Fourth quadriennal meeting on OFC function

Sept 30 – Oct 2

Brain & Spine Institute (ICM)
Paris, France

OFC 2015

Orbitofrontal Cortex and Cognition
in the City of Lights

Organizers

Geoffrey **Schoenbaum**, Jay **Gottfried**, Betsy **Murray**
Mehdi **Khamassi** & Mathias **Pessiglione**

Local organizers

Bastien **Blain** & Emmanuelle **Bioud**

Partners & Funders

SEPTEMBER30

Talks are 20 minutes plus 5-10 min questions.

8:00 – 8:30 am Pastries and coffee

8:30 – 12:00 am

Session I – READY! (Control)

Peter Rudebeck, *Sinai*
T.B.A.

Daeyeol Lee, *Yale*
Reward-dependent routing of information in the prefrontal cortex

Tricia Janak, *Johns Hopkins*
T.B.A.

30-minute coffee break

Matthew Rushworth, *Oxford University*
T.B.A.

Shannon Gourley, *Emory University*
Toggling between actions and habits: Role of the ventrolateral orbital cortex

30-minute discussion period

12:00 – 2:30 pm LUNCH TIME + POSTER SESSION

2:30 – 6:00 pm

Session II – SET! (Predict)

Mathias Pessiglione, *ICM*
The medial OFC: a value melting pot?

Wolfram Schultz, *Cambridge*
Risky behaviour

Angela Roberts, *Cambridge University*
The Regulation of Negative Emotions by the Primate Ventral Prefrontal Cortex: a Neurocognitive Account

30-minute coffee break

John O'Doherty, *Caltech*
Comparing and contrasting value-signals in the human and macaque orbital and ventromedial prefrontal cortices using fMRI

Betsy Murray, *NIMH*
Adjusting accordingly: prefrontal mechanisms for value updating

30-minute discussion period

OCTOBER1

8:00 – 8:30 am Pastries and coffee

8:30 – 12:00 am Session III – **FIRE!** (Encode)

Camillo Padoa-Schioppa, *Wash U*
T.B.A.

Thorsten Kahnt, *Northwestern University*
T.B.A.

Jon Wallis, *Berkeley*
Decoding the dynamics of orbitofrontal value information

30-minute coffee break

Ben Hayden, *Rochester*
T.B.A.

Yael Niv, *Princeton*
T.B.A.

30-minute discussion period

12:00 – 2:30 pm LUNCH TIME + POSTER SESSION

7:00 – 10:00 pm EVENING RECEPTION

Main Tower 'Zamansky', Jussieu Campus
(Université Pierre et Marie Curie - UPMC)

Remarks by Organizers + Buffet

OCTOBER2

8:00 – 8:30 am Pastries and coffee

8:30 – 12:00 am Session V – OOPS! FIRE AGAIN! (Integrate)

Tim Behrens, *Oxford University*
T.B.A.

Catharine Winstanley, *UBC*
T.B.A.

Matt Shapiro, *Sinai*
Got Expectations: Stable Contingencies Drive OFC Predictive Codes

30-minute coffee break

Howard Eichenbaum, *Boston University*
T.B.A.

Yogita Chudasama, *McGill*
T.B.A.

30-minute discussion period

12:00 – 2:30 pm LUNCH TIME + POSTER SESSION

2:30 – 6:00 pm Session VI – TIME TO EAT! (All things appetitive)

Lesley Fellows, *McGill*
T.B.A.

Jay Gottfried, *Northwestern University*
Deconstructing Value

Christina Gremel, *UCSD*
OFC output gating decision-making strategies.

30-minute coffee break

Philippe Tobler, *Zurich*
Reward in the OFC: cocaine and dopamine but little magnitude-based salience

Geoffrey Schoenbaum, *NIDA-IRP*
Cholinergic interneurons and orbitofrontal-dependent state correlates in dorsal striatum

30-minute discussion period

Meeting venues

Sept 30 – Oct 2: Institut du Cerveau et de la Moelle Epinière (ICM)

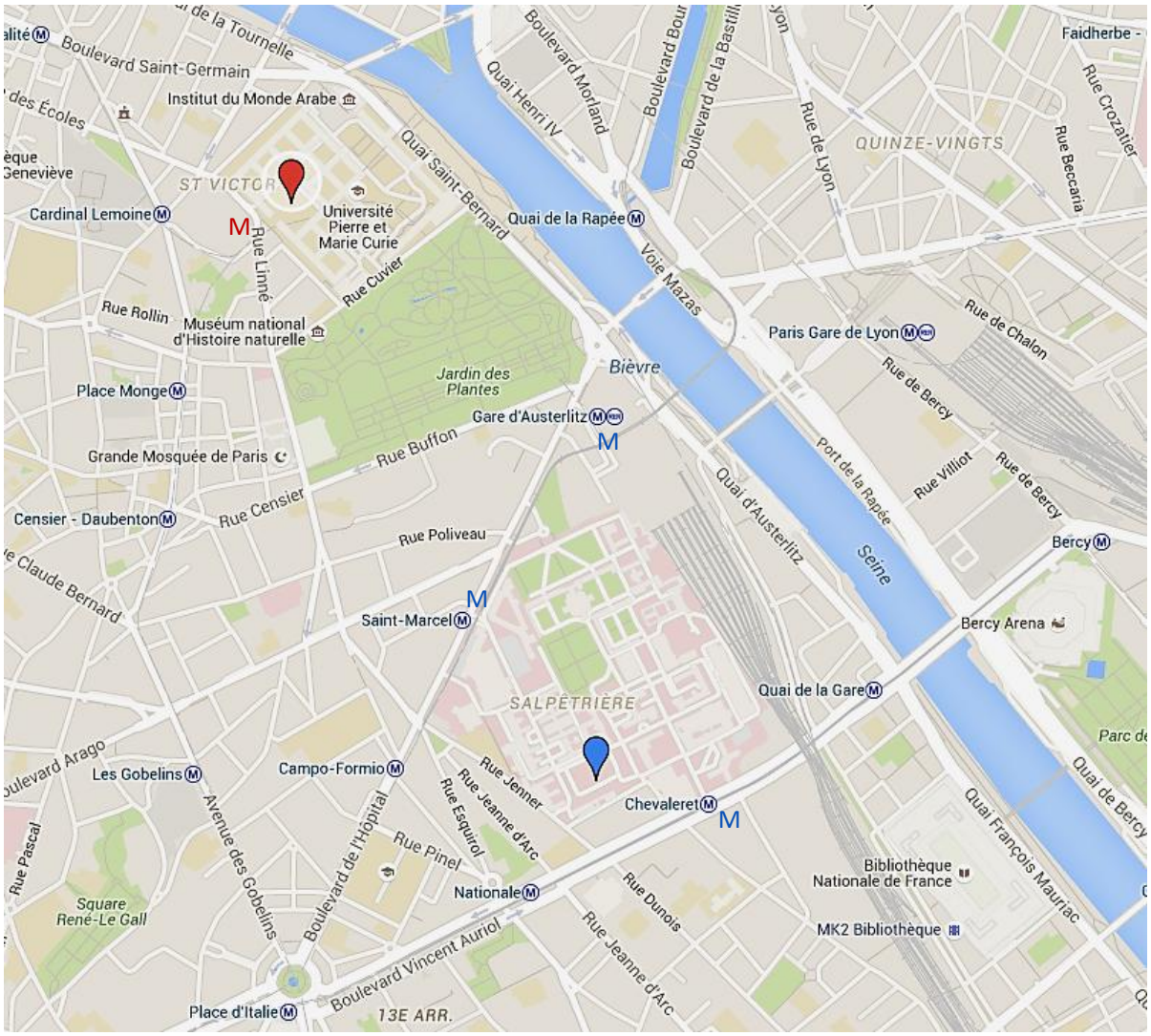
Hôpital Pitié-Salpêtrière, 47 boulevard de l'hôpital – 75013 Paris (blue location on the map below)

M *Closest metro stations:* ***CHEVALERET*** *(line 6),* ***SAINT-MARCEL*** *(line 5) and* ***GARE D'AUSTERLITZ*** *(lines 5 , 10 and RER C)*

Social event (Oct 1 evening): Zamansky Tower (24th fl.), UPMC campus

Univ. Pierre & Marie Curie, 4 place Jussieu – 75005 Paris (red location on the map below)

M *Metro station:* ***JUSSIEU*** *(lines 7 , 10)*



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[1] A Bayesian Method of Categorizing OFC Neurons Based on Functional Properties

Tommy C. Blanchard[1], Steven T. Piantadosi[2], Benjamin Y. Hayden[2]
[1] *Psychology, Harvard University*
[2] *Brain and Cognitive Sciences, University of Rochester*

[2] Neural encoding in orbitofrontal cortex of value signals relevant for managing the explore-exploit tradeoff

Vincent D. Costa & Bruno B. Averbeck
National Institute of Mental Health, National Institutes of Health, USA

[3] Neural correlates of value-based decision-making processes in young males explored through resting state functional connectivity

Yacila I. Deza Araujo[1], Lydia Hellrung[1], Nils B. Kroemer[1,2,3], Stephan Nebe[1], Michael N. Smolka[1]
[1]*Department of Psychiatry and Psychotherapy, Technische Universität, Dresden, Dresden, Germany*
[2]*Psychiatry Department, Yale University, New Haven, Connecticut, United States*
[3]*John B. Pierce Laboratory, New Haven, Connecticut, United States*

[4] Intertemporal choice under uncertainty: A discrete choice experiment on correlation aversion

Olivia Döll[1] & Bruno Lanz[2]
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[5] The OFC-amygdala functional connectivity mediates the effect of *COMT* Val158Met polymorphism on the susceptibility to framing in decision-making

Xiaoxue Gao[1†], Pingyuan Gong [2†], Jinting Liu[1†], Jie Hu[1], Yue Li[1], Hongbo Yu[1], Xiaoliang Gong[5], Yang Xiang[5], Changjun Jiang[5], Xiaolin Zhou[1, 3, 4*]
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Beijing 100871, China
[5] *Key Laboratory of Embedded System and Service Computing (Ministry of Education), Tongji University, Shanghai 201804, China*

[6] Role of primate amygdala neurons in decision-making

Fabian Grabenhorst & Wolfram Schultz
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[7] Neural coding of sensory-specific choice values in human orbitofrontal cortex

James D. Howard[1] & Thorsten Kahnt[1]
[1]*Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*

[8] Serotonin-dopamine interactions between the orbitofrontal cortex and amygdala and their relevance to reversal learning in marmosets

SAW Jackson, N Horst, TW Robbins & AC Roberts
Dept. Of Psychology and the Behavioural and Clinical Neuroscience institute, University of Cambridge U.K.

[9] Image value and reward receipt distinguish vmPFC area 32 from OFC areas 11, 13 and 14 in macaque monkeys

Kaskan PM, Costa VD, Eaton HP, Zemskova JA, Mitz AR, Leopold DA, Ungerleider LG & Murray EA
Section on Neurobiology of Learning and Memory, Unit on Learning and Decision Making, Section on Cognitive Neurophysiology and Imaging, Laboratory of Neuropsychology. Section on Neurocircuitry, Laboratory of Brain and Cognition. National Institute of Mental Health, National Institutes of Health.

[10] Sleepiness moderates the effect of L-DOPA on the arbitration between goal-directed and habitual control

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[11] Dissociable populations of orbitofrontal neurons acquire responses to upshifted and downshifted (and blocked) cues during Pavlovian unblocking

Nina Lopatina[1,3], Michael A McDannald[2], Brian F. Sadacca[1], and Geoffrey Schoenbaum[1, 4, 5]
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[12] Role of prior preference in shaping the neural format of subjective value

Alizée Lopez-Persem[1,2], Philippe Domenech[3,4], Mathias Pessiglione[1,2].
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[13] Incentivisation by reward is altered by lesions to medial OFC

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[14] Orbitofrontal cortex value signals depend on fixation location during free viewing

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[2]California Institute of Technology Division of the Humanities and Social Sciences
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[15] Effects of reward conditioning on subsequent learning: Generalization and individual differences

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[16] The opportunity to experience intense sensory stimulation activates neural 'reward' circuitry in behaviourally-defined high sensation-seekers

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[17] The anterior and posterior OFC independently regulate anxiety responses in the common marmoset

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[18] Less is More: Ventromedial Prefrontal Cortex and Evaluation of Compound Options

Georgios K. Papageorgiou[1], Jerome Sallet[1], Mark J. Buckley[1] & Matthew F.S. Rushworth[1]
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[19] Encoding of stimulus value estimates in high-frequency epicortical signals in human OFC

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[20] Integration of beliefs and affective values in human decision-making

Marion Rouault[1], Jan Drugowitsch[2], Anne-Dominique Lodeho[1], Etienne Koechlin[1]
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[21] Correlates of inferred associations in orbitofrontal neurons observed during sensory preconditioning

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[22] Structural and functional changes in brain circuits associated with learning rules in macaques

J Sallet[1*], MP Noonan[1*], A Thomas[2,3], FX Neubert[1], JX O'Reilly[2], B Ahmed[4], J Smith[4], A Bell[1,5], MJ Buckley[1], K Krug[4], RB Mars[1,2,6], MFS Rushworth[1,2]

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[23] Human Orbitofrontal Cortex Represents a Cognitive Map of State Space

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[24] Similarities and differences in the expression of cytoskeletal regulatory factors in the developing orbital and medial prefrontal cortices

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[25] Revealing prefronto-subcortical circuits in negative emotion regulation using ^{18}F-FDG microPET in marmoset monkeys.

Yoshiro Shiba[1,2], Tim Frye[3,4], Young Hong[3,4], Stephen Sawiak[2,3,4], Roger Tait[5,6], John Suckling[5,7,8], Andrea M Santangelo[1,2], Angela Roberts[1,2]

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[26] Compulsion and probabilistic reversal learning in OCD and cocaine addiction

Pauline Smith[1], Nabil Benzina[1], Florence Vorspan[2], Luc Mallet[1], Karim N'Diaye[1]

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[27] Restricting the Sirens: Stimulating Frontopolar Cortex Enhances Precommitment

Alexander Soutschek[1], Giuseppe Ugazio[1], Christian Ruff[1], Tobias Kalenscher[2], Molly J. Crockett[3], Philippe N. Tobler[1]

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[28] State-signaling in putative cholinergic interneurons in dorsomedial striatum depends on orbitofrontal cortex

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[29] Effects of damage to human prefrontal cortex on learning in a dynamic, multidimensional environment

Avinash R. Vaidya, & Lesley K. Fellows

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[30] Frontal beta oscillations reflect the effect of reward motivation on the active maintenance of representations in working memory

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[3]Pázmány Péter Catholic University, Faculty of Information Technology and Bionics, Budapest, Hungary

[31] Hippocampal contributions to prospective orbitofrontal outcome representations

Andrew M. Wikenheiser[1] and Geoffrey Schoenbaum[1]

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[32] Self-Other Confusion in Prefrontal Cortex

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OFC 2015// Abstracts of the posters

Authors by alphabetical order

[1] A Bayesian Method of Categorizing OFC Neurons Based on Functional Properties

Tommy C. Blanchard[1], Steven T. Piantadosi[2], Benjamin Y. Hayden[2]
[1] *Psychology, Harvard University*
[2] *Brain and Cognitive Sciences, University of Rochester*

Historically, it has often been useful to classify neurons in cortical regions, including the orbitofrontal cortex, as belonging to one of a few discrete functional categories based on their tuning properties to different variables (Niki and Watanabe, 1979; Padoa-Schioppa, 2013; Shima and Tanji, 1998). However, there has recently been a surge in research finding that cortical neurons often have mixed selectivities and lack discrete functional categories (Raposo et al., 2014; Rigotti et al., 2013). Instead, in some cortical regions, neurons have been found to have a seemingly random distribution of tuning properties without any obvious pattern, and that this seeming randomness may actually carry computational advantages (Rigotti et al., 2013).

To investigate the tuning properties of neurons and how they may relate to functional categories of neurons, we developed a Bayesian clustering method. This method involves modeling neural tuning properties as mixtures of distributions with different properties. We then compare models with different mixture components to determine which model best describes the data. This method allows us to test for whether the tuning properties of neurons in a dataset are best characterized as coming from the same distribution or from multiple distributions (categories). Our approach also allows us to determine when the data leaves high uncertainty about the existence of categories. It also allows us to test for systematic relationships between how neurons encode one variable and another variable.

Our method additionally allows us to estimate the proportion of neurons in a dataset that are not tuned to task variables. Researchers have typically used arbitrary significance thresholds to determine if a neuron's activity is task-related or not. The use of thresholds means that the estimate of the proportion of neurons that are not task responsive will be systematically overestimated, and would change depending on the number of data points per neuron. In contrast, our method allows us to fit a model with a noise component. A weighting for the noise component is fit to the data, giving an estimate (and level of certainty) of the proportion of neurons with activity unrelated to task variables.

To demonstrate the accuracy of our method, we show that it is able to discover the properties of simulated data sets where the correct properties of the responses are known. We also demonstrate our method on previously collected datasets, including one from the orbitofrontal cortex (Blanchard et al., 2015). Our method is able to reproduce previous published findings using these datasets in addition to answering further population-level questions, such as whether there are discrete functional categories of neurons.

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Padoa-Schioppa, C. (2013). Neuronal Origins of Choice Variability in Economic Decisions. Neuron 80, 1322–1336.

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Rigotti, M., Barak, O., Warden, M.R., Wang, X.-J., Daw, N.D., Miller, E.K., and Fusi, S. (2013). The importance of mixed selectivity in complex cognitive tasks. Nature advance online publication.

Shima, K., and Tanji, J. (1998). Role for cingulate motor area cells in voluntary movement selection based on reward. Science 282, 1335–1338.

[2] Neural encoding in orbitofrontal cortex of value signals relevant for managing the explore-exploit tradeoff

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Novelty seeking refers to the tendency of humans and other animals to explore novel and unfamiliar stimuli and environments in pursuit of potential reward. It therefore represents a specific case of the explore/exploit dilemma that underlies decisions between multiple choice options. From this perspective the utility of exploring novel options can be formally characterized as a combination of its immediate expected value (IEV) and its future expected value (FEV). FEV characterizes the value of future actions that can be made after choosing an option and receiving feedback. The difference in the FEV between novel and familiar choice options therefore defines an exploration bonus (BON), which quantifies the utility of exploring novelty. We used a finite state, discrete time, infinite-horizon Markov decision process (MDP) to derive IEV, FEV, and BON estimates for each of the monkeys' choices. To examine neural encoding of these value signals, we recorded single-unit neural responses (n=191) in lateral orbitofrontal cortex (Walker's area 11/13) in three rhesus macaques as they played a three armed bandit task. During the task, the monkeys learned to choose between three, probabilistically rewarded images. Periodically one of the three choices was replaced with a novel image the monkey had not yet associated with reward. The choice behavior of the monkeys' indicated they well managed the explore-exploit tradeoff. They showed an initial preference to explore novel choice options and learned to discriminate cues on the basis of assigned reward probabilities. At the population level between 25-30% of task-related cells recorded in OFC encoded one or more of the MDP derived value signals associated with the chosen option and most cells encoded these value signals in a stimulus dependent manner. Also, we found evidence of stronger encoding of the IEV and novelty related BON value of the animals' choices, compared to the FEV of the chosen option. These results suggest the orbitofrontal cortex likely contributes to novelty based, exploratory decision making.

[3] Neural correlates of value-based decision-making processes in young males explored through resting state functional connectivity

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Decision-making is the main concern of many disciplines that try to unravel the computational and neurobiological basis of this process. Several lesion studies have associated two main areas in the PFC with strong connections to the limbic system and parietal lobes as responsible of the motivating and controlling behaviours[1]. In the same way, functional task-based neuroimaging studies have revealed valuation, cognitive control and imagery networks, each one with corresponding brain areas mainly located in the PFC, VS, cingulate cortex and temporal lobes[2]. Some resting-state studies have linked the sub-processes of the value-based decision-making (VBDM) to different brain networks; however, further an extensive investigation is still necessary. In this study, we explore the VBDM profile of a large sample of males and its relationship to resting-state functional connectivity through a within network approach that may help explain the neural basis of impulsive, risk-seeking and risk-averse behaviours in young subjects.

Methods

The present study includes the resting state data of 178, 18-year old healthy men who completed the Value-Based Decision-making battery (VBDM), an in-house test that assesses delay discounting, risk-seeking and risk-aversive behaviors.

The functional data was preprocessed with FSL[3]. We used Probabilistic Independent Component analysis as implemented in MELODIC. Forty independent components (IC) were derived and 10 were selected for further analysis. Dual regression and non-parametric testing (5000 permutations)[4] were carried out in order to test the within-network relationship between the VBDM scores and the selected resting state networks on a subject level.

Results

A negative correlation was found between one cluster in the anterior DMN and the risk-seeking score in the analysis ($p > 0.01$, Bonferroni correction). This means that riskier subjects had less activation in those areas. The negative correlation included part of the frontal pole (BA 10) which has been related to monitoring and decision-making[1,5]. This may indicate that risk-seeking subjects have less engagement of this area during task-negative/mind wandering states. Other negative correlations were found in the middle and superior frontal gyrus.

Conclusion

Our findings provide a description of the relationship between the frontal intrinsic brain activity and the decision-making processes in a large sample of young males. The investigation of the between- network connectivity will be the following step in order to better understand how decision-making modulates the communication of different brain networks.

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1 Gläscher et al., 2012

2 Peters & Büchel, 2011

3 *FSL Version 5.0.8* www.fmrib.ox.ac.uk/fsl

4 Nichols and Holmes, 2002

5 Koechlin, E, 2011

[4] Intertemporal choice under uncertainty: A discrete choice experiment on correlation aversion

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We design an experiment consisting of binary lottery choices to jointly identify four measures of intertemporal preferences: the discount rate, (static) relative risk aversion, intertemporal elasticity of substitution, and correlation aversion. The concept of correlation aversion allows distinguishing between preferences for consumption smoothing over time (intertemporal elasticity of substitution) and willingness to tradeoff consumption over states of the world (relative risk aversion). Analyzing observed choices in the Random Utility Framework, we compare the standard discounted utility model, in which correlation aversion is constrained to zero and relative risk aversion is the inverse of the intertemporal elasticity of substitution, with a flexible second order Taylor expansion of the intertemporal utility function that imposes little a priori restrictions on the preferences of participants. Our results support the separation of risk aversion and intertemporal elasticity of substitution as distinct concepts. However we cannot reject the discounted utility model as a valid representation of intertemporal preferences at the individual level.

Keywords: Intertemporal choice; Discounting behavior; Risk aversion; Correlation aversion; Discrete choice experiment; Random utility model; Behavioral microeconomics.

JEL classification: C25, C91, D03, D12, D81, D91.

[5] The OFC-amygdala functional connectivity mediates the effect of *COMT* Val158Met polymorphism on the susceptibility to framing in decision-making

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Individuals tend to avoid risk in a gain frame in which options are presented in a positive way but seek risk in a loss frame in which the same options are presented negatively, a phenomenon known as the "framing effect". Previous studies suggest that emotional responses play a critical role in this effect. Given that the Met allele of the *COMT* Val158Met polymorphism (rs4680) is associated with a negative bias during emotion processing, the current study investigated whether this polymorphism modulates the framing effect and what brain areas subserve this modulation. Participants were scanned in resting state and then completed a gambling task in which they made choices between receiving a certain guaranteed amount of monetary remuneration from the initial amount (i.e., the sure option) and taking a risky option that could enable them, with a certain probability, to receive all or none of the initial amount (i.e., the risky or gamble option). The sure option was presented either as money retained from the initial amount (i.e., the gain frame) (e.g., 'Keep ¥20 out of a total of ¥50') or as money lost from the initial amount (i.e., the loss frame) (e.g., 'Lose ¥30 out of a total of ¥50'). Met allele carriers (N=56) showed a greater framing effect than Val/Val homozygotes (N=55), as the former gambled more frequently than the latter in the loss frame. This effect was absent in the gain frame. Moreover, the gene-behavior association was mediated by resting-state functional connectivity (RSFC) between orbitofrontal cortex (OFC) and bilateral amygdala. Met allele carriers showed decreased RSFC, thereby demonstrating higher susceptibility to framing than Val/Val homozygotes. Given the important role of OFC-amygdala connectivity in emotion regulation, Met allele carriers with lower OFC-amygdala connectivity may be associated with worse performance in emotion regulation during decision-making under different frames, which in turn increases the influence of emotional biases on choices and increases their susceptibility to the framing effect.

These findings demonstrate the involvement of *COMT* Val158Met polymorphism in the framing effect and suggest that RSFC between OFC and amygdala is an important neural mediator underlying this gene-behavior association.

[6] Role of primate amygdala neurons in decision-making

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The amygdala is considered a key system for reward and emotion with a classic function in fear; however, recent evidence suggests that it also participates in decision-making beyond reward processing. We recently showed that primate amygdala neurons signal economic choices (Grabenhorst et al., 2012) and plans for internal, distant reward goals (Hernadi et al., 2015). Despite these advances, the amygdala's role in decisions is poorly understood. Because the amygdala is implicated in a wide spectrum of behaviors and pathological conditions, it is critical to know whether its neurons express a decision function.

Here we recorded the activity of 180 amygdala neurons as a monkey chose between sequentially presented visual objects based on learned reward probability and cued reward magnitude. On each trial, two objects appeared sequentially in a central position, separated by a delay, before reappearing in randomized left-right positions as saccade targets. Object-specific reward probabilities changed over trial blocks and had to be learned through experience; reward magnitudes changed trial-by-trial and were cued sequentially with the objects thus requiring flexible computation of expected value. Our design separated valuation, decision-making and action planning: the monkey could not make its choice until seeing the second object and could not plan its action until seeing the final object positions.

We found evidence for gradually unfolding decisions in amygdala neurons. At first object presentation, a significant number of neurons (18%) encoded object-specific values reflecting both reward probability and magnitude. Such 'object values' seem suited as inputs for a competitive decision process. At second object presentation, neurons encoded the value of the second object relative to the first object (value comparison, 17%) and upcoming choice for first or second object, irrespective of its identity (11%). At left-right object presentation, many neurons encoded the identity of the chosen object (21%), thus signaling the output of an object-based decision process.

These results indicate that amygdala neurons encode the principal stages of reward-based decision-making—converting object values input via value comparison to object choice output. The data are consistent with a decision function for this key reward structure.

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[7] Neural coding of sensory-specific choice values in human orbitofrontal cortex

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In order to make optimal choices, animals must generate internal representations of the expected value of specific outcomes. Moreover, these predictive value representations must be sensitive to fluctuations in internal state, such that reward-seeking behavior can be flexibly adapted according to current homeostatic needs. Recent studies have identified orbitofrontal cortex (OFC) as a key region for signaling specific expected outcomes. However, the neurobiological mechanisms by which these predictive representations inform goal-directed choices in the human brain remain unknown. Here we conducted an experiment in which human subjects (N=17) learned to associate abstract visual symbols with two distinct appetizing food odors. Importantly, the odors were selected for each individual such that they were equal in rated pleasantness, or value. Subjects then performed a task in which they made choices among these symbols in order to receive low-intensity (i.e. low value) or high-intensity (i.e. high value) versions of these odors, while undergoing functional magnetic resonance imaging (fMRI). The choice task scanning was conducted first while the participants were hungry, and then again immediately after they had eaten food corresponding to one of the two food odors to satiety. We found that in the hungry state, participants consistently chose to smell the high intensity versions of both food odors with similar frequency. However, after eating, the choices switched to low-intensity versions for the sated food odor, while the non-sated food odor choices remained unchanged. Pattern-based analysis of the imaging data from the pre-satiety session revealed that at the offer onset, i.e. when the participants first viewed the predictive symbols, the posterior OFC contained robust information about the specific identity of the to-be-chosen odor outcome. At the time the decision was actually made, we found general, non-specific, value signals in the ventromedial prefrontal cortex (vmPFC). Ongoing analyses will test how these identity-specific and identity-general value representations change with satiety-related changes in choice behavior.

[8] Serotonin-dopamine interactions between the orbitofrontal cortex and amygdala and their relevance to reversal learning in marmosets

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Orbitofrontal (OFC) serotonin has been shown to be crucial for normal performance in reversal learning, a paradigm widely used to investigate cognitive flexibility. However, the OFC is just one component of a circuit important for reversal learning; other previously identified structures include the striatum and amygdala to which the OFC sends strong projections. Given that the OFC can modulate activity in the serotoninergic and dopaminergic neurons of the dorsal raphé and ventral tegmental area respectively and thus has the potential to affect levels of these monoamines subcortically, we determined the effects of OFC serotonin depletion on monoamine activity in the striatum and amygdala. Following unilateral selective serotonin depletion of the anterior OFC with 5,7 dihydroxytryptamine in five marmoset monkeys, we performed localised dissections within the striatum and amygdala and measured *post-mortem* tissue monoamine levels using high performance liquid chromatography (HLPC). A robust, significant up-regulation of dopamine (DA) was observed in the amygdala but not the striatum and no other changes in monoamine function were observed in either the striatum or amygdala.
To determine whether up-regulation of DA function in the amygdala contributes to the observed effects of OFC serotonin depletion on reversal learning we are investigating the effects of blocking the action of DA up-regulation on post-synaptic DA receptors in the amygdala. Two marmosets have received bilateral serotonin depletion in the anterior OFC to induce a reversal learning deficit and will receive an infusion of alpha-flupenthixol, a general dopamine receptor antagonist, into the amygdala, in an attempt to ameliorate the reversal deficit. Successful amelioration of the reversal deficit will implicate associated changes in amygdala dopamine function in the cognitive flexibility impairments induced by OFC serotonin depletion.
Implications of this work for the understanding of reversal learning and cognitive flexibility, and its wider relevance for understanding compulsivity, as in e.g. obsessive-compulsive disorder (OCD), will be discussed.

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[9] Image value and reward receipt distinguish vmPFC area 32 from OFC areas 11, 13 and 14 in macaque monkeys

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In macaques, OFC includes areas 11 and 13 on the orbital surface and area 14, which extends from the medial orbital sulcus to the rostral sulcus on the medial surface. Neurons in areas 11 and 13 reflect choice preferences and signal reward size, probability and effort required to obtain rewards (Padoa-Schioppa and Assad, 2006; Tremblay and Schultz, 1999; Kennerley et al., 2008). Less is known about neural responses on the medial surface, though the activity of these neurons has been correlated with internal states (satiety) (Bouret and Richmond, 2010) and monkeys' attention towards valuable cues (Kaping et al., 2011).

In contrast, most fMRI studies in humans report signals related to cue or image value, or the values of choices or rewarding outcomes in ventromedial prefrontal cortex (vmPFC), a region distinct from neighboring OFC (Knutson et al., 2005; Kable and Glimcher, 2007; Kahnt et al., 2010; Kim et al, 2010). It is not understood why signals related to multiple aspects of value are often reported in areas 11 and 13 of macaques, yet are often reported in human vmPFC, a separate and distinct region.

In an effort to clarify this apparent discrepancy, we conducted fast event-related fMRI recordings in macaques while they viewed images that predicted either high (75%) or low (25%) probabilities of reward. We modeled choices with a reinforcement learning algorithm to estimate image values. Our goals were to: 1) identify areas where BOLD signals changed as a result of learning; 2) identify which areas encoded value; and 3) determine whether in monkeys, as in humans, vmPFC encodes image value. Given human fMRI findings and data from electrophysiological recordings in monkeys, we expected to identify value-related responses in both OFC and vmPFC.

Both OFC and vmPFC in monkeys had tSNR values within expected ranges from models and empirical data (Murphy et al., 2007), indicating that we could effectively record BOLD responses in these areas.

OFC areas 11, 13 and 14 were strongly responsive to reward receipt whereas a separate and distinct area along the medial wall, vmPFC area 32, encoded image value. These results suggest vmPFC is an evolutionarily conserved node in the network processing valuable visual information.

[10] Sleepiness moderates the effect of L-DOPA on the arbitration between goal-directed and habitual control

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Increasing dopamine levels seem to promote goal-directed control over habitual control of choice behaviour [1], but what happens when we are sleepy? Cools and D'Esposito [2] proposed the 'inverted u-shape hypothesis', where increasing DA pharmacologically *improved* task performance in individuals with *low* endogenous DA levels, but *impaired* performance in individuals with *high* endogenous DA levels. Executive functioning impairments following sleep deprivation involve reduced DA levels [3, 4], thus sleepiness could reflect compromised DA functioning. Here, we investigated if sleepiness moderates the effect of L-DOPA on the arbitration between goal-directed and habitual control.

Forty-three healthy participants from this ongoing study were included in this analysis. Each participant had two visits. At each visit, they took the medication (L-DOPA/placebo) and completed the Karolinska Sleepiness Questionnaire (KSS; German version, [5]) which measured their subjective sleepiness immediately before entering the fMRI scanner. They then did a modified two-stage decision task [6,7] in the scanner approximately 40 minutes post-medication. Using model fitting as reported previously [7], we estimated ω, the degree of goal-directed over habitual control for each individual per visit (*the greater the ω, the greater the shift towards goal-directed control*). Sleepiness was the average of KSS scores across visits. First level statistics of fMRI data were set up as detailed in [6], where parameter estimates for the first regressor represented brain activity associated with the 1st and 2nd stage outcome onsets (outcome signal). We then tested for the effects of drug condition and sleepiness (mean-centered) on the dependent variables of interest (ω, whole-brain and ROI-based outcome signal) using repeated measures ANCOVA. All analyses were controlled for order of visits.

There was a main effect of sleepiness on ω, $F(1,40) = 4.82$, $p = .034$, where sleepiness was negatively associated with ω averaged across visits ($r = -.33$, $p = .034$). We found that effect of L-DOPA on ω depended on sleepiness, $F(1,40) = 6.28$, $p = .016$. L-DOPA increased ω in sleepy individuals, but impaired alert individuals. We found a positive interaction between drug condition and sleepiness across visits on vmPFC outcome signal ($t_{max} = 5.89$, $p < .05$, whole-brain FWE cor.). L-DOPA augmented vmPFC activity in sleepy individuals, but decreased that of alert individuals. vmPFC activity was positively correlated with ω under placebo ($r = .35$, $p = .025$), but not under L-DOPA ($r = -.08$, $p = .60$).
We conclude that our observations are in line with "the inverted u-shape hypothesis" [2], where sleepy individuals with less DA benefited from L-DOPA, but impaired alert individuals. Future studies should clarify the relationship between vulnerabilities to sleep loss [8] and endogenous DA levels.

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[11] Dissociable populations of orbitofrontal neurons acquire responses to upshifted and downshifted (and blocked) cues during Pavlovian unblocking

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The orbitofrontal cortex (OFC) has been described as signaling outcome expectancies or value. The former framework links coding of value to representation of outcome features, whereas the latter often describes this area as signaling value that is independent of the outcome. To test what is represented by OFC neurons, we have previously used unblocking to show that OFC neurons would respond to a predictive cue signaling a 'valueless' change in outcome flavor. However in that experiment we also found many OFC neurons that fired to a cue that simply predicted more reward. Here we employed a variant of this task to test whether these neurons were responding to value or to idiosyncratic features of the additional reward. Neurons were recorded in an unblocking task as rats learned about cues that signaled either more (upshift), less (downshift) or the same (blocked) amount of reward.

We found that lateral OFC (lOFC) neurons acquired responses to all of these cues, however very few lOFC neurons exhibited firing across the three cues consistent with a linear or anti-linear value representation. Instead most associative neurons developed responses specifically to one of the three cues and did not fire to the other two. These results show that lOFC neurons fire even to valued cues in a way that is more consistent with signaling of the predicted features rather than the general or cached value of the impending outcome.

[12] Role of prior preference in shaping the neural format of subjective value

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Decision theory assumes that when faced with a binary choice, individuals first assign subjective values to each option, and then compare the two values to select the best. Understanding how option values are encoded and compared is a key objective for neuroeconomics. A large body of evidence suggests that activity in the ventromedial prefrontal cortex (vmPFC) correlates with option value. However, the frame of value representation remains unclear: according to some studies vmPFC activity might represent pre-choice variables such as the sum of the two option values, in others the vmPFC would represent a decision variable such as left minus right or attended minus unattended option value, and in a last set of studies the vmPFC is suggested to represent a post-choice variable such as chosen minus unchosen option value.

We propose an alternative hypothesis, according to which the frame of value coding in the vmPFC is imposed by a default policy. This means that the brain reframes economic binary choices (A vs. B) as stay vs. switch choices. This hypothesis makes predictions at both the behavioral and neuronal level. At the behavioral level, it predicts that one set of options corresponding to the default policy should be chosen more often and more quickly than others. At the neural level, it predicts that the vmPFC should encode the value of the default option.

In order to test this hypothesis, we developed a task involving subjects (n=24) choosing between two options pertaining to different categories (e.g., jazz vs. rock CD). We inferred the preference between categories from the mean of likeability ratings assigned to every item prior to performing the choice task. Choice data confirmed that items belonging to the preferred category were chosen more often and more quickly, even when regressing out the difference in likeability ratings. This behavior was well captured by a drift diffusion model that included a start bias in favor of the preferred category. FMRI data showed that vmPFC activity encoded the value of the option belonging to the preferred category (the default option), irrespective of choice. This framing of value coding was not related to the pattern of gaze fixations, since eye-tracking data showed that subjects looked equally at the default and alternative options. We therefore conclude that prior preferences can elicit a default policy that frames the neural representation of option values during binary choices.

[13] Incentivisation by reward is altered by lesions to medial OFC

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Damage to medial prefrontal cortex results in a perplexing variety of behavioural changes, including seemingly contradictory effects of apathy and impulsivity, flat affect and emotional lability, depression and improved mood. These syndromes play a major part in many neurological diseases, but their neuroanatomical underpinning is poorly understood. Recent imaging studies implicate human medial orbitofrontal cortex (OFC) in valuation of rewards, which might lead one to expect that damage to this area could affect value-driven actions. But causal evidence for such a role is lacking and it remains unclear whether the effects of reward on action would be increased or decreased following lesions to this region.

To examine whether reward evaluation processes require medial frontal cortex, we selected 19 patients from a database of 453 who had suffered subarachnoid haemorrhage. The individuals we studied had isolated, focal damage in ventral and medial regions of prefrontal cortex. Using a speeded saccadic task, we manipulated incentivisation by reward on a trial-by-trial basis using an auditory cue that indicated monetary gains. At the group level, patients exhibited reduced effects of reward on invigorating saccadic velocity. Measurement of pupil dilatation also revealed blunted autonomic responses to reward cues, indicating that evaluation of incentives was affected. Crucially, however, there was significant heterogeneity among patients, with some individuals showing abnormally strong incentivisation effects.

Increased sensitivity to rewards within the group of medial frontal patients correlated with damage at specific coordinates in medial OFC, overlapping with subgenual anterior cingulate and subcallosal cortex, that have been implicated in encoding reward value in functional imaging studies. Lesions specifically in medial OFC were also associated with increased autonomic value responses, compared to lesions elsewhere. Lesion correlations with clinical apathy suggested that damage at these coordinates confers protection from this syndrome. Voxel-based analysis revealed ventromedial subregions, overlapping with putative Brodmann areas 32 and 14, which correlated with higher motivation by rewards.

These findings reveal that medial frontal lesions generally make individuals less sensitive to reward value, but crucially damage to key subregions can paradoxically increase reward sensitivity and protect from this effect. This study provides causal evidence for a role of medial OFC in the evaluation of rewards: in regulation of and control over reward representations, rather than simply being necessary for mediating incentivised behaviour.

[14] Orbitofrontal cortex value signals depend on fixation location during free viewing

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How do OFC neurons represent the economic value of the objects that we see? A major obstacle in answering this question is the fact that what we see changes whenever we move our eyes, which we do constantly throughout waking life. To address this challenge, we presented monkeys with value-associated visual cues, and took the unusual step of allowing them unrestricted free viewing while we recorded the activity of OFC neurons.

Using Pavlovian conditioning, we trained monkeys to associate three distinct visual cues with juice rewards of 0, 1 and ~3 drops. After these associations were learned (indicated by anticipatory licking), we recorded the activity of OFC neurons as the monkeys viewed the cues, presented one at a time, for four seconds. In these trials, the monkeys naturally distributed their fixations between the cue and non-cue locations; this variability allowed us to identify neurons that encoded gaze location, specifically, the current distance of fixation from the cue. Surprisingly, across the population these gaze distance-dependent signals were nearly as abundant as value signals. Moreover, gaze distance and value signals were mixed within single neurons, consistent with random and independent distribution of the two signals across the population. Encoding of gaze distance was also evident in a separate behavioral context (fixation point onset at the beginning of each trial), in the same subset of neurons.

In some sessions, we also issued trials in which two of the three cues, chosen at random, were shown simultaneously on the screen, again for four seconds. In these trials, monkeys typically fixated on each cue at least once, and our analysis focused on responses evoked by these on-cue fixations. Our key question was whether these responses reflected only the value of the currently fixated cue, or whether they also reflected the other, non-fixated cue value. Within the subset of neurons that was sensitive to gaze location, we found encoding of both the fixated and non-fixated cue values. However, sensitivity to the non-fixated cue was contingent on the value of the *current* fixation target. Specifically, neurons were most sensitive to a non-fixated cue when the current target of gaze was of low value.

In summary: a subset of OFC neurons exhibits value signals that change moment-by-moment according to where we move our eyes. They not only represent the value of the current target of gaze, but also appear to take into account the value of other visible, but un-fixated stimuli. The existence of such a dynamic value code may have major implications for neural mechanisms of decision-making and other motivated behaviors that we engage in during everyday waking life.

[15] Effects of reward conditioning on subsequent learning: Generalization and individual differences

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Expectation of reward produces a state of motivation that enables reward-predictive learning. In this process, functional interactions between the medial temporal lobe and striatum enhance memory for rewarded information. Yet, it is unclear whether memory advantage for rewarded stimuli is maintained when stimuli are first rewarded and then used in a memory task. We designed an fMRI experiment to test whether reward conditioning influences hippocampus-dependent learning in a subsequent task, and whether reward value may transfer from the specific rewarded cues to semantically related ones.
In a first phase, participants underwent a monetary reward conditioning procedure with 2 levels of reward (high and low) respectively associated with photographs from 2 distinct semantic categories. In a second phase, participants performed a picture-location learning task with the same high and low reward pictures, and with new semantically-related pictures. In a third phase, occurring 24h later, participants returned for a re-test that additionally tested source memory.

Reward conditioning was successful: high (vs. low) reward cues evoked higher activation in the ventral tegmental area (VTA); high (vs. low) reward cues were judged as more pleasant after conditioning. Data from the picture-location memory task revealed effects of prior reward conditioning. Firstly, the ventral striatum (VS) and the hippocampus showed reduced activity during the encoding of subsequently remembered picture-locations for pictures belonging to the previously rewarded semantic category (both old and new ones). Specifically, the distance to target (i.e. the degree of error) on a given trial was proportionate to the activation in the VS and in the medial orbitofrontal cortex (mOFC) during encoding of high-reward associated pictures throughout the task with generalization to new semantically-related pictures early in the learning.

Secondly, source memory accuracy 24h later was enhanced for all reward-related pictures. Accuracy in the picture-location learning task was modulated by individual trait reward-responsiveness such that higher reward-responsiveness led to better performance for high-reward pictures.
Our results show that reward association may support later memory formation in reward-sensitive individuals, even when no actual monetary reward is delivered in the learning context. Learning subsequent to reward conditioning leads to deactivation of reward-sensitive areas in response to high-value items as well as semantically similar information and is related with error in performance in a hippocampus-dependent task.

[16] The opportunity to experience intense sensory stimulation activates neural 'reward' circuitry in behaviourally-defined high sensation-seekers

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Sensation-seeking, or motivation for 'intense and unusual' sensory experiences, is a vulnerability factor for a variety of psychopathologies with high social cost – particularly gambling and substance addictions. However, such motivation remains underexplored in humans, and little is known about its neural correlates – in part due to a previous lack of paradigms allowing precise investigation of sensation-seeking-like behaviour *in the laboratory*. For example, do people high in sensation-seeking personality attribute value to intense sensory experiences in the same way as other (more traditionally conceived) rewards?

Recently, we have developed a novel instrumental measure of human sensation-seeking. Specifically, our paradigm probes how the opportunity to experience an additional 'intense' sensory stimulus (mild electric stimulation, or MES) influences participants' behaviour on an economic decision-making task. Initially, participants choose between abstract visual stimuli to obtain monetary reward. Subsequent association of some choice stimuli with the chance of receiving MES enables quantification of the change in subjective value of such stimuli using a simple computational model. Specifically, this allows precise derivation of the *economic* value (positive or negative) that individuals assign to the opportunity to receive the additional sensory stimulation (henceforth, θ). Here, we investigated the neural mechanisms underlying individual differences in performance on this measure using functional magnetic resonance imaging (fMRI) (N=26).
The value individuals assigned to the opportunity to receive MES (θ) was significantly positively related to self-reported sensation-seeking personality (r=0.391, p<0.05). We found significant positive associations between derived values of θ and blood oxygenation level-dependent (BOLD) signal in brain regions associated with value processing (the medial orbitofrontal cortex, OFC, and ventral caudate; both p<0.05, FWE small volume corrected), during choice of MES-associated as opposed to non MES-associated stimuli. Critically, conjunction analysis demonstrated selective activation of a brain region positive encoding monetary value (an orthogonal contrast) when choosing MES-associated stimuli in high behavioural sensation-seekers (defined as θ>0, N=8). This region was located within OFC coordinates previously identified via metaanalysis as being involved in the representation of value across different kinds of rewards (Levy and Glimcher, 2012, *Curr Opin Neurobiol*). Conversely, there was selective activation of brain regions negatively encoding monetary value (including the insular cortex; p<0.05 FWE whole brain corrected) when choosing MES-associated stimuli in low behavioural sensation-seekers (defined as θ<0, N=18).

This suggests that individuals weighed the opportunity to experience the MES in the same way as the economic value of chosen stimuli, and, crucially, that this opportunity was encoded in the same regions as economic reward in high behavioural sensation-seekers.

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[17] The anterior and posterior OFC independently regulate anxiety responses in the common marmoset

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Studies of human imaging have implicated dysregulation in the OFC in anxiety disorders, yet the evidence from animal models regarding its contributions is mixed. In macaque monkeys lesions that include the anterior and posterior regions of the OFC (area 11,13) reduce negative emotion in response to an unfamiliar human, whereas in the marmoset localised lesions to the anterior OFC (primarily area 11) increase it; whilst the role of the posterior OFC remains unknown. However, in comparison to area 11, it is area 13 that exhibits the densest bidirectional connections with the amygdala, a core emotion area, highlighting the potential importance of this brain region in emotion regulation. In order to investigate the role of area 13 (posterior OFC) and differentiate its contribution to the regulation of anxiety from that of area 11, we transiently inactivated these two prefrontal areas by infusing $GABA_{A\&B}$ agonists (0.1mM muscimol & 1.0mM baclofen; 0.5 µl infused at 0.25µl/min) and tested the marmoset's response to a human intruder, a common anxiogenic stimulus. Inactivation of the antOFC (n=4) increased distance from the intruder and greatly decreased time spent at front locations, a pattern suggesting increases in anxiety.

A similar effect was observed with postOFC inactivation (n=3). The effects observed were primarily restricted to distance (indicative of state anxiety) and did not extend to the full repertoire of behaviours (locomotion, head-bobbing, calls) that contribute to an overall anxiety trait, as seen following permanent lesions of the antOFC (Augustin-Pavon et al., 2012, Shiba et al., 2014). Nevertheless, preliminary evidence suggests that in those animals that did make reactive calls antOFC inactivation decreased them (n=2), whereas postOFC inactivation increased them (n=1). These results highlight the independent involvement of OFC sub-regions in negative emotion regulation and suggest possible differences in their contributions to anxiety.

[18] Less is More: Ventromedial Prefrontal Cortex and Evaluation of Compound Options

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Aims

Decision-making processes and value encoding of expected outcomes are often linked to the ventromedial prefrontal cortex (vmPFC)/medial orbitofrontal cortex (mOFC). However, it is not clear what role the vmPFC/mOFC plays in cases of irrational decisions or when subjects have to choose based on multi-faceted outcomes. Such case is the 'less is more' effect where subjects have the tendency to choose options that are less valuable than others.

Methods

The experiment involved 6 adult macaque monkeys (controls: 4, vmPFC/mOFC: 2). All animals were trained on a 2-choice 6-options behavioural task in which 3 of the options led to 3 different types of reward and the other 3 options led to no reward delivery. One of these rewarded options led to a highly valued reward ('High option'), a second option led to a low valued reward ('Low option') and a third option led to the combination of the two ('Compound option'). After the completion of this stage of the experiment, the 4 control animals, executed a modified version of this task inside the fMRI scanner.

Results

During the behavioural testing, the vmPFC/mOFC animals exhibited a similar behavioural pattern with the controls and chose the 'High option' over the 'Low option' and the 'Compound option' over the 'Low option' in the vast majority of their choices. Interestingly, though, the vmPFC/mOFC animals were more optimal from the controls in the critical decision-making pair and chose the 'Compound option' over the 'High option' more often. Further analyses of the fMRI data at the time of the stimulus presentation showed stronger vmPFC/mOFC activation for the 'High option' in comparison with the 'Compound option'.

Conclusion

These results suggest that the vmPFC/mOFC plays an important role during this kind of decisions where multifaceted options come into play and damage to this area may lead to suboptimal decision-making.

[19] Encoding of stimulus value estimates in high-frequency epicortical signals in human OFC

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The orbitofrontal cortex (OFC) is required for making adaptive choices based on past experience. In both human and animal subjects, OFC damage results in inconsistent choice behavior, and recordings in animals show that OFC encodes information about stimuli and environments that likely contribute to this function. However, nearly all of our knowledge of OFC neurophysiology has come from animals engaged in decision-making tasks. To advance our understanding of OFC function and apply this knowledge to novel therapeutics, we must correlate results from animal studies with recordings from the human brain. Here, we aimed to understand neurophysiological mechanisms of OFC involvement in learning and decision-making in human subjects.

Patients undergoing clinical evaluation for epilepsy surgery were implanted with electrocorticography (ECoG) arrays in multiple brain regions, including the superior temporal, parietal and prefrontal cortex. Here we present preliminary analyses of 4 patients with 8 to 64 electrodes in the OFC. Each patient performed a reinforcement-learning (RL) task in which nonsense speech sounds (vowel-consonant-vowel conjunctions) were arbitrarily assigned a positive, negative or neutral value. On each trial, two of the three possible stimuli were presented in sequence and patients chose one with a button press. After a choice, they were shown the number of points won or lost, and their earned points were added to a running tally. Points associated with each stimulus were drawn from overlapping Gaussian distributions with means of +15, 0 and -15. Before and after this learning task, patients passively listened to multiple presentations of all stimuli in random order.

We first determined whether task stimuli were represented in OFC ECoG signals during passive listening before and after learning. Across multiple frequency bands, there were no consistent changes in the neurophysiological signal dependent on stimulus identity. This is in contrast to electrodes in the superior temporal gyrus, a region involved in speech and language processing, which strongly differentiated stimulus identity. We also assessed whether OFC exhibited stimulus non-specific power fluctuations during passive stimulus presentation, however again there was little evidence for modulation of the OFC signal. In contrast to passive listening, over 70% of OFC electrodes exhibited fluctuations in power in one or more frequency bands during learning. The most consistent response was increased high-frequency power in epochs surrounding the subjects' choice. To determine whether learning-related variables were encoded in this high-frequency signal, each subject's learning was fit with a temporal-difference model to derive stimulus value estimates on each trial. For all patients, at least one OFC electrode significantly encoded the value estimate of the option that was ultimately chosen, with the most encoding around the time that the choice was registered. Interestingly, nearly all significant electrodes had negative relationships between the value estimate and high-frequency power. Finally, there was little evidence that OFC electrodes encoded the value of the unchosen option, a reward prediction error signal, or the sequential position of the item that was chosen. Overall, as in animal subjects, the neurophysiological signal in human OFC correlates with subjective value estimates in an RL paradigm, consistent with the notion that OFC is critically involved in learning or predicting outcomes of one's choices.

[20] Integration of beliefs and affective values in human decision-making

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Executive control relies on evaluating action outcomes for adjusting subsequent action. Action outcomes, however, may convey two types of value signals:
- *Affective values* (Av), representing the valuation of action outcomes given subjective preferences
- *Belief values* (Bv), about how actions map onto outcome contingencies.
Av stems from reinforcement learning (RL), whereas Bv stems from Bayesian models. Previous experimental paradigms usually confounded Av and Bv: a higher reward usually informs about more appropriate choices.

Here we present a probabilistic reversal adaptive task aiming at dissociating Av from Bv. Healthy human subjects had to decide between two shapes, one of which was more frequently rewarded than the other one. The potential rewards to gain for each shape were displayed before each choice. Crucially, we manipulated the reward distributions underlying each shape to dissociate Av from Bv. We developed a computational model of monitoring and decision, integrating two parallel systems: RL, dealing with Av, and Bayesian inference, dealing with Bv. This model fitted behavioral performance better than many alternative models.

We then investigated whether beliefs and affective values had distinct neural bases using fMRI. BOLD signal was regressed against choice-dependent (linear) and choice-independent (quadratic) beliefs and affective values. Medial orbitofrontal cortex and adjacent ventromedial prefrontal cortex (MOFC) and anterior cingulate cortex (ACC) activity correlated with both choice-dependent variables.
A region showing a choice-independent quadratic effect was more activated when both beliefs/affective values were far from each other, which could correspond to unsigned pre-choice preferences or to a post-choice confidence signal (more confidence when both beliefs/affective values are away). We found a double-dissociation between MOFC and ACC regarding choice-independent variables; with MOFC encoding choice-independent beliefs, whereas ACC encoded choice-independent affective values. Such a pattern demonstrates a separate monitoring of beliefs and affective values. These belief and confidence signals could contribute to the brain implementation of metacognitive processes.

Additionally, activity in lateral prefrontal cortex (LPFC) increased when decision values (i.e. mixture of beliefs and affective values) got closer to each other and action selection became more difficult. Taken together, these results suggest that before decision, MOFC and ACC separately encode beliefs and affective values respectively. LPFC combines both signals to decide, then feeds back choice information to the medial regions, presumably for updating these value signals according to action outcomes.

[21] Correlates of inferred associations in orbitofrontal neurons observed during sensory preconditioning

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The orbitofrontal cortex (OFC) has been implicated in a range of functions, but converging evidence points to OFC's role in supporting 'model-based' decision making. Such decisions are characteristically based on the use of inference, where the value of options is calculated on the fly from the animal's broader experience. Our lab has shown that the orbitofrontal cortex was necessary for just such a process through the use of a sensory-preconditioning task, in which rats learn associations between pairs of cues in the absence of reward, and then learn that one cue of one pair leads to a food reward. Normal rats are able to use information acquired independently in these phases of learning later, to infer the value of the preconditioned cue both to guide behavior and to direct future learning, whereas rats in which the OFC is inactivated cannot. To identify neural correlates of this process, we recorded single-neuron activity in orbitofrontal cortex of 20 rats as they learned a sensory-preconditioning task. During the initial pre-conditioning phase of the task, as rats learned a relationship between pairs of cues in the absence of reward, OFC neurons tracked the association of cue pairs, responding more similarly to cues within an associated pair than to cues which were unpaired. This similarity in responding, while diminished, remained after the subsequent conditioning phase. Specifically, on the final test day, single neuron responses to cues that were paired during pre-conditioning were more similar to each-other than to control cues. Thus the encoding of the cue pairs established during preconditioning may be the neural basis for OFC's role in inferring the relationship among cues required to perform a sensory preconditioning task and, more broadly, for OFC's role in inferential reasoning.

[22] Structural and functional changes in brain circuits associated with learning rules in macaques

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In discrimination reversal (DisRev) learning tasks animals learn that one choice leads to reward while another does not. Animals also learn that when the reward assignments are switched, the previously unrewarded choice has become the one followed by reward. Behavioural flexibility in DisRev has often been thought to rely on a brain circuit centered on the orbitofrontal cortex (OFC).

To identify the components of this circuit we sought brain regions where structure and activity changes were associated with DisRev experience in a group of nine macaques: 4 animals choosing between target identities, 5 animals choosing between target locations. We obtained structural and functional MRI (fMRI) measures of activity at two time points while animals were at rest. At time 1 the animals already had learned that pressing a target on a touchscreen, either on a left or a right side of the screen, was associated with a juice reward. At time 2 the animals had negotiated 5 sessions with 5 reversals within a session and with performance above 85% correct.

Compared with 12 control animals, significant grey matter increases were associated with DisRev experience in amygdala, basal forebrain, and medial thalamus, medial orbitofrontal cortex, anterior cingulate cortex (ACC), and the lateral prefrontal cortex (lPFC). No significant changes were observed in the central OFC (cOFC). As well as structural changes functional coupling changes were also found between the same regions.

Second, to examine further whether these areas might constitute the circuit affected by OFC aspiration lesions, we examined the impact of OFC lesions in two macaques on grey matter and activity coupling in and between these same areas. Structural and fMRI data revealed that OFC lesions were associated with significant changes in grey matter in many of the same areas including medial thalamus, lPFC, mOFC, medial forebrain, and amygdala. In most cases the changes were decrements in grey matter but increased grey matter was found in the amygdala and hippocampus.

Although we failed to identify changes in cOFC associated with DisRev we were able to show that adjacent frontal areas, likely to be disconnected by OFC aspiration lesions, are important in DisRev. The results are consistent with the view that fluent DisRev performance is mediated not just by choice-reward association learning mechanisms linked to OFC, but also by acquisition of a cognitive set or task model, dependent on many interacting brain regions, representing the inter-relationships between the different choice-reward associations active in the task at different times.

[23] Human Orbitofrontal Cortex Represents a Cognitive Map of State Space

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If Bob bought or sold stocks based on whether he saw his neighbor walking the dog or not, he wouldn't be a very successful investor. Obviously, making a choice based on the wrong information will lead to wrong decisions. Reinforcement learning processes presuppose a compilation of all decision-relevant information into a single Markovian "state" of the environment, for which values are learned and on which choices are based. Where do these states reside in the human brain?

We have previously hypothesized that the OFC may play a key role in representing task states, especially when these are only partially observable (Wilson et al., 2014, Neuron). Here we test this idea in humans, using multivariate decoding and representational similarity analysis of functional magnetic resonance imaging (fMRI) signals. In line with our hypothesis, we find that information about the current, partially observable, state of the task can be decoded from OFC fMRI activity patterns. In addition, we find that the similarities between state-dependent activity patterns in OFC are highly systematic and reflect environmental statistics as well as differences between states that are associated with different mental operations. Moreover, we show that the fidelity of the state information in OFC, and the similarity between different states as they are represented neurally, robustly relate to performance differences. Preliminary results from a second fMRI experiment indicate that the development of these neural representations is closely linked to performance improvements over time.

These results show that internal state representations can be "read out" from OFC activity patterns, and the geometry of the individual state space can be used to make predictions about individual performance characteristics.

[24] Similarities and differences in the expression of cytoskeletal regulatory factors in the developing orbital and medial prefrontal cortices

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The prefrontal cortex, including the orbitofrontal (oPFC) and medial (mPFC) subregions, undergoes considerable structural maturation during adolescence. The molecular mechanisms regulating these processes remain incompletely defined; this is despite widespread appreciation that adolescence is a period of vulnerability to the development of multiple psychopathologies. We begin to address this concern by mapping the ontogeny of several cytoskeletal regulatory factors in the oPFC relative to the mPFC of adolescent mice, with tissue samples collected on postnatal days 35, 42, and 56. PSD95 expression conformed to an inverted U-shaped curve in both PFC regions, as expected. Expression of the dendrite stabilizing factor Arg (Abl2) kinase was also robust in both structures, but lower in the oPFC relative to the mPFC. In early adolescence, expression of p120RasGAP was elevated in the oPFC relative to mPFC but these effects were transient. Meanwhile, expression of the RhoA GTPase, which orchestrates neurite contraction, progressively increased as a function of age while expression of the downstream Rho kinase, LIM kinase and cofilin remained constant. These patterns were distinct from those identified in the ventral hippocampus, a region that innervates the PFC. Here, PSD95 expression progressively decreased compared to the dorsal hippocampus while cofilin progressively increased. Expression of Rho kinase and LIM kinase in the ventral hippocampus conformed to an inverted U-shaped curve. As in the oPFC, however, RhoA expression increased. These findings illustrate the dynamic expression of cytoskeletal regulatory factors during adolescent development and may provide insight into the structural modifications occurring in the PFC during this period and their sensitivities to pathological stimuli such as stress or drugs of abuse.

[25] Revealing prefronto-subcortical circuits in negative emotion regulation using ^{18}F-FDG microPET in marmoset monkeys.

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Background

Impaired regulation of physiological and cognitive reactivity to potential threat is a core feature of affective disorders including mood and anxiety disorders. However, the neural mechanisms underlying this emotion regulation are poorly understood. It has been suggested that the prefrontal cortex (PFC) plays a crucial role in modulating neural activity in subcortical structures that are responsible for the processing and expression of fear and anxiety. Recent studies from our laboratory showed that an anxious phenotype, including enhanced anxiety to a social stimulus, innate fear and conditioned fear (Agustin-Pavon et al, Biol Psychiat. 2012; Shiba et al 2015 Front Sys Neurosci) was induced by excitotoxic lesions of either the anterior orbitofrontal cortex (antOFC) or ventrolateral PFC (vlPFC) independently. These results raise the question as to whether the antOFC and vlPFC act on common or distinct downstream subcortical targets to down-regulate negative emotion.

Method

To address this question, the present study combined localised excitotoxic lesions in the PFC of a non-human primate and functional neuroimaging (^{18}F-FDG microPET) with a fear-inducing behavioral paradigm. Marmoset monkeys with unilateral lesions of either antOFC (area 11) or vlPFC (area 12) were scanned immediately following exposures to a fearful (rubber snake and darkness) or 'safe' context, and the differences in regional ligand uptake were compared.

Results

Analysis of four antOFC lesioned animals so far has revealed that, in the intact hemisphere, FDG uptake in the amygdala was significantly increased in response to the fearful context compared to the 'safe' context. However, this difference in FDG uptake between the two contexts was not seen in the amygdala of the lesioned hemisphere, being high in both fear and 'safe' contexts. These results suggest that the antOFC has a crucial role in down-regulation of the amygdala responsivity in the context where a threat is no longer present.

The results from the antOFC lesioned animals will be compared with those of the vlPFC, providing important new insight into the top-down control of the subcortical emotion network. It may also progress our understanding of the neurocognitive mechanisms underlying marked symptomatic differences in mood and anxiety disorders, which in turn could lead to the refinement of diagnoses and the individual tailoring of therapeutic strategies.

[26] Compulsion and probabilistic reversal learning in OCD and cocaine addiction

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Compulsive behavior is a core symptom of both obsessive compulsive disorder (OCD) and cocaine addiction (CA). Across both pathologies, one can identify *a priori* goal-directed actions (purportedly anxiolytic checking or washing in OCD and pleasure-seeking drug use in addiction) that turn into rigid, ritualized and repetitive behaviors over which the patient loses control.

One possible psychopathological mechanism underlying compulsivity is behavioral inflexibility, namely a deficit in the aptitude to dynamically adapt to novel contexts and changing reward rules. The probabilistic reversal learning paradigm allows to objectively assess behavioral flexibility by challenging participants with a task where they have to learn through trials-and-errors which of two stimuli is the most-often rewarded one, while adjusting to sudden inconspicuous contingency reversals. We therefore hypothesized that both OCD and CA would be associated with impaired cognitive flexibility, as measured through perseverative response rate following contingency reversals in this task. Interestingly, impulsivity may also be assessed within this task via the tendency of participants to switch from one stimulus to the other following probabilistic errors.

To investigate cognitive inflexibility in relation to CA and OCD respectively, we first compared the performance in a probabilistic reversal learning task of cocaine users, ex cocaine users (abstinent for 2 months or more), and controls, as well as that of participants from the general population whose obsessive-compulsive traits were assessed using the OCI-R, a well-validated self-questionnaire.
Our task yielded results similar to those found in the literature: cocaine addicts changed their responses more often, and learned less effectively. Ex-cocaine addicts performed better than addicts but worse than controls, suggesting that addicts' poor results may be in part explained by reversible cognitive consequences of addiction. Addicts with less cognitive impairments may also be less likely to relapse. Regarding the relationship of flexibility to subclinical OCD traits, we found no link between OCI-R score and perseveration, or between impulsiveness and excessive switching.

[27] Restricting the Sirens: Stimulating Frontopolar Cortex Enhances Precommitment

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Willpower failures represent a prevalent problem in everyday life as well as in many psychiatric disorders. One strategy to overcome such willpower failures is to voluntarily restrict one's future action options by making binding choices (precommitment). However, the neural mechanisms underlying precommitment remained unclear so far. The current study tested whether precommitment can be improved by stimulating the frontopolar/orbitofrontal cortex (FPC) with transcranial direct current stimulation (tDCS). Participants performed a self-control task requiring them to suppress the impulse of selecting an immediately available smaller reward while waiting for the delivery of a delayed larger reward. In one task condition, participants could decide to make a binding choice for the delayed reward. We found that upregulating FPC function using anodal tDCS increased the number of binding choices for the delayed option, while we found no tDCS effects on the exertion of willpower. Our data provide support for a neuronal model of precommitment ascribing the FPC a causal role in monitoring the expected value of precommitment.

[28] State-signaling in putative cholinergic interneurons in dorsomedial striatum depends on orbitofrontal cortex

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Behavioral flexibility is facilitated when learning can be compartmentalized according to the context or *state* in which it occurs. Activity in cholinergic interneurons in the dorsomedial striatum (CINs) is thought to be necessary for this function. Orbitofrontal cortex (OFC) has been proposed to be necessary for disambiguating states, particularly inferred states that are not signaled by explicit cues. Here we tested the interaction of these two systems by recording putative CINs in rats with sham or ipsilateral OFC lesions performing a choice task across four different states defined by the sets of response-outcome contingencies available in each. Choices were between two actions to obtain different amounts of two flavored milk solutions (chocolate and vanilla). Trials were presented in blocks such that each block had consistent action-outcome contingencies, which changed across four unsignaled block transitions in each session. Putative CINs in dorsomedial striatum showed strong state-selectivity, with individual neurons showing consistent selectivity across the entire trial period. State decoding was significantly stronger in CIN ensembles as compared to medium spiny neuron (MSN) ensembles recorded in the same sessions. Furthermore, sub-optimal choices were associated with pre-choice miscoding of the block by CIN ensembles but not MSN ensembles. In rats with ipsilateral OFC lesions, state-selectivity in CINs largely disappeared and was not consistent across the trial period. State decoding in these CINs was at chance across the trial, and state miscoding was dissociated from sub-optimal choices. These data are consistent with a circuit in which OFC supplies state-related information to dorsomedial striatal CINs, allowing learned action-outcome contingencies appropriate for different states to be kept separate and driving choice behavior.

[29] Effects of damage to human prefrontal cortex on learning in a dynamic, multidimensional environment

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Decision-making, whether between foods or universities, often depends on considering options with multiple features. Devoting attention to features that are relevant for future outcomes can help facilitate learning and later choices. Previous work has shown that damage to orbitofrontal cortex disrupts dynamic stimulus-reward learning, while a separate line of work has implicated this region in the integration of option features during choice. Here, we asked how damage to this region in humans affects learning in a dynamic environment where options were defined by multiple features. OFC damaged patients, and patients with prefrontal damage sparing OFC, were tested in a multidimensional probabilistic reversal-learning task, in which each option was defined by two stimulus features (a shape and color) and a response, but only one feature (shape) was relevant to whether an option was rewarding. Healthy subjects learned to choose based on the reward history of the relevant feature, with only a slight influence from the irrelevant stimulus and response features. Subjects with OFC and left lateral frontal damage were impaired in this aspect of the task, but showed different patterns of performance. While subjects with left lateral frontal damage attributed rewards to the irrelevant stimulus or response dimensions, OFC damaged subjects did not attribute rewards to either stimulus dimension. These results suggest this region plays a critical role in adaptively attributing rewards to option features.

[30] Frontal beta oscillations reflect the effect of reward motivation on the active maintenance of representations in working memory

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Reward improves behavioral performance in a wide range of cognitive tasks, including working memory (WM). However, the neural mechanisms underlying the effect of reward motivation on WM processes are less known. Rewarding events have been shown to excite midbrain dopamine (DA) neurons that supposedly provide a motivational signal to brain systems involved in cognitive processing. Furthermore, reward-signaling stimuli have been shown to modulate oscillatory activity in the beta (20-30 Hz) frequency range, supposedly reflecting the modulation of medial prefrontal cortical activity by midbrain DA signals. Here we investigated the putative link between reward-based WM enhancement and the modulation of frontal beta oscillations in a change detection task involving the short term retention of the color and position of briefly presented squares. Our results revealed an increase in WM capacity when monetary reward could be obtained for correct performance, when compared to a condition in which no reward was available. Reward also increased the power of frontal beta oscillations during the delay period. Moreover, this increase was positively related to behavioral performance, that is, the greater the increase of beta power, the greater the enhancement of WM capacity by reward. Finally, increasing task difficulty by adding distractor items to the stimulus display did not modulate the effect of reward on either frontal beta power or WM capacity. Our results suggest that frontal beta activity marks the effect of reward motivation on the active maintenance of representations in working memory.

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[31] Hippocampal contributions to prospective orbitofrontal outcome representations

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The hippocampal formation and the orbitofrontal cortex (OFC) have been increasingly ascribed similar functional roles. Despite divergent neurochemical, anatomical, and physiological properties, both structures have been associated with the expression of flexible behavior. More specifically, within the framework of computational reinforcement learning theories, the OFC and the hippocampus have been identified with "model-based" reasoning, with the OFC implicated in signaling outcome expectancies and possibly forming a neural representation of task state and the hippocampus providing a potential neural substrate for representing and exploring state spaces, including both physical spaces and more abstract relational arrangements of stimuli. However, despite these seemingly related functional roles, few studies have examined how interactions between the hippocampus and OFC affect neural representations or information processing within each structure.

Here we tested the functional impact of hippocampal input on OFC neural representations. Rats were trained to perform a decision making task in which odors either cued an action (forced choice trials) or indicated a free choice. Actions were associated with rewards that differed in both flavor and magnitude, and action-outcome contingencies reversed across blocks of trials within a session. Following behavioral training, a virus expressing halorhodopsin was infused bilaterally into the ventral subiculum, and optical fibers were implanted above each infusion site. Electrode bundles were implanted targeting the lateral orbitofrontal region. In subsequent recording sessions, light stimulation was applied for the full duration of task trials, from trial initiation to reward delivery. In some sessions (control stimulation sessions), the frequency of delivered light stimulation was outside the range of sensitivity for halorhodopsin; in the remainder of sessions (halo stimulation sessions) 620 nm orange light was delivered to inhibit neurons in the subiculum.

Rats performed equally well on forced choice trials during both control and halo stimulation sessions. On free choice trials, however, rats were slower to adjust to changes in action-outcome contingencies over block switches during halo stimulation sessions. In both control and halo stimulation sessions, OFC neurons were differentially active at different time points throughout the task. Many neurons were maximally active during the waiting period immediately before reward delivery. The fraction of neurons active during this reward anticipation period was significantly reduced by halo stimulation compared to control stimulation sessions. Consistent with previous work, the selectivity of OFC neurons during reward anticipation reflected both rats' actions (response direction selectivity) and features of impending rewards (for example, flavor or magnitude). Preliminary analyses indicate that halo stimulation greatly attenuated the response direction selectivity of OFC neurons, pointing to a potential role for hippocampal-OFC interactions in integration of previous actions with future outcomes. Further analyses will explore the impact of hippocampal inactivation on OFC coding of outcome features.

[32] Self-Other Confusion in Prefrontal Cortex

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We show that people's estimates of their own abilities are not just influenced by their own performance but by the performance of others. This influence depends on social context (i.e. cooperation vs. competition). Prefrontal areas tracking self and other estimates predict the degree of such self-other confusion.

Knowledge about what oneself and what other people can do is the basis for many decisions in our social world. We are frequently in subtle "friend or foe" situations, where we can cooperate with or compete against others, for example when forming academic collaborations. During those decisions, information such as the "value" of these others (e.g. their performance level) is crucial. While it is relatively well established how we assign values to choices that we and other people have made[1-4], we know much less about the neural correlates of tracking value of ourselves or other social agents.

While in a magnetic resonance imaging (MRI) scanner, participants and two confederates (alleged other players) performed tasks and received explicit performance feedback. Within-subjects, we varied whether participants were in a cooperative or competitive relationship with another player.

We found, not surprisingly, that participants' estimates of their own performances were influenced by how well they had actually performed. In addition, however, participants' estimates of their own performance were influenced by the other players' performance history in a context-dependent way: The participants' self-rating increased as a function of the other's performance in cooperation, but decreased as a function of the other person's performance in competition. The same pattern of self-other confusion effects was found for the performance estimates of other players. In other words, the evaluation of other people's performance was in turn influenced by the participants' own performance history.

Neurally, we found distinct areas within of prefrontal cortex tracking the history of self and other performances. Signal strength in these areas was predictive of the degree of the self-other confusion effects found behaviourally.

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