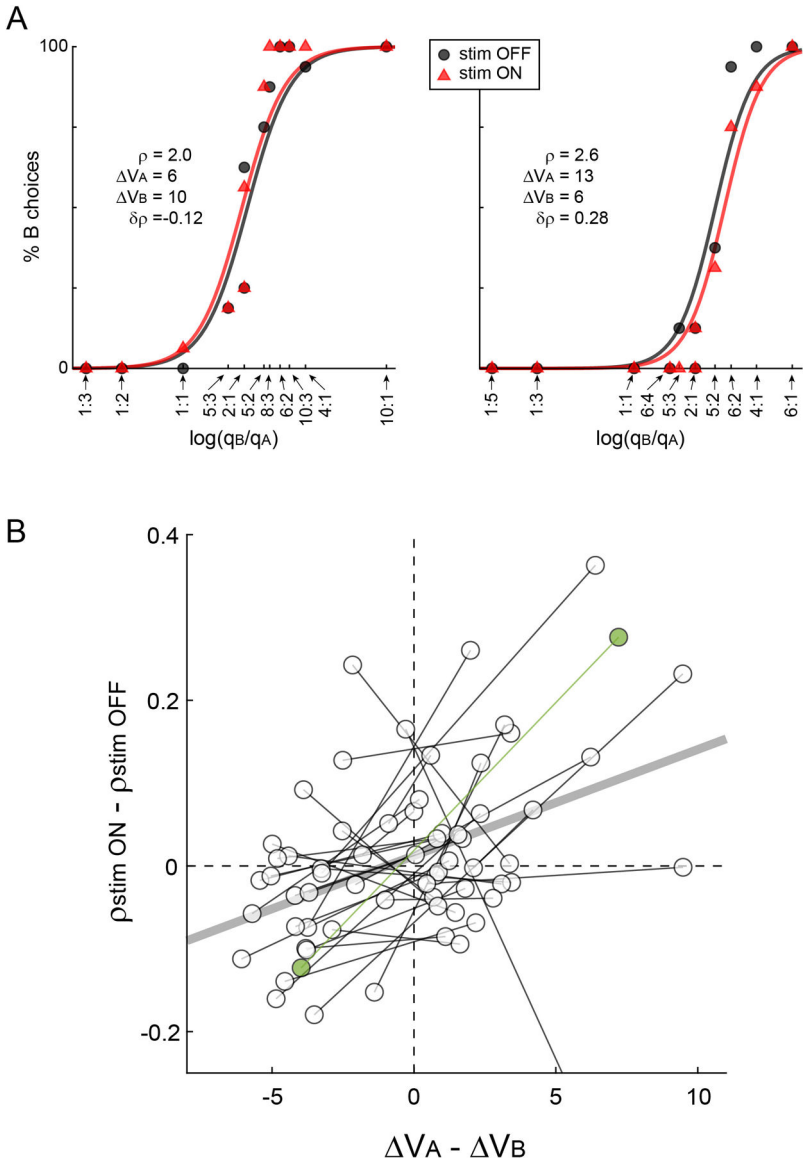
Extended Data



Extended Data Figure 1.

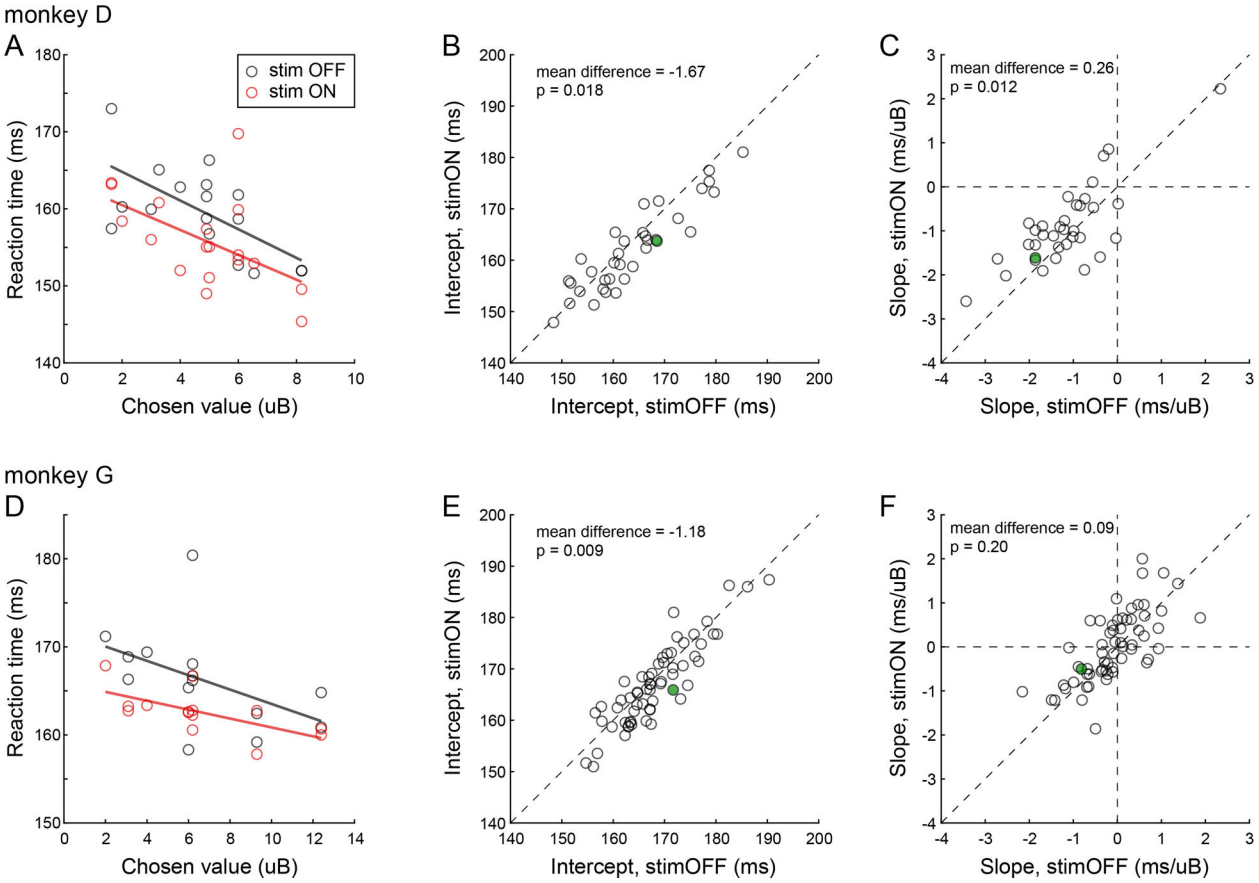
Exp.2, control for choice frequency. We noticed that across sessions the difference in value range ($\Delta V_A - \Delta V_B$) was correlated with the fraction of trials in which the animal chose juice A (% A choice) and with the relative value (ρ). In principle, these correlations could represent confounding factors. Indeed, 50 μA stimulation could partly disrupt the valuation process. As a result, the animal might respond by defaulting to the juice type most frequently chosen in that session, or to the preferred juice type. If so, the range-dependent bias would be akin to the order bias (Exp.1), in the sense that it would result from functional

disruption as opposed to facilitation. To address this concern, we identified a subset of sessions for which choices between the two juices were split almost evenly. In this subset of sessions, the difference in value range and the fraction of A choices were not correlated. We reasoned that if the range-dependent bias observed for the whole data set was driven by a default to the most frequently chosen option, the bias should disappear when the analysis was restricted to this subset of sessions. However, this was not the case. In fact, the range-dependent bias measured for the selected subset was larger than that measured for the entire population. We concluded that range-dependent biases did not reflect simple heuristics. **A.** Correlation between the difference in value range and the fraction of A choices. Each data point represents one session. Considering the entire data set (black data points, N=96 sessions), the two measures were significantly correlated ($r \geq 0.71$, $p<10^{-15}$, Pearson and Spearman correlation tests). We defined a small ellipse centered on coordinates [0, 50] (axes = [9, 14]). The ellipse identified a subset of data (pink data points, N=31 sessions) for which the difference in value range and the fraction of A choices were not correlated ($p \geq 0.69$, Pearson and Spearman correlation tests). **B.** Correlation between the difference in value range and the relative value. Considering the entire data set, the two measures were significantly correlated ($r \geq 0.33$, $p \leq 0.001$, Pearson and Spearman correlation tests). However, when the analysis was restricted to the subset of sessions identified in panel A (pink data points), the correlation changed sign. **C.** Range-dependent bias, same data as in Fig.4CD. Considering the entire data set, the change in relative value was significantly correlated with the difference in value range ($r \geq 0.34$, $p \leq 0.0007$, Pearson and Spearman correlation tests). The correlation did not dissipate when the analysis was restricted to the subset of sessions identified in panel A (pink data points; $r \geq 0.45$, $p \leq 0.01$, Pearson and Spearman correlation tests). In this figure, data from the two animals are combined. Black and pink lines in the three panels were obtained from Deming regressions.



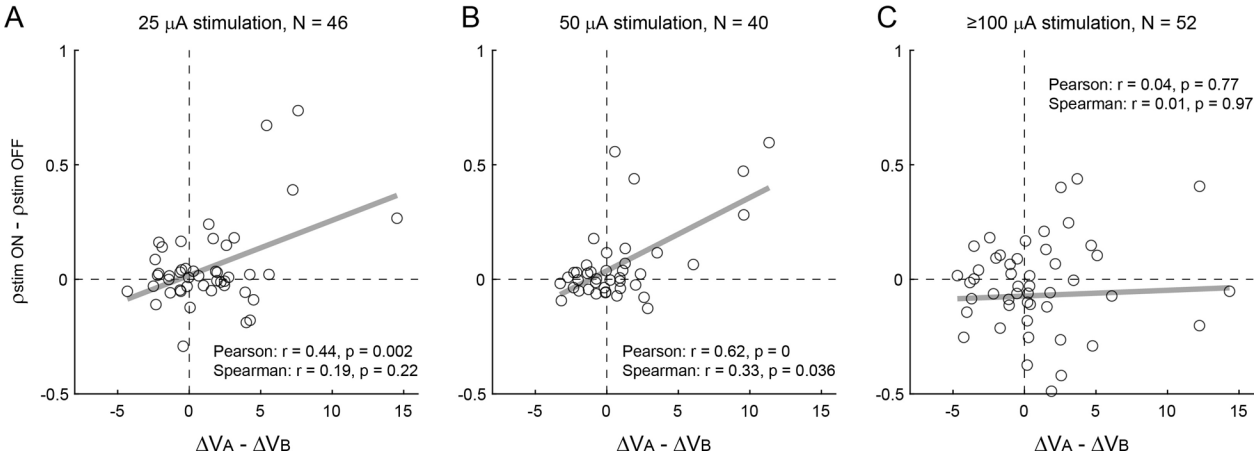
Extended Data Figure 2.

Exp.2, results obtained in paired sessions. In N=33 instances, we ran two back-to-back sessions offering the same two juices and leaving the electrode in place, but changing the quantity ranges such that ΔV_A–ΔV_B would differ. **A.** Example of paired sessions. **B.** Population analysis. Each pair of sessions in the scatter plot is connected by a line, of which we computed the slope. Data points filled in green correspond to sessions in panel A. Data from the two monkeys are pooled. Across the population, slopes were typically >0 (p = 0.007, two-tailed Wilcoxon signed-rank test). Hence, range-dependent biases were not dictated by the juice pair or by the location of the electrode within OFC.



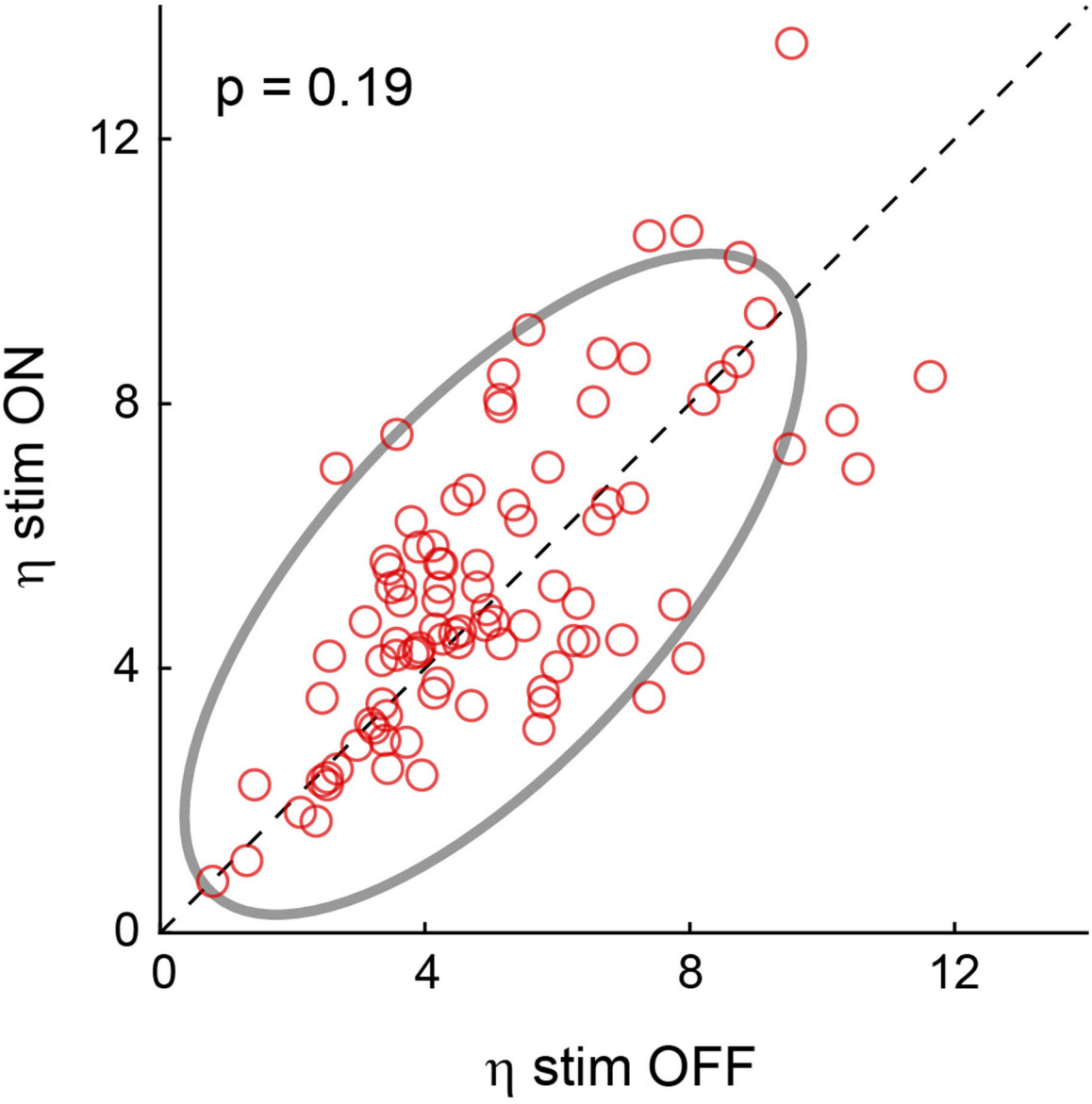
Extended Data Figure 3.

Exp.2, analysis of response times (RTs). **A.** Example session 1. Each data point represents one trial type and the two lines were obtained from linear regressions. Under normal conditions (stimOFF, black), RTs decreased as a function of the chosen value (x-axis). Electrical stimulation (stimON, red) generally reduced RTs. Linear fits reveal that lower RTs were due to a lower intercept, as opposed to a steeper (i.e., more negative) slope. **BC.** Population analysis, monkey D (N=35). For each session, we regressed RTs onto the chosen value, separately for stimOFF and stimON trials. We then compared the intercepts and the slopes at the population level. The picture emerging from panel A was confirmed for the population. In panel B (intercept), each data point represents one session. The population is significantly displaced below the identity line (p=0.018, two-tailed Wilcoxon test). In panel C (slope), it can be noticed that the slope under stimulation was shallower (less negative), probably due to a floor effect. Filled data points correspond to the session shown in panel A. **D.** Example session 2. Same format as in panel A. **EF.** Population analysis, monkey G (N=61). Same format as in panels BC. Electrical stimulation significantly lowered the intercept but did not significantly alter the slope. Filled data points correspond to the session shown in panel D. In panels BCEF, values indicated in the insert refer to the difference between the stimON measure and the stimOFF measure, averaged across the population. All p values are from two-tailed Wilcoxon tests, and t tests provided very similar results.



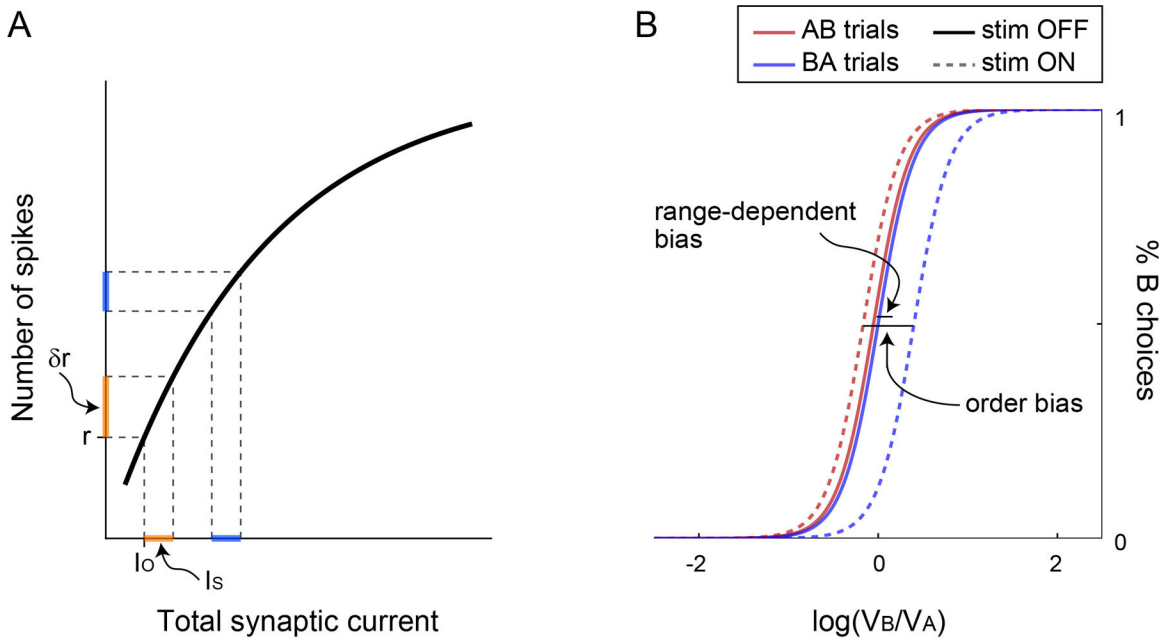
Extended Data Figure 4.

Exp.1, range-dependent choice biases. **ABC.** Results obtained when electric current was delivered at 25 μA, 50 μA and ≥100 μA. In each panel, x- and y-axes represent the difference in value range (in uB) and the difference in relative value, respectively. Each data point represents one session. Sessions from the two animals and with different stimulation times (offer1 or offer2) were pooled. Gray lines were obtained from linear regressions. Each panel indicates the p values obtained from Pearson and Spearman correlation tests. In essence, the choice bias imposed by the stimulation (δρ) was correlated with the difference in value ranges (ΔV_A–ΔV_B) at low current (25 μA; weakly) and intermediate current (50 μA), but not at high current (≥100 μA).



Extended Data Figure 5.

Stimulation in Exp.2 did not systematically alter the sigmoid steepness. For this analysis, the two groups of trials (stimOFF, stimON) were examined separately (see Methods). The two axes represent the sigmoid steepness in the two conditions. Sessions from the two animals were pooled (N=95, 2 outliers removed), and each data point represents one session. The gray ellipse represents the 90% confidence interval. The p value is from a Wilcoxon test and similar results were obtained with a t test.



Extended Data Figure 6.

Exp.1, interpretation of the order bias. **A.** Decelerating response function. The black line represents an ideal response function, which relates the number of spikes emitted by a cell in a given time window (y-axis) to the synaptic current entering the cell (x-axis). In the condition highlighted in yellow, I_O is the synaptic current due to the offer on the monitor, r is the corresponding response, I_S is the synaptic current due to the stimulation, and δr is the corresponding increase in the number of spikes. The condition highlighted in blue is similar, except that I_O is larger ($I_{O,blue} > I_{O,yellow}$). Because the response function is decelerating, δr in the blue condition is smaller ($\delta r_{blue} < \delta r_{yellow}$). In Exp.1, only one good was presented at the time. Neurons associated with that good were naturally more active (higher I_O) than neurons associated with the other good. Thus deceleration in the response function induced a bias favoring the good not offered during the stimulation (order bias). For given $I_{O,yellow}$ and $I_{O,blue}$, the difference $\delta r_{yellow} - \delta r_{blue}$ increases with I_S. Hence, higher stimulation currents induced larger order biases. **B.** Concurrent presence of order bias and range-dependent bias. The cartoon illustrates an ideal session in Exp.1. We assume that under normal conditions there is no order bias (stimOFF, continuous lines). Thus the two sigmoids for AB trials and BA trials coincide. We also assume that stimulation is delivered during offer1, and that $\Delta V_A - \Delta V_B > 0$. The order bias separates the two sigmoids such that under stimulation the sigmoid for AB trials is on the left of that for BA trials (stimON, dashed lines). The range-dependent bias imposes a shift on the total sigmoid, including both AB and BA trials (not shown), which moves to the right compared to normal conditions. The two choice biases are complementary and independent.

Extended Data Table 1.

Exact p values for the statistical tests ran for Fig.2. All p values are from two-tailed Wilcoxon tests.

Parameter	Stimulation interval	Current level	P value	P<.005
Relative value	control	0 μA	0.61	
	offer 1	25 μA	0.20	
		50 μA	0.37	
		≥100 μA	0.48	
	offer 2	25 μA	0.83	
		50 μA	0.34	
		≥100 μA	0.16	
Steepness	control	0 μA	0.43	
	offer 1	25 μA	0.47	
		50μA	0.20	
		≥100 μA	0.84	
	offer 2	25μA	0.27	
		50 μA	0.10	
		≥100 μA	0.0025	*
Order bias	control	0 μA	0.39	
	offer 1	25μA	0.46	
		50 μA	$5.5\ 10^{-4}$	*
		≥100 μA	$8.8\ 10^{-6}$	*
	offer 2	25μA	0.69	
		50μA	0.0041	*
		≥100 μA	$3.0\ 10^{-4}$	*

Extended Data Table 2.

Data set for Exp.1. Labels uni/bi indicate unilateral/bilateral stimulation. For the 54 sessions labeled as ≥100 μA, the current was typically set at 125 μA (47/54 = 87% sessions). In the remaining cases, the current was set at 100 μA (2/54 = 4%), 150 μA (4/54 = 7%) and 200 μA (1/54 = 2%). Removing from the data set sessions at 100, 150 and 200 μA did not substantially alter the results of this study.

Stimulation interval	Current level	Mode	Number of sessions		
			monkey G	monkey J	total
offer 1	≥100 μA	uni bi	5 15	8 1	29
	50 μA	uni bi	9 4	7 2	22
	25 μA	uni bi	11 14	4 0	29

Stimulation interval	Current level	Mode	Number of sessions		
			monkey G	monkey J	total
offer 2	≥100 μA	uni bi	14 3	6 2	25
	50 μA	uni bi	11 0	11 0	22
	25 μA	uni bi	9 2	6 0	17
control	0 μA	--	30	20	50
Total	--	--	127	67	194

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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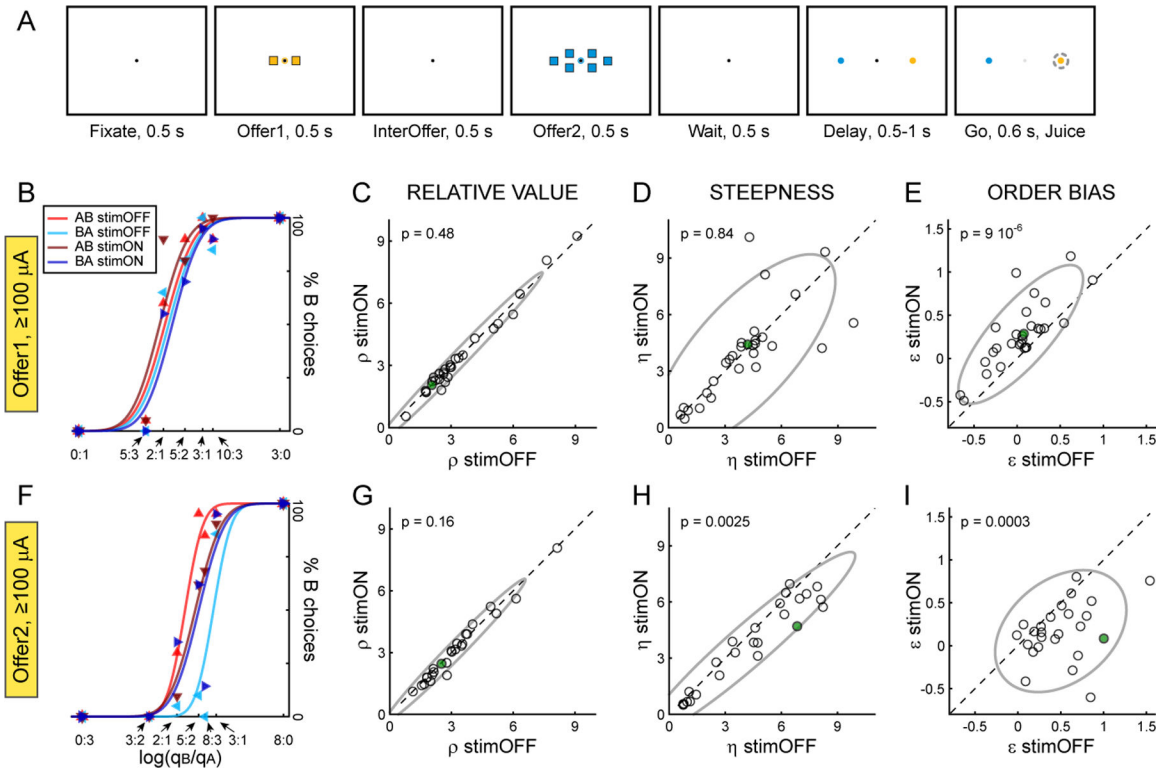

Figure 1.

High-current stimulation of OFC disrupts valuation. **A.** Experiment 1, design. Offers, represented by sets of squares, appeared centrally and sequentially. In this trial, the animal chose between 2 drops of grape juice and 6 drops of peppermint tea. **B.** Example session 1. In half of the trials, we delivered 125 µA current during offer1. The panel illustrates the choice pattern for AB trials (red) and BA trials (blue), separately for stimOFF trials (light) and stimON trials (dark). Data points are behavioral measures and lines are from probit regressions (Eq.1). In each condition (stimOFF, stimON), the order bias (ε) quantified the distance between the two flex points. In stimOFF trials, a small order bias favored offer2 ($\varepsilon_{stimOFF}$ =0.02). In stimON trials, the order bias increased (ε_{stimON} =0.07). Hence, stimulation biased choices in favor of offer2. **CDE.** Population results for stimulation during offer1 (N=29 sessions, ≥100 µA). Stimulation did not affect relative values (C); it did not consistently affect the sigmoid steepness (D); and it biased choices in favor of offer2 (E). **F.** Example session 2. Here 125 µA current was delivered during offer2. Stimulation induced a bias in favor of offer1 ($\varepsilon_{stimON}<\varepsilon_{stimOFF}$) and increased choice variability (shallower sigmoids in stimON trials; $\eta_{stimON}<\eta_{stimOFF}$). **GHI.** Population results for stimulation during offer2 (N=25 sessions, ≥100 µA). Stimulation did not affect relative values (G); it reduced the sigmoid steepness (H); and it biased choices in favor of offer1 (I). In panels CDEGHI, green symbols are from sessions shown in B and F; ellipses indicate 90% confidence intervals. All p values are from two-tailed Wilcoxon tests, and very similar results were obtained using t tests.

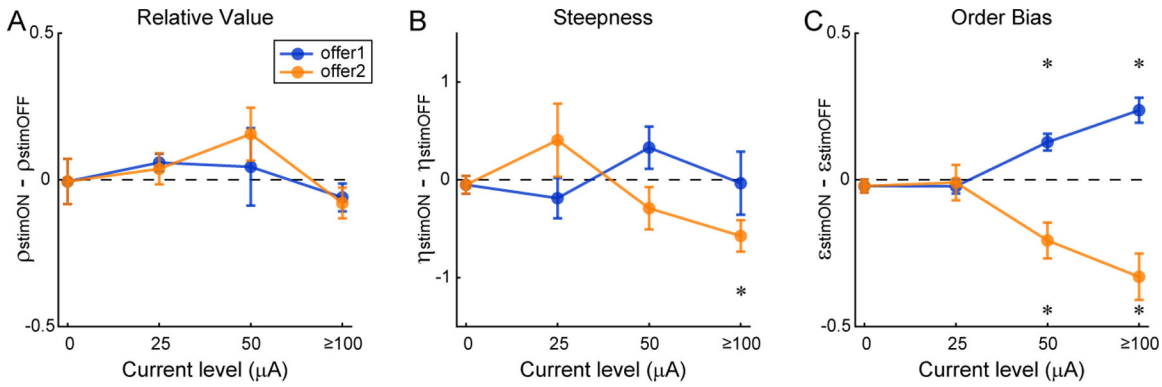

Figure 2.

Effects of electrical stimulation at different current levels. The whole data set includes N=29/22/29 sessions in which 25/50/≥100 μA were delivered during offer1, N=17/22/25 sessions in which 25/50/≥100 μA were delivered during offer2, and N=50 control sessions (0 μA; 194 sessions total). **A.** Relative value. **B.** Sigmoid steepness. **C.** Order bias. In each panel, blue and yellow refer to stimulation during offer1 and offer2, respectively. Data points are averages across sessions and error bars indicate SEM. Asterisks highlight measures that differed significantly from zero (all $p<0.005$, two-tailed Wilcoxon test). All other measures were statistically indistinguishable from zero (all $p>0.05$, two-tailed Wilcoxon test). Extended Data Table 1 provides the exact p values. Statistical analyses based on t tests provided very similar results.

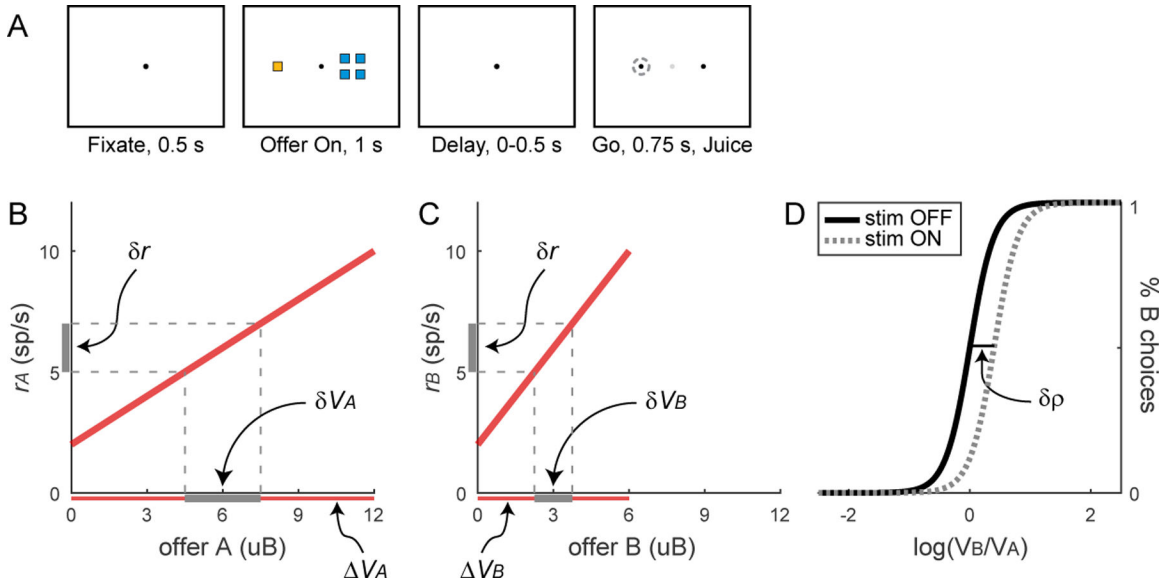

Figure 3.

Prediction of range-dependent choice bias induced by electrical stimulation (facilitation). **A.** Experiment 2, design. Two offers are presented simultaneously. After a brief delay, the animal indicates its choice with a saccade. Electrical stimulation (50 μA) is delivered throughout offer presentation. **BCD.** Predictions for one example session. In OFC, the encoding of offer values is predominantly positive (higher activity for higher values). Panels B and C represent the (mean) tuning curves for pools of offer value A cells and offer value B cells under adapted conditions. Firing rates (y-axis) are plotted as a function of the offer values (x-axis) expressed in units of juice B (uB). Red horizontal lines represent the two value ranges, with $\Delta V_A > \Delta V_B$. The same firing rate interval δr corresponds to different value intervals, with $\delta V_A > \delta V_B$. Panel D represents choice patterns. Electrical stimulation increases both offer values, but the net effect is a choice bias in favor of juice A ($\delta\rho > 0$). Conversely, in sessions where $\Delta V_A < \Delta V_B$, δr induces $\delta V_A < \delta V_B$, and electrical stimulation biases choices in favor of juice B ($\delta\rho < 0$, not shown). See Methods.

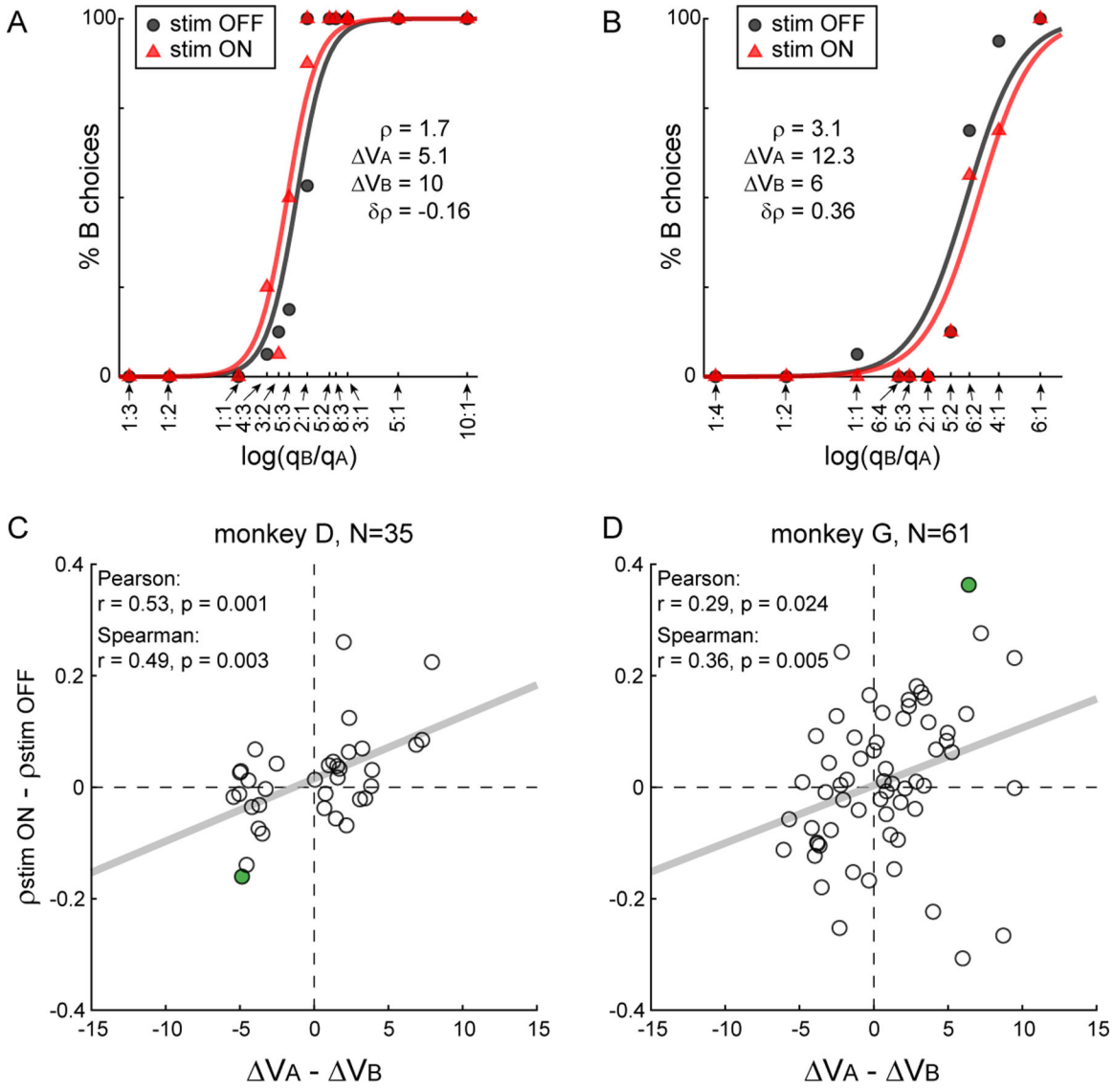

Figure 4.

Range-dependent choice bias induced by neuronal facilitation of OFC. **A.** Example session 1. In this session, we set $\Delta V_A<\Delta V_B$. Consistent with the prediction, electrical stimulation biased choices in favor of juice B ($\delta\rho<0$). **B.** Example session 2. In this case, we set $\Delta V_A>\Delta V_B$. Electrical stimulation biased choices in favor of juice A ($\delta\rho>0$). **CD.** Population analysis. The two panels refer to the two animals. In each panel, the choice bias ($\delta\rho$, y-axis) is plotted against the difference in value range ($\Delta V_A–\Delta V_B$, x-axis). Each data point represents one session, and the gray line is from a linear regression. Value ranges are expressed in units of juice B (uB). The two measures are significantly correlated in both monkey D (r=0.53, p=0.001, Pearson correlation test; r=0.49, p=0.003, Spearman correlation test) and monkey G (r=0.29, p=0.024, Pearson correlation test; r=0.36, p=0.005, Spearman correlation test). Green data points are from sessions illustrated in panels A and B.