nature research

Peer Review File

Manuscript Title: Values Encoded in Orbitofrontal Cortex Are Causal to Economic Choices

Reviewer Comments & Author Rebuttals

Redactions – Third Party Material

Parts of this Peer Review File have been redacted as indicated to remove third-party material.

Reviewer Reports on the Initial Version:

Referees' comments:

Referee #1 (Remarks to the Author):

This study uses electrical microstimulation to determine whether orbitofrontal cortex (OFC) makes a causal contribution to economic choice. In the ideal experiment, one would want to target the specific population of neurons that encode the value of one of the options in order to change that option's value relative to the alternative. However, a challenge with respect to OFC is that neurons encoding the value of different options are not anatomically segregated. The authors overcome this obstacle in a couple of different ways. In the first experiment, they temporally separated the presentation of the two options and stimulated after each presentation. Stimulation biased choice towards the alternative option. In the second experiment, the authors took advantage of the fact that OFC neurons adjust the gain on the neuronal response as a function of the value range of a given option. Consequently, stimulation will have a bigger effect on neurons with a high gain. Indeed, this prediction was confirmed. The experiments are elegant and well-designed, the results are relatively straightforward, and the authors do a good job in presenting the results clearly. I think the paper makes an important contribution to the literature and will be of interest to a broad range neuroscientists and clinicians. The comments I have are only minor.

Comments

1. Page 3: the text refers to juices K and J, whereas the equation references juices A and B.

2. The terminology that the authors use to describe their stimulation is non-standard, I think. They refer to "bipolar pulses", but this seems to conflate two different terms. Monopolar/bipolar stimulation typically refers to whether a single stimulating electrode is used, in which case current spread is assumed to be uniform around the electrode tip, or whether two electrodes are used, where one serves as the current source and the second is the sink. It would be good to know whether the authors used monopolar or bipolar stimulation. Regarding the pulse shape, it can be either monophasic, or more commonly biphasic, which ensures charge balance. I'm assuming the authors mean their pulses are biphasic.

3. Supplementary Note, 4th line: ironically, the word "two" occurs twice.

4. Figure S1: I think its hard to justify a one-tailed test here. Negative slopes can (and do!) occur. The result will still be significant, and this figure makes a relatively minor point anyway.

5. Figure S2: were these Wilcoxon tests one-tailed or two-tailed?

Referee #2 (Remarks to the Author):

In the current study, the authors studied the important question of whether the orbitofrontal cortex causally contributes to value-based decision making. It has been well known that OFC neurons encode value. It is, however, unknown whether they are directly involved in value-based decision making in the primates, partly because the OFC is a big region in the primates with no known functional organization. Building on previous recording experiments, the authors designed two clever experiments to circumvent these obstacles and show that microstimulations in the OFC affect monkeys' choices in a manner consistent with its suggested roles in value-based decision making from previous recording experiments. The data and the analyses provided convincing evidence that the OFC is an integral part of the value-based decision circuitry in the primates and directly contributes to value-based decisions.

I only have a few minor comments:

1. I think the results from the Exp1 should be taken more cautiously. While many studies have shown that large currents lead to a disruption of functions, many have been attributed to non-specific effects, such as the stimulation of passing axons, which lead to the disruption of upstream or downstream structures.

2. I don't agree that the microstimulation results during Offer 2 support the idea that the value comparison occurs in the OFC. Instead, they are against it. If the value comparison occurs in the OFC during Offer 2, there should be a representation of offer value 1 during the offer 2 period. This representation of offer value 1 should be equally (or at least partly) affected by the microstimulation. One would see to a weaker or even an absence of effects of the microstimulation during Offer 2. The data are not consistent with this expectation. Looking at Fig 1E and Fig 1I, I think the microstimulation effects during Offer 2 are as strong as, if not stronger than, those during Offer 1. This, to me, is the evidence that there's little representation of offer value 1 during the offer 2 period.

The slight change of choice variability caused by the microstimulation during Offer 2 could be explained by the non-specific effects of microstimulation.

Therefore, I would suggest removing the last sentence of the 2nd paragraph on pg 3: "This effect is interpreted as high-current stimulation disrupting value comparison (i.e., the decision), which took place upon presentation of offer2. " and the last sentence in the summary paragraph on pg 5: "In addition, the increase of choice variability observed in Exp.1 (upon stimulation during offer2 but not during offer1) indicates that OFC is directly involved in value comparison (i.e., the decision)."

3. I would suggest removing the color in Fig 1C-E and G-I. They are unnecessary and distracting.

4. I think Fig2 can be in the supplementary.

5. The last paragraph on pg 5 seems out of place.

Referee #3 (Remarks to the Author):

This paper by Ballesta and colleagues examines the effect of electrical microstimulation in the monkey orbitofrontal cortex on economic choice behavior, with the goal of testing whether OFC activity can be causally linked to decision making. They show an effect of microstimulation in two different ways, both of which address the experimental difficulty of the lack of clear topography/columnar organization in OFC. In a sequential decision task, high current stimulation (100 uA) during one of the option offers biases

choice behavior towards the other, unstimulated offer. In a simultaneous decision task, low current stimulation (50 uA) biases choice towards the offer with a larger past value range - a finding that relies on previously reported range adaptation effects.

Decision making is a critical cognitive process, and despite much electrophysiological and neuroimaging work the neural circuitry underlying choice remains relatively unclear. Recent work has focused increasingly on frontal brain areas like OFC, and this current work adds to lesion and recording data that suggests a role for frontal cortex in reward-guided choice. The effects reported here appear to relatively consistent, and the authors use two clever paradigms to selectively change choice behavior despite heterogenous coding in OFC. However, there are some outstanding issues regarding assumptions and interpretations that I would like to see the authors address:

(1) Effect of high current stimulation. The authors find that high current stimulation during one of two sequential offers selectively biases choice towards the non-stimulated offer, and conclude that this is due to inactivation/disruption of the valuation process for the stimulated offer. Certainly, the results confirm that microstimulation causes an offer-specific choice bias. However, the link between high current stimulation and the observed bias effects are not quite so clear, and it would help if the authors clarified their interpretation.

One issue is how might the presumed disruption caused by stimulation result in a choice bias. In the Murasagi 1993 paper cited by the authors, the effect of high current stimulation is largely an increase in *choice variability* rather than a bias. The presumptive mechanism in that work, which involved microstimulation in MT during a motion discrimination task, was a spread of current-induced activation beyond a single cortical column: at lower currents, stimulation activates neurons selective for one direction of motion (inducing a choice bias), while at higher currents, activation occurs for neurons representing multiple motion directions (increasing stochasticity). While not an identical task, the general idea behind the sequential presentation here is to stimulate neurons selective for one option (analogous to direction-specific columnar stimulation in MT). How do the authors suggest that stimulation during one offer causes a shift rather than an increase in choice stochasticity?

A second issue is the presumption of inactivation/disruption at 100 uA currents. The authors link the choice bias effects to disruption of value computation processes, but the general literature suggests that stimulation at these currents are *activating* rather than inactivating. For example, microstimulation at ~ 100 uA elicits behavioral responses in a number of brain areas: saccades at 100-200 uA in LIP (Thier & Andersen 1998), complex movements at 50-150 uA in PM (Graziano et al. 2002). Furthermore, optical (Histed et al. 2009) and neuroimaging (Tolias et al. 2005) studies also imply increasing activation with increasing current, even for much larger currents. If the proposed mechanism is a disruption, it cannot be a long lasting inactivation, since overall choice is preserved (and presumably offer 1 stimulation leaves offer 2 processing intact). Also, 50 uA is seen as activating in Expt 2, but inactivating/disrupting in Expt 1 (order bias, Fig 2) - can the authors reconcile these effects?

Can the authors provide a more concrete interpretation of the observed bias effects, and how a momentary disruption leads to a preferential bias in choice? Specifically, is there any reason to believe that a momentary disruption (or activation, for that matter) would lead to a *shift* in choice curves equivalent to a subtraction in value? In the context of circuit-based models of OFC decision making, such as that previously proposed by the authors (e.g. Rustichini & Pasoa-Schioppa 2015), do the authors view high current stimulation as disrupting all types of neurons (offer value, chosen value, juice type) or only a subset?

On a related note, the authors describe RT effects in Expt 2 supporting the idea of increases in value at low currents. Are there any RT effects in Task 1, and are they consistent with an inactivation effect?

(2) Value range effects in Expt 2. The use of range adaptation to probe OFC stimulation effects is a clever way to overcome the lack of option-specific structure in neural organization. This is certainly the most novel and innovative part of the current approach, but also the ones that relies most on an assumed underlying mechanism, and there are some issues the authors could clarify regarding the assumptions and data supporting the hypothesized effect (stimulation increasing relative value of the higher value range option).

The results focus on a change in relative value - were there changes in other behavioral parameters? In particular was there an effect on choice stochasticity (steepness)? I wonder about stochasticity for two reasons. First, if the disruptions during offer 2 stimulation in Expt 1 are driven by disrupted comparison, one would expect similar effects here. Second, are there projected effects on stochasticity that follow from the range adaptation hypothesis (i.e. Fig 3)?

While the value range effects (Fig. 4) are striking, I am a little concerned that value range differences may be confounded with other underlying task conditions. Is there a systematic relationship, for example, between value range difference and proportion of overall choices (or relative value rho)? In other words, do offers (juices) with larger value ranges also happen to be those chosen more often in that session (by design)? This seems to be the case for the examples in Fig 4AB, but it would help to see across all the data)e.g. by correlation). The issue is whether the effects could be driven by a different mechanism than the range adaptation one put forth by the authors; for example, perhaps in the face of stimulation the animals could not process either option at all and default to the option chosen more often in the past (a choice history effect).

Finally, the proposed mechanism for the Expt 2 results hinge on low current stimulation *increasing* neural value representations. However, neurons in frontal brain areas to be both positively and negatively modulated by variables such as reward, and this is a point that needs to be more directly discussed in the paper. If positive and negative coding neurons were equal in the population, then stimulation effects would cancel out and there should be no value range-dependent response; I know that the authors have previously reported a bias for positive-encoding cells, and this should be mentioned in the main text.

Other points

(1) Description of Expt 1. The Methods (pg. 12) state that a small colored circle was presented around fixation with the offers. Was there a particular reason behind the circle presentation (did the circle present any information not contained in the colors of the accompanying squares)? Also, the task figure (Fig 1A) should include these as well.

(2) The Methods state that for Expt 1 “We designed offer types such that in most trials the animal necessarily waited for offer2 before making a decision”. What exactly does this sentence refer to? If A the amounts and order presentation of offers are varied, 50% of the time the better option should occur in offer 2 - is this what is meant?

(3) Variability in stimulation parameters. There appears to be considerable variability in the stimulation onset time (0-100 ms after offer onset), duration (300-600 ms), and frequency (100-333 Hz) in Expt 1. Was there a reason for such variability, and were any of the stimulation parameters titrated for behavior/neural responses? Also, it would help to know exactly what the “>125 uA” data included: how was that data split up between different current intensities, and is there a particular reason they are grouped rather than split up?

(4) There are existing lesion studies of monkey OFC that suggest that at least some aspects of reward-guided learning are not disrupted by lesions (Walton et al, 2010; Noonan et al. 2010; Rudebeck &

Murray 2011). I don't think this argues against the authors' view that OFC is contributing to economic choice, but does suggest that OFC is not necessarily critical for implementation. In any case, this previous work should be cited, probably in the last few paragraphs.

Author Rebuttals to Initial Comments:

Referee #1 (Remarks to the Author):

> This study uses electrical microstimulation to determine whether orbitofrontal cortex (OFC) makes a causal contribution to economic choice. In the ideal experiment, one would want to target the specific population of neurons that encode the value of one of the options in order to change that option's value relative to the alternative. However, a challenge with respect to OFC is that neurons encoding the value of different options are not anatomically segregated. The authors overcome this obstacle in a couple of different ways. In the first experiment, they temporally separated the presentation of the two options and stimulated after each presentation. Stimulation biased choice towards the alternative option. In the second experiment, the authors took advantage of the fact that OFC neurons adjust the gain on the neuronal response as a function of the value range of a given option. Consequently, stimulation will have a bigger effect on neurons with a high gain. Indeed, this prediction was confirmed. The experiments are elegant and well-designed, the results are relatively straightforward, and the authors do a good job in presenting the results clearly. I think the paper makes an important contribution to the literature and will be of interest to a broad range neuroscientists and clinicians. The comments I have are only minor.

We thank Reviewer 1 for the positive evaluation and for the constructive comments.

> Comments
>
> 1. Page 3: the text refers to juices K and J, whereas the equation references juices A and B.

We corrected the text removed reference to J and K.

> 2. The terminology that the authors use to describe their stimulation is non-standard, I think. They refer to "bipolar pulses", but this seems to conflate two different terms. Monopolar/bipolar stimulation typically refers to whether a single stimulating electrode is used, in which case current spread is assumed to be uniform around the electrode tip, or whether two electrodes are used, where one serves as the current source and the second is the sink. It would be good to know whether the authors used monopolar or bipolar stimulation. Regarding the pulse shape, it can be either monophasic, or more commonly biphasic, which ensures charge balance. I'm assuming the authors mean their pulses are biphasic.

Reviewer 1 is correct – thanks for catching this! Our stimulation was monopolar and the pulse shape was biphasic. We corrected the ms (p.14).

3. Supplementary Note, 4th line: ironically, the word "two" occurs twice.

:-) Thanks!

4. Figure S1: I think its hard to justify a one-tailed test here. Negative slopes can (and do!) occur. The result will still be significant, and this figure makes a relatively minor point anyway.

We changed the test to two-tailed.

1. Figure S2: were these Wilcoxon tests one-tailed or two-tailed?

These tests are two-tailed, and we clarified the figure legend.

Referee #2 (Remarks to the Author):

In the current study, the authors studied the important question of whether the orbitofrontal cortex causally contributes to value-based decision making. It has been well known that OFC neurons encode value. It is, however, unknown whether they are directly involved in value-based decision making in the primates, partly because the OFC is a big region in the primates with no known functional organization. Building on previous recording experiments, the authors designed two clever experiments to circumvent these obstacles and show that microstimulations in the OFC affect monkeys' choices in a manner consistent with its suggested roles in value-based decision making from previous recording experiments. The data and the analyses provided convincing evidence that the OFC is an integral part of the value-based decision circuitry in the primates and directly contributes to value-based decisions.

We thank Reviewer 2 for the positive evaluation and for the constructive comments.

I only have a few minor comments:

1. [A] I think the results from the Exp1 should be taken more cautiously. While many studies have shown that large currents lead to a disruption of functions, many have been attributed to non-specific effects, such as the stimulation of passing axons, which lead to the disruption of upstream or downstream structures.

2. [B] I don't agree that the microstimulation results during Offer 2 support the idea that the value comparison occurs in the OFC. Instead, they are against it. If the value comparison occurs in the OFC during Offer 2, there should be a representation of offer value 1 during the offer 2 period. This representation of offer value 1 should be equally (or at least partly) affected by the microstimulation. One would see to a weaker or even an absence of effects of the

microstimulation during Offer 2. The data are not consistent with this expectation. Looking at Fig 1E and Fig 1I, I think the microstimulation effects during Offer 2 are as strong as, if not stronger than, those during Offer 1. This, to me, is the evidence that there's little representation of offer value 1 during the offer 2 period.

[C] The slight change of choice variability caused by the microstimulation during Offer 2 could be explained by the non-specific effects of microstimulation.

Thank you for these comments. We took the liberty of addressing them in a different order. Square brackets [ ] are ours.

and [C] *Fibers of passage and increase in choice variability*. If we understand these comments correctly, Reviewer 2 does not question the idea that the increase in choice variability is due to the electric current interfering with the decision process (value comparison). The question is whether the decision process disrupted by the stimulation takes place within OFC or elsewhere. In the latter scenario, stimulation would disrupt the decision through fibers passing in the vicinity of OFC. To put this comment in context, there is an open question in the field as for where and how value-based decisions take place. One hypothesis is that good-based decisions take place within OFC (Padoa-Schioppa and Conen, 2017); another hypothesis is that decisions generally involve many brain regions and a "distributed consensus" (Cisek, 2012; Hunt and Hayden, 2017); other proposals have also been put forth.

We do not pretend to settle this question in the present study, and we rephrased the ms to provide a more nuanced interpretation (see below). Also, we cannot exclude that high-current stimulation affected passing fibers. However, we think that the increase in choice variability observed in Exp.1 upon stimulation during offer2 (**Fig.1H**) was most likely due to interference with neural processes taking place within OFC. The reason is that we obtained very similar effects in a mouse study in which OFC was inactivated using optogenetics (Kuwabara et al., 2020). In that study, animals performed decisions similar to those examined here and OFC inactivation induced a consistent increase in choice variability. Critically, the use of optogenetics excluded that this effect was mediated by passing fibers.

[A] *Plausibility of decisions taking place in OFC*. To summarize this comment, Reviewer 2 deems it is implausible that decisions may take place within OFC, given that high current stimulation during offer2 biased choices in favor of offer1. We appreciate the rationale for this comment, but we differ on the conclusions. Let us elaborate on this point.

Our understanding is based on a recent study, in which we examined the activity of neurons in OFC while monkeys chose between juices offered sequentially (Ballesta and Padoa-Schioppa, 2019). We refer to that paper for the details, but we can summarize the main findings as follows. First, an analysis of neuronal activity across time windows revealed the presence of different groups of cells analogous to those previously identified under simultaneous offers (Padoa-Schioppa and Assad, 2006). In other words, different groups of neurons encoded individual offer values, the juice identity, and the chosen value. Second, we analyzed the activity of these cell groups over the course of the trial. As correctly guessed by Reviewer 2, *offer value* cells

encoding the value of offer1 did not maintain a sustained activity throughout the delay separating the two offers (**Fig.R1A**). We speculate that the working memory of offer1 value may be maintained at the synaptic level (Mongillo et al., 2008; Stokes, 2015) or involve other brain regions. Third, immediately before offer2 presentation, *chosen juice* cells associated with the second offer presented an activity offset negatively related to the first offer value (**Fig.R1B**).

These observations can be interpreted in the context of a previously published model of economic decisions (Rustichini and Padoa-Schioppa, 2015; Wang, 2002). The model is a neural network whose components are the groups of cells identified in OFC. Competition between two pools of pyramidal cells (*chosen juice* cells) is mediated by a pool of inhibitory interneurons (*chosen value* cells). Decisions result from a balance between recurrent excitation and pooled inhibition, and are strongly biased by the network's initial conditions (Rustichini and Padoa-Schioppa, 2015). In this framework, the value of offer1 appears to enter the decision by setting the initial conditions of the decision circuit (i.e., the activity offset of *chosen juice* cells), not through a sustained activity of *offer value* cells. Most importantly, the representations of offer1 value and offer2 value during offer2 are not equivalent, and stimulation may not affect the two offer values equally.
[B]

[FIGURE R1 REDACTED]
Figure R1 adapted from Fig 6CD from: Ballesta, S. and C. Padoa-Schioppa (2019). "Economic decisions through circuit inhibition." Curr Biol **29**(22): 3814-3824 e3815.

In conclusion, the actual decision mechanisms remain poorly understood. However, at least in principle, the fact that stimulation during offer2 biased choices in favor of offer1 does not exclude that decisions may take place within OFC.

Incidentally, the same neural network model also provides an interpretation for the results of Exp.1. The order bias is understood as mediated by offer value cells (see **Methods**). Conversely, the increase in choice variability would be due to the stimulation increasing the activity of the other cell groups. Specifically, in the model, increasing the activity of inhibitory interneurons (*chosen value* cells) would speed up the dynamics, resulting in more impulsive and less accurate decisions. Similarly, increasing reverberation (i.e., self-excitation in *chosen juice* cells) would make choices less accurate (Wong and Wang, 2006).

> Therefore, I would suggest removing the last sentence of the 2nd paragraph on pg 3: "This effect is interpreted as high-current stimulation disrupting value comparison (i.e., the decision), which took place upon presentation of offer2. " and the last sentence in the summary paragraph on pg 5: "In addition, the increase of choice variability observed in Exp.1 (upon stimulation during offer2 but not during offer1) indicates that OFC is directly involved in value comparison (i.e., the decision)."

We revised the ms in several ways to address these issues. First, on p.3, we rephrased the sentence to be more tentative, and we also refer to the optogenetic results from the mouse study,

as follows:

[The increase in choice variability] may be interpreted as high-current stimulation disrupting value comparison (i.e., the decision), which took place upon presentation of offer2. Similar effects were observed in mice when OFC was inactivated using optogenetics (Kuwabara et al., 2020).

Second, on p.5, we removed the sentence "In addition…", as recommended. Concurrently, we expanded the previous paragraph (now second-to-last paragraph of the ms) to summarize the points discussed above, as follows:

[…] the increase in choice variability observed in Exp.1 upon stimulation during offer2 indicates that stimulation currents interfered with the decision process. More work is necessary to ascertain the organization of the decision circuit, including the role of different brain regions (Cisek, 2012; Padoa-Schioppa and Conen, 2017). 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 (Rustichini and Padoa-Schioppa, 2015; Wang, 2002), increasing reverberation increases choice variability (Wong and Wang, 2006). Similarly, increasing the activity of chosen value cells makes choices more impulsive and thus increase variability.

Third, in response to these comments and other comments from Reviewer 3, we added a section discussing our interpretation of the results of Exp.1 (p.17-18). The first part of the section focuses on the mechanisms through which high-current stimulation of *offer value* cells would induce an order bias. The following paragraph focuses on the issues discussed above:

Prima facie, the fact that we measured the order bias upon stimulation during offer2 (and not just 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 (Ballesta and Padoa-Schioppa, 2019) 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 (Ballesta and Padoa-Schioppa, 2019). Thus stimulation during offer2 may not affect the two offer values equally. Hence the order bias is consistent with decisions taking place in OFC.

We hope that Reviewer 2 will find these changes satisfactory.

1. I would suggest removing the color in Fig 1C-E and G-I. They are unnecessary and distracting.

We removed the colors from this figure.

2. I think Fig2 can be in the supplementary.

We beg to differ. **Fig.2** summarizes the results of Exp.1 for different current levels. We think that

this result is very important and we decided to leave the figure in the main text.

> 3. The last paragraph on pg 5 seems out of place.

We removed the paragraph.

Referee #3 (Remarks to the Author):

> This paper by Ballesta and colleagues examines the effect of electrical microstimulation in the monkey orbitofrontal cortex on economic choice behavior, with the goal of testing whether OFC activity can be causally linked to decision making. They show an effect of microstimulation in two different ways, both of which address the experimental difficulty of the lack of clear topography/columnar organization in OFC. In a sequential decision task, high current stimulation (100 uA) during one of the option offers biases choice behavior towards the other, unstimulated offer. In a simultaneous decision task, low current stimulation (50 uA) biases choice towards the offer with a larger past value range - a finding that relies on previously reported range adaptation effects.
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> Decision making is a critical cognitive process, and despite much electrophysiological and neuroimaging work the neural circuitry underlying choice remains relatively unclear. Recent work has focused increasingly on frontal brain areas like OFC, and this current work adds to lesion and recording data that suggests a role for frontal cortex in reward-guided choice. The effects reported here appear to relatively consistent, and the authors use two clever paradigms to selectively change choice behavior despite heterogenous coding in OFC. However, there are some outstanding issues regarding assumptions and interpretations that I would like to see the authors address:

We thank Reviewer 3 for the positive evaluation and for the constructive comments. The comments asking us to clarify our assumptions and interpretations were particularly helpful. The revised ms incudes a new section "*High-current stimulation and the order bias*" focused on these issues (p.17-18).

> (1) Effect of high current stimulation. The authors find that high current stimulation during one of two sequential offers selectively biases choice towards the non-stimulated offer, and conclude that this is due to inactivation/disruption of the valuation process for the stimulated offer. Certainly, the results confirm that microstimulation causes an offer-specific choice bias. However, the link between high current stimulation and the observed bias effects are not quite so clear, and it would help if the authors clarified their interpretation.

Before addressing specific comments, we clarify our key assumptions.

We assume that electrical stimulation always increases neuronal spiking. As noted by

[1] Reviewer 3, an established literature supports this assumption (Graziano et al., 2002; Hao et al., 2016; Histed et al., 2009; Thier and Andersen, 1998; Tolias et al., 2005).

In our experiments, currents varied between 25 μA and 150 μA. Previous studies indicate that when currents increase in this range, the effects of stimulation on the spiking activity change in several ways. First, for any given cell and for equal number of pulses, the number of emitted spikes increases with the current (Hussin et al., 2015; Lee et al., 2013). Second, as the current increases, the stimulation affects an increasing number of cells over a larger volume (Histed et al., 2009; Stoney et al., 1968; Tolias et al., 2005). Third, a regime transition takes place around 50 μA. At lower current, electrical stimulation induces spiking only through synaptic transmission; at higher current, stimulation also induces spiking directly through the membrane (Hussin et al., 2015).

[2] Behavioral effects of stimulation. Electrical stimulation affects some fraction of neurons, especially around the electrode tip, while other neurons are largely unaffected. The behavioral effects reflect some sort of average between the affected population and the unaffected population. (This point is somewhat trivial, but worth keeping in mind.)

[3] 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 encoding the offer values of the two juices are intermixed). We assume that for each juice (A and B) the values presented in the two time windows (1 and 2) are added.

One issue is how might the presumed disruption caused by stimulation result in a choice bias.

[A] In the Murasagi 1993 paper cited by the authors, the effect of high current stimulation is largely an increase in *choice variability* rather than a bias. The presumptive mechanism in that work, which involved microstimulation in MT during a motion discrimination task, was a spread of current-induced activation beyond a single cortical column: at lower currents, stimulation activates neurons selective for one direction of motion (inducing a choice bias), while at higher currents, activation occurs for neurons representing multiple motion directions (increasing stochasticity). While not an identical task, the general idea behind the sequential presentation here is to stimulate neurons selective for one option (analogous to direction-specific columnar stimulation in MT). [B] How do the authors suggest that stimulation during one offer causes a shift rather than an increase in choice stochasticity?

[ ] Square brackets are ours. We took the liberty of addressing these questions in reverse order.

[B] We recall that in Exp.1 the two juices are offered sequentially, and stimulation is delivered during one of the two time windows. The order bias is a bias favoring the juice not present on the monitor during the stimulation. High currents may induce an order bias for at least two reasons.

(a) Decelerating response function. 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, it is safe to 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 two quantities is decelerating (Arsiero et al., 2007; La Camera et al., 2008) (**Fig.R2**). 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 the 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 (≥100 μA).

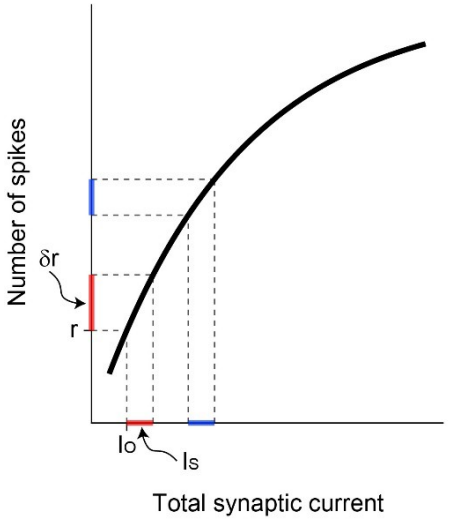

Figure R2. Decelerating response function. The black line represents the typical response function, which relates the number of spikes emitted by a cell in a given time window (y-axis) to the synaptic current entering the cell (input, x-axis). In the condition highlighted in red, I_O is the synaptic 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 ($I_{O,blue} > I_{O,red}$). Because the response function is decelerating, δr in the blue condition is smaller ($\delta r_{blue} < \delta r_{red}$). In Exp.1, only one good is presented at the time. Neurons associated with that good are naturally more active (higher I0) than neurons associated with the other good. Thus deceleration in the response function induces a bias favoring the good not currently offered (order bias). For given $I_{O,red}$ and $I_{O,blue}$, the difference $\delta r_{red} - \delta r_{blue}$ increases with I_S. In other words, higher stimulation currents will induce a larger order bias

(b) 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 (10-20 μA), simultaneous stimulation of two cortical locations has additive effects on the EMG (Ethier et al., 2006). In contrast, stimulation at high current (≥60 μA) cancels and replaces the normal EMG activity (neural hijacking) (Griffin et al., 2011; Van Acker et al., 2013). 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 (Griffin et al., 2011). Other work suggests that neural hijacking reflects a regime transition taking place around 50 μA, with stimulating cells directly through the membrane (Hussin et al., 2015). Coming to our study, 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. However, we can assume that the read-out 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 V_H the read-out value, and ξ is the fraction of offer value cells hijacked by the stimulation (same for

the two groups). 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:

stimOFF:	V_A	vs.	V_B
stimON:	$V_A (1- \xi) + \xi V_H$	vs.	$V_B + \xi V_H$

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

Decelerating response functions and neural hijacking may be viewed as interfering with the computation of value. Of note, these phenomena are not mutually exclusive because neural hijacking might take place only in a subset of neurons.

The new section of the revised ms clarifies our key assumptions and includes the present discussion (p.17-18). We also included **Fig.R2** (as **Extended Data Fig.6A**).

[A] Our interpretation of Murasugi's result coincides with that of Reviewer 3. Hence, the phenomena believed to induce the order bias differ from that increasing choice variability in the Murasugi study. We noted this point explicitly in the revised ms (p.18).

> A second issue is the presumption of inactivation/disruption at 100 uA currents. [C] The authors link the choice bias effects to disruption of value computation processes, but the general literature suggests that stimulation at these currents are *activating* rather than inactivating.
>
> For example, microstimulation at ~ 100 uA elicits behavioral responses in a number of brain areas: saccades at 100-200 uA in LIP (Thier & Andersen 1998), complex movements at 50-150 uA in PM (Graziano et al. 2002). Furthermore, optical (Histed et al. 2009) and neuroimaging (Tolias et al. 2005) studies also imply increasing activation with increasing current, even for much larger currents. If the proposed mechanism is a disruption, it cannot be a long lasting inactivation, since overall choice is preserved (and presumably offer 1 stimulation leaves offer 2 processing intact). [D] Also, 50 uA is seen as activating in Expt 2, but inactivating/disrupting in Expt 1 (order bias, Fig 2) - can the authors reconcile these effects?

[C] For clarification, when we say that high currents "disrupt" a mental function, we don't mean to imply that the disruption is due to inhibition. We completely agree that currents including high-level currents induce more spiking and are not inhibitory (see above, point [1]).

[D] 50 μA stimulation in Exp.1 induced both the order bias and the range-dependent bias. The concurrent presence of both biases is not surprising and it is consistent with any of the two mechanisms discussed above apropos the order bias. 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 induce hijacking only in a subset of cells. For other cells, 50 μA currents might simply increase firing rates, leading to the range-dependent bias.

That said, one might wonder how in any given session the stimulation could induce both biases. The answer is fairly simple. Referring to **Fig.R3**, the range-dependent bias means that the total

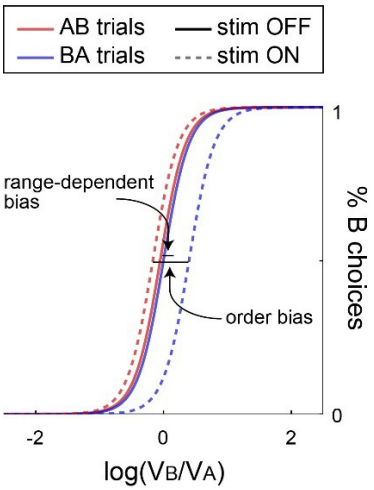

Figure R3. Concurrent presence of two biases. The cartoon illustrates one session in Exp.1. We assume that under normal conditions (stimOFF) there is no order bias. Hence, the two sigmoids for AB and BA trials are on the top of each other. We also assume that stimulation is delivered during offer1, and that ΔVA- ΔVB>0. The order bias separates the two sigmoids such that under stimON the sigmoid for AB trials is on the left of that for BA trials (dashed lines). The range-dependent bias imposes a shift on the total sigmoid, including both BA and AB trials (not shown), which moves to the right compared to the stimOFF condition. The two biases are complementary and independent.

sigmoid shifts in the direction of the larger value range. The order bias means that the two sigmoids for AB trials and BA trials separate in the positive or negative direction depending on whether the stimulation is delivered during offer1 or offer2. Referring to Eq.1 in the ms, the range-dependent bias is an effect on ρ; the order bias is an effect on ε.

The revised ms discusses this point (p.18) and includes **Fig.R3** (as **Extended Data Fig.6B**).

> [E] Can the authors provide a more concrete interpretation of the observed bias effects, and how a momentary disruption leads to a preferential bias in choice? Specifically, is there any reason to believe that a momentary disruption (or activation, for that matter) would lead toa *shift* in choice curves equivalent to a subtraction in value? [F] In the context of circuit-based models of OFC decision making, such as that previously proposed by the authors (e.g. Rustichini & Pasoa-Schioppa 2015), do the authors view high current stimulation as disrupting all types of neurons (offer value, chosen value, juice type) or only a subset?

[E] The origin of the order bias is addressed above (point [B]).

[F] Different groups of cells (offer value, chosen juice, chosen value) are intermixed in OFC. Hence, we assume that stimulation affects all cell groups. In general, we conceptualize choice as a two-stage process in which values are first computed (valuation) and then compared (decision). We interpret the order bias and the range-dependent bias in terms of electrical stimulation altering valuation through offer value cells. (We do so because consideration of offer value cells is sufficient to explain the results, and because based on current models it is unclear how increasing the firing rates of the other cell groups would induce either bias.) Conversely, we interpret the increase in choice variability recorded in Exp.1 (**Fig.1H**) in terms of electrical stimulation affecting the decision process. The rationale is as follows. In principle, high current

stimulation may increase choice variability in at least two ways: (i) it may add noise to valuation, or (ii) it may add noise to the decision. The fact that choice variability increases only when stimulation is delivered during offer2 (and not during offer1) argues against (i) and for (ii).

As noted by Reviewer 3, we previously proposed a computational model in which offer value cells provide the input to a decision circuit formed by chosen juice cells and chosen value cells (Rustichini and Padoa-Schioppa, 2015). Our results can be understood in relation to the model. In the network, competition between two pools of pyramidal cells (chosen juice cells) is mediated by a pool of inhibitory interneurons (chosen value cells). Decisions result from a balance between recurrent excitation (reverberation) and pooled inhibition. High current stimulation can increase choice variability in several ways. First, increasing the activity of inhibitory interneurons speeds up the dynamics, resulting in more impulsive decisions. As a result, choices are less accurate. Along similar lines, increasing reverberation makes choices less accurate (Wong and Wang, 2006). Finally, neural hijacking in any cell group would increase choice variability. This point is particularly clear for chosen juice cells. If their output becomes independent of the input from offer value cells, decisions are more noisy.

To summarize, we interpret the increase in choice variability recorded in Exp.1 when high current is delivered during offer2 in terms of stimulation disrupting the decision process. If values are compared within OFC, we propose that the disruption is mediated by the decision circuit including chosen juice cells and chosen value cells.

We expanded the second-to-last paragraph of the main text to discuss our interpretation in relation to the decision process and the model as follows:

The order bias observed in Exp.1 is also understood as due to the effect of stimulation on offer value cells. Conversely, the increase in choice variability observed in Exp.1 upon stimulation during offer2 indicates that stimulation currents interfered with the decision process. More work is necessary to ascertain the organization of the decision circuit, including the role of different brain regions (Cisek, 2012; Padoa-Schioppa and Conen, 2017). 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 (Rustichini and Padoa-Schioppa, 2015; Wang, 2002), increasing reverberation increases choice variability (Wong and Wang, 2006). Similarly, increasing the activity of chosen value cells makes choices more impulsive and thus increase variability.

> On a related note, the authors describe RT effects in Expt 2 supporting the idea of increases in value at low currents. Are there any RT effects in Task 1, and are they consistent with an inactivation effect?

In Exp.1 there was a 1-1.5 s delay between offer2 presentation and the go signal (**Fig.1A**). Hence, we did not expect significant effects on response times (RTs). Indeed, ≥100 μA stimulation did not significantly alter RTs ($p = 0.77$, t test; all sessions). This negative result held true when we restricted the analysis to sessions with stimulation delivered during offer2 ($p = 0.86$, t test).

> (1) Value range effects in Expt 2. The use of range adaptation to probe OFC stimulation effects is a

clever way to overcome the lack of option-specific structure in neural organization. This is certainly the most novel and innovative part of the current approach, but also the ones that relies most on an assumed underlying mechanism, and there are some issues the authors could clarify regarding the assumptions and data supporting the hypothesized effect (stimulation increasing relative value of the higher value range option).

The results focus on a change in relative value - were there changes in other behavioral parameters? In particular was there an effect on choice stochasticity (steepness)? I wonder about stochasticity for two reasons. First, if the disruptions during offer 2 stimulation in Expt 1 are driven by disrupted comparison, one would expect similar effects here. Second, are there projected effects on stochasticity that follow from the range adaptation hypothesis (i.e. Fig 3)?

In Exp.2, current was always delivered at 50 μA and stimulation did not increase choice variability (**Extended Data Fig.5**). This finding is consistent with the results of Exp.1, where we found an increase in choice variability at ≥100 μA but not at 50 μA (**Fig.2**). That said, we see two reasons why one might expect an increase in choice variability upon stimulation in Exp.2:

First, by increasing values, electrical stimulation also increases the value ranges. Under normal conditions, higher value ranges induce higher choice variability due to range adaptation in offer value cells (Rustichini et al., 2017). Hence, we might expect the stimulation in Exp.2 to increase choice variability. However, this effect should very small at best, because offer value cells don't have the time to adapt to the stimON range.

Second, as discussed above, 50 μA stimulation might hijack a subset of offer value cells. If so, the stimulation effectively reduces the number of neurons carrying a veridical signal. This should degrade the overall offer value signal and thus increase choice variability. One reason we don't measure a significant increase in choice variability may be lack of statistical power. Another possibility is that the representation of offer values may be robust to reducing the population of offer value cells. Afterall, there is a large number of offer value cells across the two hemispheres, and they all carry the same signal in a nearly independent way. Hence, reducing the effective pool by some fraction – perhaps 5% or 10% – might not significantly increase the noise.

While the value range effects (Fig. 4) are striking, I am a little concerned that value range differences may be confounded with other underlying task conditions. Is there a systematic relationship, for example, between value range difference and proportion of overall choices (or relative value rho)? In other words, do offers (juices) with larger value ranges also happen to be those chosen more often in that session (by design)? This seems to be the case for the examples in Fig 4AB, but it would help to see across all the data)e.g. by correlation). The issue is whether the effects could be driven by a different mechanism than the range adaptation one put forth by the authors; for example, perhaps in the face of stimulation the animals could not process either option at all and default to the option chosen more often in the past (a choice history effect).

Thank you for raising this important question. Indeed, we found a significant correlation between the difference in value range ($\Delta V_A - \Delta V_B$) and the fraction of trials in which the animal chose

juice A (% choice A). There also was a significant correlation between the difference in value range ($\Delta V_A - \Delta V_B$) and the relative value (ρ). Hence, in principle, the range-dependent bias described in **Fig.4** could reflect the animal defaulting to simple heuristics based on the relative value or the recent history.

To address these potentially confounding factors, we conducted the control analysis described in **Extended Data Fig.1** (included here as **Fig.R4)**. In essence, we restricted the analysis to a subset of sessions located near the axes origin in **Fig.R4A** (31/96 sessions selected). For these sessions, choices between the two juices were nearly-evenly split, there was no correlation between the difference in value range and the fraction of A choices (**Fig.R4A**), and the correlation between ($\Delta V_A - \Delta V_B$) and ρ changed sign (**Fig.R4B**). If the range-dependent bias observed for the whole population was driven by the animal defaulting to the most frequently chosen option, the bias should disappear when the analysis is restricted to this subset of sessions. However, this was not the case. If anything, the range-dependent bias measured in the selected subset was larger than that measured in the entire population (**Fig.R4C**). We conclude that the choice bias induced by the stimulation in Exp.2 was due to the difference in value range and did not reflect heuristics related to the relative value or the recent history.

> Finally, the proposed mechanism for the Expt 2 results hinge on low current stimulation
>
> *increasing* neural value representations. However, neurons in frontal brain areas to be both positively and negatively modulated by variables such as reward, and this is a point that needs to be more directly discussed in the paper. If positive and negative coding neurons were equal in the population, then stimulation effects would cancel out and there should be no value range-dependent response; I know that the authors have previously reported a bias for positive-encoding cells, and this should be mentioned in the main text.

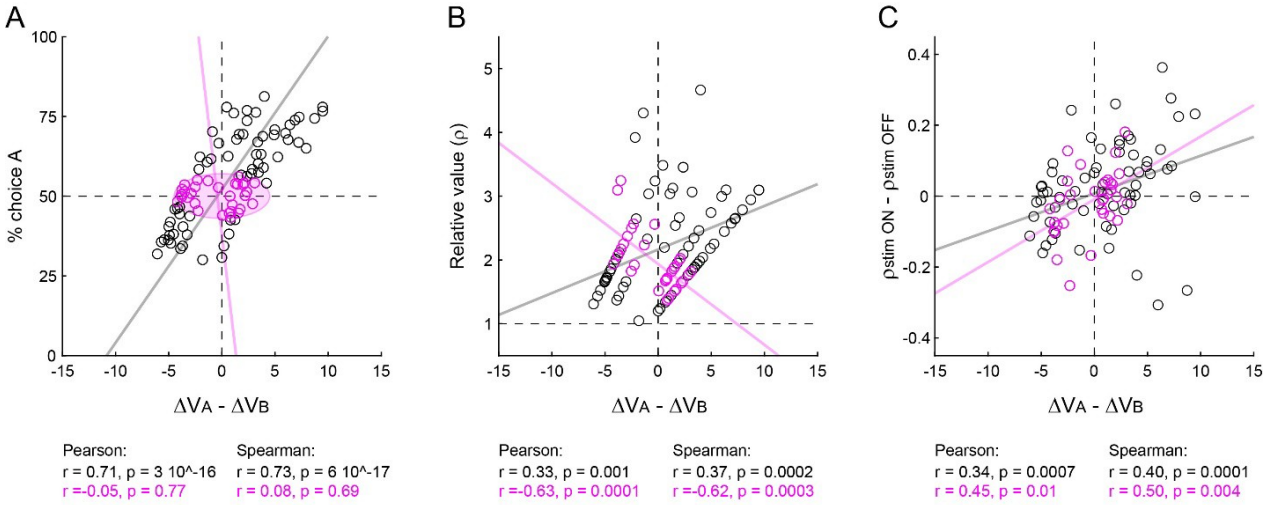

Figure R4. Control for choice frequency and relative value. **A.** Correlation between the difference in value range and the fraction of A choices. Each data point represents one session. Considering the entire data set, the two measures were significantly correlated ($r \leq -0.71$, $p<10\text{-}15$, 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 ($r \geq 0.34$, $p \leq 0.0001$, 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.

Reviewer 3 is correct: Across studies, the ratio of offer value cells with positive/negative encoding is roughly 3:1. We clarified this point in the legend of **Fig.3** and at the beginning of the section that derives our theoretical predictions (p.16).

Other points

(1) Description of Expt 1. The Methods (pg. 12) state that a small colored circle was presented around fixation with the offers. Was there a particular reason behind the circle presentation (did the circle present any information not contained in the colors of the accompanying squares)? Also, the task figure (Fig 1A) should include these as well.

The small circle was shown to indicate the identity of the non-offered juice in forced choices. This was particularly relevant when the null offer was presented first. We modified **Fig.1A** to show the circle and clarified the language on p.13.

(2) The Methods state that for Expt 1 "We designed offer types such that in most trials the animal necessarily waited for offer2 before making a decision". What exactly does this sentence refer to? If A the amounts and order presentation of offers are varied, 50% of the time the better option should occur in offer 2 - is this what is meant?

Actually, we meant to say something more stringent. We generally tried to design offer types such that for any offer1, the animal would split choices between the two offers. For example, in a session with ρ=3, when offer1 = 1A, we might include trials with offer2 = 2B and trials with offer2 = 5B. The reason was to discourage the animal from finalizing its choice prior to offer2. In practice, this was not always possible, particularly when offer1 was the null offer. (However, forced choices don't enter the present analysis anyway.) We clarified this point on p.13.

(1) Variability in stimulation parameters. There appears to be considerable variability in the stimulation onset time (0-100 ms after offer onset), duration (300-600 ms), and frequency (100-333 Hz) in Expt 1. Was there a reason for such variability, and were any of the stimulation parameters titrated for behavior/neural responses? Also, it would help to know exactly what the ">125 uA" data included: how was that data split up between different current intensities, and is there a particular reason they are grouped rather than split up?

Most of the variability comes from early sessions in monkey 1, when we were experimenting with different stimulation parameters/protocols. We eventually settled on a set of parameters that we kept mostly fixed in monkey 2 and throughout Exp.2. There was no within-session titration.

For the N = 54 sessions labelled "≥100 μA", current levels were broken down as follows:

N = 2 (4%) sessions with 100 μA
N = 47 (87%) sessions with 125 μA
N = 4 (7%) sessions with 150 μA
N = 1 (2%) sessions with 200 μA

These sessions were combined in the analysis because currents levels were similar and it did not seem worthwhile generating multiple independent data sets (which would require 40-50 sessions for each current level). We considered the idea of removing from the data set sessions at 100, 150 and 200 μA, but it seemed most reasonable to incorporate them in this data set. Removing them did not substantially alter the results of the study.

We clarified these points in the **Methods** (bottom of p.14) and in the legend to **Extended Data Table 1**. In the revision, we also included the entire data set as Supplementary Information, indicating the stimulation parameters for each session.

(2) There are existing lesion studies of monkey OFC that suggest that at least some aspects of reward-guided learning are not disrupted by lesions (Walton et al, 2010; Noonan et al. 2010; Rudebeck & Murray 2011). I don't think this argues against the authors' view that OFC is contributing to economic choice, but does suggest that OFC is not necessarily critical for implementation. In any case, this previous work should be cited, probably in the last few paragraphs.

We added to the last paragraph a reference to these papers. However, we agree with the reviewer that their results are not directly relevant to the issues examined here.

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Reviewer Reports on the First Revision

Referees' comments:

Referee #2 (Remarks to the Author):

I'm happy with the new revision and the authors' responses. I have no further comments.

Referee #3 (Remarks to the Author):

In their revised manuscript, Ballesta and colleagues have thoughtfully addressed my previous questions

and clarified their interpretation of OFC stimulation responses in both experiments. In particular, the new section on stimulation and order biases makes clear their rationale for the observed effects in Expt 1, and the control analyses on potential confounds of previous choice on range effects addresses my previous concerns.

I think the paper is suitable for publication, and I congratulate the authors on a technically clever approach and an informative and potentially very impactful set of findings. No need to answer here, but I have one conceptual point to raise, mostly for the authors to consider for future deliberation. One of their rationales for the sequential stimulation effect is a decelerating response function, in which output spikes are a decelerating function of synaptic input; this is raised here in reference to stimulation, but presumably also holds for in vivo feedforward input (i.e. value signals). However, a nonlinear decelerating function is at odds with a linear response function, which is the basis of the authors' framework for range adaptation. How do these two effects reconcile?

ADDITIONAL PRODUCTION NOTES

1. Please provide the article file as a Word document upon revision
2. The title is over budget at 79 characters with spaces.
3. There are currently 55 references. Please condense the main text references to 50
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5. Please resupply ED figures as individual files separate from the main text in one of the following formats: JPEG, EPS, TIF. The legends however main remain in the article file

Author Rebuttals to First Revision:

Referee #3 (Remarks to the Author):

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> I think the paper is suitable for publication, and I congratulate the authors on a technically clever approach and an informative and potentially very impactful set of findings. No need to answer here, but I have one conceptual point to raise, mostly for the authors to consider for future deliberation. One of their rationales for the sequential stimulation effect is a decelerating response function, in which output spikes are a decelerating function of synaptic input; this is raised here in reference to stimulation, but presumably also holds for in vivo feedforward input (i.e. value signals). However, a nonlinear decelerating function is at odds with a linear response function, which is the basis of the authors' framework for range adaptation. How do these two effects reconcile?

We agree that this is a good question, and we'll keep it in mind as we move forward. Currently, our thinking is along two lines. First, high current stimulation might push neurons into a "non-biological" range, which likely falls in a more sharply decelerating portion of the response function; in contrast, value responses in the typical task presumably fall in a closer-to-linear

portion. As a caveat, the tuning curves of offer value cells are, in fact, slightly convex (Rustichini et al, 2017), suggesting that this explanation is at best partial. Second, we don't know much about the biological inputs to offer value cells; in principle, these inputs might not be linear in the offered quantity (they could be supralinear). We are now planning new sets of experiments (including experiments in mice) to examine these inputs. Hopefully we will be able to say something more firmly soon.

Thanks again for helping us improve this ms.