OFC

2024

Poster sessions

Poster session n°1 **Tuesday, April 23**

12:00 p.m. - 2:00 p.m.

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2	Behavioural and Neural Influences of Social Partner's Motivational Type on Food Preference
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21	Characterizing orbitofrontal task representation during schema formation and generalization within the anterior and posterior subregions of ventral and lateral orbitofrontal cortex in rats
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34	Roles of the orbitofrontal cortex in human emotion, depression, and memory
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36	The encoding of economic decision variables in OFC is longitudinally stable and varies by cortical layer
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Representations of the intrinsic value of information in mouse orbitofrontal cortex

Jennifer Bussell[1, 2], Ryan Badman[3, 4], Christian Márton[5], Ethan Bromberg-Martin[6], Larry Abbott[1, 2], Kanaka Rajan[3, 4] and Richard Axel[1, 2, 7]

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[7] Howard Hughes Medical Institute

Animals are motivated to acquire knowledge of their world. They often seek information that does not influence reward outcomes suggesting that information has intrinsic value. We have asked whether mice value information and whether a representation of information value can be detected in mouse orbitofrontal cortex (OFC). We developed an odor-based behavioral task in which mice choose to acquire information even though it does not alter the reward outcome. We observe that mice choose to acquire knowledge about uncertain reward and are willing to sacrifice water for information suggesting that knowledge is of intrinsic value to a mouse. We imaged neural activity in OFC while mice performed the information seeking task and observed different but overlapping populations of neurons responsive to odors predictive of information and odors predictive of water reward. Moreover, a nonlinear latent variable model recapitulated these distinct representations in the low-dimensional dynamics of OFC neuronal population activity. These data suggest that mice have evolved distinct pathways in OFC that represent the intrinsic value of knowledge and the extrinsic value of water reward. Thus, the desire to acquire knowledge is observed in mice and the value of knowledge is represented in the OFC.

Behavioural and Neural Influences of Social Partner's Motivational Type on Food Preference

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The orbitofrontal cortex (OFC) integrates the sensory and nutrient properties of foods into subjective values that guide food preferences. Separately, the OFC is implicated in processing social information, including the faces, choices, and rewards of others. However, it remains unclear whether the OFC and related brain areas also process more complex social factors, such as the motivation behind a partner's decision, and how these factors might influence one's own preferences. Here we address these questions in a human behavioural and fMRI experiment, by investigating how a social partner's motivation influences subjects' food choices and related neural activities. We follow the approach of Self-Determination Theory (SDT) that the reasons for undertaking a particular behaviour can be grouped into five motivational types (e.g., external vs. introjected). Emerging evidence suggests that one's motivational type may also influence the choices of peers. Accordingly, in the present experiment, participants rate motivational type and other attributes of different social partners after studying their biographical profiles. In a subsequent social food-choice task, participants observe these partners' choices between foods varying in nutrients and sensory attributes before making a choice themselves. Behavioural and neural data will indicate the mechanisms by which others' motivational type can influence one's own food-preference decisions.

Grid-like representation in value-based decision-making

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Increasing reward value is encoded in the 'brain valuation system (BVS)', comprised of a network of regions including ventromedial prefrontal cortex (vmPFC) and posterior cingulate cortex (PCC). This signal has been shown to reflect subjective value—how rewarding something is based on an individual's preference. Yet, how a given rewarding option gets transformed into a subjective value signal is unclear. Here, we hypothesize that a grid code, a key part of the brain's cognitive mapping system, is utilized to efficiently represent subjective attributes of rewarding options and to guide inference. Grid-like hexagonal modulation of BOLD activity and theta power of local field potentials characteristic of the underlying grid code have been found in human entorhinal cortex (EC) and mPFC. In this study, we hypothesized these regions would represent decision vectors in a 2D subjective value space. Participants (N = 35) were asked to make binary choices between two sequentially shown shape options that varied along two continuous dimensions (such as width and orientation) corresponding to reward amount ($) and probability (%), respectively, during fMRI. Cumulative Prospect Theory was used to calculate the subjective value of choice options. We use two separate GLMs to test if BOLD activity is associated with 1) subjective value and 2) subjectively-weighted hexagonal modulation, characteristic of a grid-like representation. We identified a subjective value comparison effect at decision time in vmPFC and PCC (P [TFCE-SV] < 0.05). In parallel, we find a grid-like representation of decision vectors between options through individuals' subjective value spaces in bilateral EC (P [TFCE-SV] < 0.05), and, marginally, in vmPFC (P [TFCE-SV] = 0.07). This representation is specific to a six-fold periodicity (vs 4-, 5-, 7-, or 8-fold control periodicities). To our knowledge, this is the first demonstration of a grid-like representation of decision-vectors in a subjective value space.

Distinct Information Processing Across the Medial-to-Lateral Orbitofrontal Cortex During Economic Decision-Making in Rats.

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Diverse roles have been suggested for the rat orbitofrontal cortex (OFC) in economic decision-making. However, the OFC is heterogenous, and it is unclear how the OFC's diverse roles change with that heterogeneity. To address this issue, we recorded neural ensembles across the medial (MO) to ventral (VO) to lateral (LO) span from three simultaneously implanted silicon probes in 8 FBNF-1 rats (4M 4F) on the Restaurant Row neuroeconomic task. Rats earned their daily food intake on a time-limited budget by foraging for sequentially encountered delayed rewards. Rats made an initial accept/reject decision in the "offer zone" (OZ), where a tone signaled reward delay for that offer (1-30 s). If the offer was accepted by entering a "wait zone" (WZ), the delay counted down and rats reevaluated their initial decision by waiting for reward or quitting to go to the next restaurant. Rats learned to reject long-delay offers while accepting short-delay offers in the OZ. If long-delay offers were mistakenly accepted in the OZ, rats often quit in the WZ. In the OZ, LO ensembles showed an initial burst followed by sustained activity until a decision was made. The sustained LO activity was greater for better offers and aligned to tone presentation. VO activity gradually rose with time spent in the OZ. This rise was steeper for worse offers. These data were consistent with a model in which LO drove a probability of accepting the offer, repeated with each tone presentation, while VO encoded the opportunity cost of waiting. In the WZ, LO activity increased as time to reward approached. VO activity was elevated in the WZ before quits and burst when the quit decision was made. For the first second of the WZ, MO activity did not differentiate encounters in which the rat stayed through the WZ versus those it quit; however, MO activity then dropped if the rat planned to stay, while remaining elevated if it eventually quit. Collectively, these results are consistent with the notion that LO encodes information about time to reward and participates in decision systems that govern reward approach. VO encodes information about opportunity costs and participates in decision systems that allow rats to resist temptations to earn reward and explore other options. MO seems to be related specifically to decision systems that help rats reevaluate their decisions.

The orbitofrontal cortex shapes accumbal dopamine responses to inferred prediction errors

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Dopamine is classically thought to drive learning based on errors in the prediction of rewards and punishments. However, animals also learn to predict cues with no intrinsic value and later use that information to infer the structure of their environment, and it is unclear if such latent learning also relies on dopaminergic prediction errors. Here, we tested this by recording dopamine release in the nucleus accumbens and dorsomedial striatum while rats executed a task that incorporates both types of learning. We found that dopamine release in both regions correlated with errors in predicting value-neutral cues during latent learning and with errors in predicting reward during reward-based conditioning. Interestingly, in the probe test dopamine responses were similar to cues that reflected inferred value and those that did not. However, inactivation of the orbitofrontal cortex activity during this phase led to a selective reduction in dopamine responses to the cue with inferred value in the nucleus accumbens, suggesting that while dopamine responses to certain cues may seem similar in shape and intensity, their circuit underpinnings may differ depending on behavioral context. Our findings indicate that dopamine signals prediction errors about both valued and neutral stimuli, as well as inferred valued, even when the underlying computations for each prediction error component is distinct. This is consistent with the view that striatal dopamine acts as a general teaching signal that supports model-based learning across different domains of experience.

Spatial firing fields in hippocampus and orbitofrontal cortex are not modulated by goals that predict reward in either consistent or random locations

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Hippocampal place cells in rats generally distribute uniformly over neutral environments, but evidence on representations of behaviorally-significant locations is mixed. For instance, rewarded locations often accumulate an increased density of place fields, while locations that rats must visit to trigger reward delivery elsewhere only sometimes show this effect. Here, we examined whether the spatial reward predictability of a location affected representations in hippocampus (HC) and orbitofrontal cortex (OFC), another brain region that frequently exhibits both spatial tuning and reward-related representations. Rats (n = 4) learned two unmarked goal locations in an open field arena. Pausing in either goal caused reward to be delivered, but one goal delivered reward in a fixed, predictable location while the other goal delivered reward to a random location. Over 94 sessions, we recorded 753 OFC units and 613 HC units. Of these, 82% of HC units and 43% of OFC units showed spatial tuning. Spatial fields did not cluster around goal locations relative to non-goal locations, and approximately equal numbers of fields occurred near the two goals in both structures. This data suggests that place fields in the HC and spatial fields in the OFC do not differentially represent goal locations based on their predictability of reward location. To assess whether value affects spatial tuning in OFC cells, we designed a novel behavioral paradigm in which the probability of reward across space varied in a structured but un-cued way. Here, rats (n = 5) approached and paused at cued locations in an open field arena; they received a food pellet based on the reward probability of the chosen cued location. Preliminary data shows rats' decisions on simultaneous trials were driven by the underlying reward-probability map; as the difference in value between stimuli increased, rats favored the higher-probability option. Neural recordings from OFC as rats perform this task are ongoing.

Neural networks supporting the formation and utilization of an abstract representation of task structure during generalization

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Abstract representations of task structure are thought to be key for allowing us to act flexibly in novel situations. Several findings have suggested that such a representation is encoded in the orbitofrontal cortex and medial prefrontal cortex, along with the hippocampus and entorhinal cortex (i.e. the OMPFC-MTL network). A separate line of work has implicated the frontoparietal network in maintaining the same kind of abstract task representations in the context of cognitive control. One possible reconciliation of these divergent streams of research is that these distinct networks represent the same information to fulfill different behavioral demands. Namely, the OMPFC-MTL network may be involved specifically in forming a representation of this abstract task structure and making inferences, while the frontoparietal network may be involved in utilizing this information to control behavior. We are currently testing this hypothesis in an fMRI experiment using an acquired equivalence task. In this task, participants learn that the stimulus-reward associations of multiple contexts are equivalent. After acquiring new stimulus-reward associations in a subset of these contexts, participants are tested on these new stimuli in the held-out contexts without feedback. Successful generalization here requires inferring the value of these stimuli based on the abstract relationships between the different contexts. We expect that the OMPFC-MTL network will represent this abstract task structure during the training, when participants are acquiring this structure and first inferring the values of context-stimulus pairs during generalization. In contrast, we expect that the frontoparietal network will represent this information later during the generalization phase, when participants are primarily applying the inferred stimulus-response mappings to control behavior.

Dissociable intracranial signals for choosing the better of two goods or the lesser of two evils

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This study investigates the mechanisms underlying the construction and the comparison of value for positive hedonic valence (pleasant) or negative valence (unpleasant) contexts as a function of task goal (i.e., choosing the better of two goods vs. the lesser of two evils) by combining valuation and binary choices tasks with intracerebral recordings from epileptic patients. We leveraged a large-scale dataset of iEEG recordings obtained from 25 patients that totaled to 3279 recording sites. We found that during valuation tasks, broadband gamma activity (BGA, 50-150 Hz) recorded from the ventro medial prefrontal cortex (vmPFC) scaled positively with value and exhibited a higher valence selectivity (pleasant value encoding > unpleasant value encoding) whereas BGA from dorsal anterior insula scaled negatively with value with weak valence selectivity. In contrast to previous neuroimaging findings, during binary choices, we found that neural activity in the vmPFC for an encoding of pleasant options as a function of how pleasant they were : the most pleasant item dominated representation patterns independently from the goal. To conclude, our study represents a step forward in elucidating how subjective value is represented in the human brain by showing that the vmPFC positively signal pleasant value whereas the daINS negatively signals values independently from pleasantness domain. We also provide novel insights into the value comparison processes thought to underlie binary-decisions by showing that relative value signals were better framed in the brain by their relative hedonic value compared to their relative goal-value.

Higher-order cortico-cortical synergistic interactions encode update signals in goal-directed learning

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Goal-directed learning is the ability to acquire action-outcome relations and select actions according to expected outcomes, current goals and motivational state. At the neural level, goal-directed learning emerges from the coordinated activity of the associative and limbic fronto-striatal circuits. Here, we investigate the underlying brain interactions in terms of functional segregation and integration processes. Participants performed an arbitrary visuomotor learning task, where the relation between the visual stimulus, the action and its outcome is arbitrary and causal. Single-trial and atlas-based high-gamma activity (HGA, from 60 to 120Hz) was estimated from MEG data. Cortical interactions were inferred from statistical dependency between co-modulations in HGA and learning signals (reward prediction errors and Bayesian surprise). To do so, we quantified redundant and synergistic interactions, evidencing functional segregation and integration, respectively, using the Partial Information Decomposition framework. We observed interactions significantly encoding Bayesian surprise after the presentation of the outcome. Redundant interactions were observed over the visual system, spreading over the right temporal and lateral prefrontal (lPFC) cortices. From 0.6 to 1s after outcome, Bayesian surprise signal was encoded redundantly by pairs of brain regions in the orbitofrontal cortex (OFC). Interactions were also found to encode synergistically Bayesian surprise in a distributed network including the visual system, lPFC and OFC. Finally, we observed significant higher-order cortico-cortical synergistic interactions encoding Bayesian surprise. More interestingly, we observed that the core areas were centred over the limbic system including the vmPFC and OFC. Overall, these results demonstrate the pairwise and higher-order cortico-cortical synergistic interactions encode model update in goal-directed learning in a distributed network and place the OFC as a central hub.

Event-specific and persistent representations for contextual states in orbitofrontal neurons

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Flexible and context-dependent behaviors require animals, including humans, to identify their current contextual state for proper rules to apply, especially when information that defines these states is partially observable. Depending on behavioral needs, contextual states usually persist for prolonged periods and across other events, including sensory stimuli, actions, and rewards, highlighting prominent challenges of holding a reliable state representation. The orbitofrontal cortex (OFC) is crucial in behaviors requiring the identification of the current context (e.g., reversal learning); however, how single units in the OFC accomplish this function has not been assessed. Do they maintain such information persistently, in separate populations from those responding phasically to events within a task, or is contextual information dynamic and embedded in these phasic responses? Here, we investigated this question by recording single units from OFC in rats performing a task that required them to identify the current contextual state related to estimated proximity to future reward with distracting olfactory cues. We found that while some OFC neurons encode contextual states, most change their selectivity upon the transition of task events. Nevertheless, despite dynamic activities in single neurons, the neural populations maintain persistent representations regarding current contextual states within particular neural subspaces.

Decision-making in the context of multi-attribute options

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Often decisions are made between options with multiple attributes that are relevant to one's choice (e.g., taste and cost). The orbitofrontal cortex (OFC) is important for decision-making and OFC neurons represent associations between stimuli and their overall values. However, it is unknown whether OFC only evaluates options on the basis of their integrated value, as suboptimal decision-making effects such as the attraction effect indicate that within-attribute comparison may also contribute to decision-making. To investigate how multi-attribute options are represented in neural activity, we trained two rhesus macaques on a decision making task in which two simultaneously-presented options were represented by stimuli reflecting the sweetness of that option's sucrose reward, and the probability of receipt. These stimuli represented information about the attributes with separate bars that either increased or decreased with increasing attribute value, allowing us to investigate both free-viewing gaze behavior and changes in choice behavior due to perturbations in attribute presentation. We recorded neurons in OFC and frontal eye fields (FEF) using acute electrodes and multi-contact linear probes. When comparable attributes did not share a presentation mode (e.g., swt bar A increased in size with increasing sweetness, while swt bar B decreased), choices became suboptimal, implying a role for within-attribute comparison. Likewise, gaze transitions a preference for within-attribute over within-option comparisons, even as similar proportions of either transition are made across trial types. Neuronal analysis indicates a greater presence of independent information relating to attribute than integrated value of the chosen option in OFC and FEF firing rates. Our interim results support the notion that value-based decisions take place, at least partially, in the space of individual attributes, and may depend on attribute value representations in OFC.

Neural mechanisms of the influence of reward expectations on behavior

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Expectations of reward play a critical role in cognition and decision-making, allowing us to predict the outcomes of certain actions. These expectations can influence which actions we take and also inform how we interpret sensory input. However, when our expectations are wrong, the ability to flexibly shift our behavior in response to unanticipated circumstances is critical for our well-being. For example, recognizing that the milk in the fridge that you thought was still good has actually spoiled protects you from an unfortunate episode of food poisoning. In order to better understand the neural dynamics involved in these processes, I trained monkeys to perform a task in which different image cues predicted the taste of a fluid bolus (from sweet to bitter). Each trial could be either forced-choice (where only one image was presented for selection) or free-choice (where a choice between two images was presented). In order to select an image, the monkey was required to fixate the image and release a touch-sensitive bar, which was followed by an initial bolus of fluid. Next, there was a four-second period during which each tap the monkey made on the touch-sensitive bar delivered a small, additional bolus of the same fluid. Monkeys consistently chose sweeter options, and tapped more for them. Once associations were well established, a small percentage of trials became "mismatch" trials, in which the fluid delivered did not match the cue image. On these trials, tapping behavior initially reflected the expected outcome, but shifted over the four-second window in accordance with the actual fluid received. To understand the neural dynamics of expectation in taste perception and motivated behavior, I recorded simultaneously from the orbitofrontal cortex and the gustatory cortex during this task. Previous work has suggested that the activity of the orbitofrontal cortex is flexibly modulated by expectations of taste.

Lateral orbitofrontal cortex contributes to strategic decision making following changes in reward expectation

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The negative feelings people can get due to unexpected reward loss relates to the major symptom of sadness and is a core feature of depression. Previous studies have suggested that the lateral orbitofrontal cortex (LOFC) is activated by reward loss or more generally by violations of expectations. Consequently, in this project I am determining whether altered activity in primate LOFC contributes to an animal's sensitivity selectively to unexpected reward loss or to unexpected reward gain too. Using an approach-avoidance task marmoset monkeys' decision-making behaviour was assessed in response to their receiving lower or higher amounts of reward to their expectations. In this task, variable interval reward schedules (9-15s) are imposed on two identical stimuli on both sides of a touch-screen with weekly probe sessions increasing or decreasing the interval of one of them to look at unexpected reward loss or gain, respectively. The LOFC region is cannulated bilaterally to investigate whether acute inactivation of this region alters marmoset's response strategy during such probe sessions. Since LOFC (A47) is a large heterogenous area in primates, consisting of area 47M, 47O and 47L, one pair of cannulae targeted the anterior sector (A47M) and the other, a posterior sector (A47O) to assess possible functional specialisation. Results from the first two marmosets show that LOFC inactivation (induced by infusions of GABA-A and B receptor agonists, muscimol and baclofen) produces a consistent increase in their sensitivity to both unexpected gain or reduction in reward. This was reflected in marked changes in response strategy, whereby marmosets showed greater bias away from the response side leading to unexpected reward loss, and greater bias towards the response side leading to unexpected reward gain. Differential effects were not observed between anterior and posterior inactivation. (Funded by Wellcome Trust 224432/Z/21/Z to ACR)

Hippocampal and orbitofrontal neurons contribute to complementary aspects of associative structure

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The ability to establish associations between environmental stimuli is fundamental for higher-order cognitive functions, such as state inference and generalization. The hippocampus and orbitofrontal cortex (OFC) play pivotal roles in this, demonstrating activities that appear to predict outcomes and contribute to associative memory formation. To determine their specific roles in representing learned cue-outcome associations, we trained head-restrained mice using various paired sequences of 'odor -> outcome', altering task variables including past and current cues, task schema (i.e., shared task structure between sequence pairs), and expected outcome—with the idea that examining how these task variables affect neural generalization between sequence pairs could reveal particular contents in learned associations. Calcium imaging during the mice's learning found sequence-splitting signals that distinguished between paired sequences, indicating the formation of associative memory in both brain regions. Critically, when examining how these task variables affected the generalization of such signals between sequence pairs, we observed that hippocampal splitting signals were linked to past and current odor cues. In contrast, the OFC splitting signals showed similarity between sequence pairs that shared the same task schema and expected outcome. These findings suggest that the hippocampus and OFC uniquely and complementarily organize the acquired associative structure.

Orbitofrontal ensembles integrate taste, movement, and reward predictions during learning

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[1] NIDA IRP

Learning the meaning of cues is necessary for survival. Road signs tell us where to turn to acquire food, which specific food is offered, as well as whether food is offered at all. We also discriminate cues which share the same meaning. The integrated representation of these features of the behavioral landscape has been called a "cognitive map", the construction and use of which confer the ability to make predictions based on direct experience and to make inferences in novel situations. But how is this kind of information acquired, integrated, and used - what neural circuits underly cognitive map formation? The orbitofrontal cortex (OFC) is thought to be important for cognitive map formation, particularly generating reward predictions. Generally these studies were performed in well trained subjects and not during learning, when maps are formed, leaving unanswered questions about how the OFC forms integrated representations and how their activity evolves to highlight information of biological relevance. We recorded OFC ensemble spiking activity while rats learned a task that permitted dissociation of sensory from motor, taste, and reward encoding. During learning OFC ensemble activity evolved toward simpler representations of rewards and movements. Once learning had occurred information about specific taste outcomes accounted for little variance in OFC activity. However, devaluation of one taste prior to testing revealed latent taste-predictive information in OFC ensembles. These data suggest that cognitive map formation in the OFC involves simplifying task demands into whichever information is most directly relevant to solving the problem, while information which is not directly used for making correct decisions remains latent in the OFC. Our findings have important implications for understanding the role of the OFC in learning and using predictive information to make correct decisions.

Creativity involves the subjective valuation of ideas via the Brain Valuation System

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[1] Paris Brain Institute (ICM)

Creativity is thought to rely on a generation phase associated with the default-mode network (DMN) and an evaluation phase supported by the executive control network (ECN). In the current study, we aimed to show the involvement of subjective valuation (or preferences) in creativity, as suggested by Lopez-Persem et al. (2023). At the neural level, we wanted to find which regions support these processes during creativity. We conducted creativity tasks, decision-making tasks and fMRI imaging on forty healthy participants. We performed behavioral model fitting and whole-brain parametric modulation analyses. Results show that: (i) the subjective value of an idea depends on its originality and adequacy: value $= (\alpha \times \text{originality}^{\delta} + (1-\alpha) \times \text{adequacy}^{\delta})^{\frac{1}{\delta}}$ (ii) preferences vary between subjects: some value originality more than adequacy ($\alpha > 0.5$) and vice-versa (iii) during the creative process, valuation is supported by the brain valuation system (BVS), a network classically involved in decision-making (iv) surprisingly, originality and adequacy evaluation are respectively supported by the DMN and the ECN and (v) preferences parameters (α and δ) correlate with real-life creative abilities, as measured by a battery of tests. Overall, we replicate the behavioral results of Lopez-Persem et al. (2023), showing the involvement of subjective valuation in creativity. At the neural level, we demonstrate which regions encode the originality, adequacy and the subjective value of ideas. Overall, this study completes the current understanding of the neurocognitive bases of creativity and demonstrates the involvement of the BVS in creativity.

Decoding the Motives for Goal-Directed Actions: Investigating the Role of the Orbitofrontal Cortex

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One hallmark of human cognition is the ability to engage in behaviors that result in specific outcomes – termed goal-directed behavior. Implementing goal-directed behavior requires the ability to evaluate actions based on associative knowledge of the environment and the specific outcome of actions. For example, seeing a Domino's pizza sign indicates pizza is locally available, and efforts to obtain pizza are likely to be rewarded. However, we lack a detailed understanding of the neural mechanisms which support transforming associative knowledge into goal-directed actions. We developed a novel construction of the specific Pavlovian-to-instrumental transfer paradigm to test whether expected outcome representations (EORs) in lateral orbitofrontal cortex (lOFC) motivate goal-directed actions. In this task, participants are first trained to associate four sets of two cues with two different rewarding food odors, or a non-reward outcome. One set of cues are associated with a 50-50 chance of getting each reward ("stochastic cue" condition). In phase two, participants learn to forage for specific rewards in a "planetary foraging task". They first select a planet on which to forage, then search as many locations as possible in three seconds to uncover hidden rewards. The rewards that can be foraged on each planet are determined by the "season", known only when the choice period begins, decoupling EORs from specific actions representations. In the test phase, participants are presented with cues and then make free instrumental responses. We expect that EORs will be decodable from functional imaging data in the lOFC and will predict the to-be-selected action during foraging. Further, in the stochastic cue condition, the strength of one EOR over the other will predict foraging for that outcome on a trial-by-trial basis. These results will inform theories of decision making by illuminating the neural mechanisms supporting motivation for specific goal-directed actions.

Mapping the world around us: A topology-preserved schema of space that supports goal-directed navigation

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Successful goal-directed navigation requires estimating one's current position in the environment, representing the future goal location, and maintaining a map that preserves the topological relationship between positions. In addition, we often need to implement similar navigational strategies in a continuously changing environment, thereby necessitating certain invariance in the underlying spatial maps. Previous research has identified neurons in the hippocampus and parahippocampal cortices that fire specifically when an animal visits a particular location, implying the presence of a spatial map in the brain. However, this map specifically encodes the current position but not the future goal of an animal and is largely context-dependent, whereby changing the room or shape of the arena results in a new map orthogonal to the previous one. These observations raise the question, are there other spatial maps that fulfill the cognitive requirements necessary for goal-directed navigation? Using a goal-directed navigation task with multiple reward locations, we observed that neurons in the orbitofrontal cortex (OFC) exhibit distinct firing patterns depending on the goal location, and this goal-specific OFC activity originates even before the onset of the journey. Further, the difference in the ensemble firing patterns representing two target locations is proportional to the physical distance between these locations, implying the preservation of spatial topology. Finally, carrying out the task across different spatial contexts revealed that the mapping of target locations in the OFC is largely preserved and that the maps formed in two different contexts occupy similar neural subspaces and could be aligned by a linear transformation. Taken together, the OFC forms a topology-preserved schema of spatial locations that is used to represent the future spatial goal, making it a potentially crucial brain region for planning context-invariant goal-directed navigational strategies.

A tale of two regions: Orbitofrontal subregions show functional specialization during value-based decision making

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The primate orbitofrontal cortex (OFC) plays a critical role in value-based decision making. However, the underlying mechanisms through which value information represented in the OFC is ultimately translated into decision outcomes is not clear. At a high level, theories of OFC function parallel larger debates within neuroeconomics about whether the most critical computations are made at the level of economic goods or at the level of the actions necessary to obtain those goods. Within a goods-based framework, decisions are made within the OFC itself by comparing the values of competing offers. Under an action-oriented framework, the role of the OFC is to convey information about available options to downstream structures where a decision is rendered between alternative actions.

A potential explanation for the diverse views of OFC function lies in the fact that the term 'OFC' can refer to many different combinations of distinct subregions. Areas 11 and 13, are two of the most studied of these subregions. Despite differences in their cytoarchitecture and connectivity, these subregions are not often considered independently. Using simultaneous, multi-channel recordings, we identified distinct functional specializations for the two subregions in macaque monkeys making simple two-alternative choices. Neurons in area 13 reflected the comparison of offer values in an abstract manner, and neurons in area 11 reflected the value associated with the actions performed on each trial. These results are consistent with the two regions' respective connectivity profiles: Whereas area 13 receives convergent sensory and limbic inputs making it well suited for representing items in a goods-based framework, area 11's relative proximity to motor effectors, makes it better suited to reflecting action-based computations. Taken together, these results suggest that independent consideration of these subregions may help reconcile debates on the OFC's role in value-based decision making.

A comparison of learning and reward signals in orbitofrontal cortex and secondary motor cortex using single-cell imaging in freely-behaving rats

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Orbitofrontal Cortex (OFC) and Secondary Motor Cortex (M2) have both been linked to action-based reward learning and responding to or detecting reversals. Previous data suggests that although M2 and OFC are involved in flexible learning and decision-making, they could be involved in different facets of learning. To test this, we designed a restless bandit task where the location of the highest rewarded side reverses every 75 trials, along with the probability of reward. We tested animals across 6 sessions of learning totaling 225 trials each, with schedules progressing from less to more reward uncertainty (100:0 to 70:30). Before rats performed this task, we implanted lenses unilaterally in OFC (n=4) or M2 (n=3), confirmed with histological verification of GCaMP and lens placement, to image calcium activity in these regions using miniscopes. A mixed effects GLM resulted in a significant effect of session, and a reversal x session interaction but no effect of lens implant, indicating there was learning and adjustment to reversal in both implanted groups. We compared the difference in activity per frame to 1 sec before the reward epoch using an ROC, and performed bootstrapping using shifted data. In OFC, we found a significantly greater ratio of neurons than in M2 that was selective to reward, particularly in early learning. Conversely, we found a significantly greater proportion of neurons selective to spatial side in M2 compared to OFC that varied more by block/schedule, beginning in early learning. A SVM trained via a leave-one-out procedure resulted in our ability to decode with high accuracy chosen side and whether the trial was rewarded or not before a choice was made, earliest and most consistently in M2. However, decoding accuracy in OFC increased to the level of M2 during the reward epoch in the most probabilistic conditions. Ongoing analysis is focused on characterizing the influence of reward history on future choices in both OFC and M2 across learning.

Characterizing orbitofrontal task representation during schema formation and generalization within the anterior and posterior subregions of ventral and lateral orbitofrontal cortex in rats

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Rapidly adapting behavior in changing environments can be aided by generalizing from prior knowledge to novel but structurally similar situations. Neural representations of these underlying common task structures – or schemas – has been found within orbitofrontal cortex (OFC), which likely accounts for the fundamental role of OFC in behavioural flexibility. While the majority of evidence for the role of rodent OFC in behavioral flexibility comes from lateral OFC (LO), relatively few studies have targeted the adjacent ventral OFC (VO) subregion. Furthermore, emerging evidence suggests that there are functional and neuroanatomical differences between anterior and posterior areas within OFC subregions. Despite the potential heterogeneity between- and within-OFC subregions, neural activity has never been systematically compared between these subregions, and for some subregions, never been recorded. Thus, the extent to which all these OFC subregions are engaged in neural computations relevant to schema formation and generalization is unknown. Therefore, we sought to characterize how task and schema representations in neural ensembles are distributed across OFC subregions in rats. Rats were trained in an odor-discrimination generalization task designed to encourage the formation of schemas of underlying task structure. We found behavioral evidence of successful discrimination, and rapid generalization within and between sessions to novel odor exemplars, consistent with the formation of a task specific schema. Single-unit activity was recorded simultaneously from four OFC subregions - anterior and posterior areas within both LO and VO – to directly compare signals in these understudied subregions with the well characterized posterior LO. We present how the neural representations in OFC underpinning behavioral generalization in this task simultaneously evolve within these subregions.

Modulating Cognitive Flexibility through Selective Activation of Astrocytes in the Lateral Orbitofrontal Cortex

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The lateral orbitofrontal cortex (lOFC) is pivotal for adapting strategies, a key aspect of cognitive flexibility. While astrocytes play active roles in synaptic regulation and cognitive functions, their specific contributions to cognitive flexibility in the lOFC is unclear. Using chemogenetic techniques, this study selectively activates astrocytes, providing novel insights into the cellular mechanisms of adaptive decision-making. Astrocyte activation, with astrocyte-specific DREADD gfaABC1D-Gq and DCZ agonist, occurred acutely (1 day 1 ug/kg IP) and chronically (14 days 10 ug/kg SQ). lOFC activation was validated by assessing calcium activity with two-photon microscopy in response to DCZ or CNO. Immunolabelling with S100B and SOX9 was used to indicate changes in astrocyte size and number, alongside RFP to confirm DREADD expression. Cytokine levels in the lOFC from chronically vehicle- or DCZ-treated mice was quantified using a high-sensitivity assay. The impact of DREADD-induced lOFC astrocyte activation on decision-making was explored in a reinforcement-based task (DCZ or VEH 100 ug/kg IP). Co-expression of the DREADD reporter in lOFC astrocytes was established, showcasing their responsiveness to DCZ. Acute activation had no noticeable effect on astrocyte size and number, while chronic activation increased S100B labeling intensity and volume. Minimal changes in SOX9 expression and cytokine levels were observed. Successful modulation of astrocyte activity was evidenced by increased calcium transients. Acute astrocyte activation impaired mice's ability to select actions based on likely outcomes. In conclusion, acute activation of lOFC astrocytes in mice hinders decision-making, while chronic activation induces astrocyte hypertrophy without substantial neuroinflammation. These findings have implications for disorders with altered decision-making, guiding future research on astrocyte-mediated cognitive functions within the lOFC.

Structure learning in the human hippocampus and orbitofrontal cortex

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Humans possess remarkable cognitive capabilities for extracting the abstract structures underlying various phenomena. Our brains can build 'cognitive maps' to organise structural knowledge, affording novel inferences and flexible decisions. The hippocampus (HC) and orbitofrontal cortex (OFC) are both implicated in the formation of cognitive maps, but whether they might differ in their roles and how they interact with each other is currently a topic of debate. Here, we propose that cognitive map construction involves two separate processes: First, HC encodes the relationships between different states (i.e., state-state associations), akin to mapping maze pathways. Second, OFC associates states with their corresponding goals (i.e., state-goal associations), distinguishing different outcomes to guide actions.

To test this hypothesis, we designed a task that requires learning both 'state-state' and 'state-goal' associations, along with reversals in both types of associations: The 'transition reversal' alters the probability of transitions between states, without changing the underlying abstract structure, while the 'goal reversal' inverts the goals associated with specific states. Participants performed this 'double-reversal-learning' task while their brain activities were recorded with functional magnetic resonance imaging (fMRI).

The behavioural results and computational models revealed that participants effectively grasped and utilized abstract structural knowledge to make novel inferences about transitions among states. Using representational similarity analyses (RSA), we found the transition structure (the 'state-state' association) was persistently represented in the HC and medial OFC (mOFC) / ventromedial prefrontal cortex (vmPFC), and especially prominent at the time of the outcome. By contrast, the lateral OFC (lOFC) encoded the identity of each state and its prospective goal (the 'state-goal' association).

In summary, the results suggest that a distributed circuit spanning HC and mOFC/vmPFC encodes the abstract task structure, while lOFC represents each specific event in a more concrete format. The synergy of both HC and subregions of OFC enables the construction of a comprehensive cognitive map of the task space, supporting flexible and goal-directed behaviours.

Causes and consequences of effort in foraging decisions

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In many decisions in everyday life, choice options arise sequentially, and agents need to decide whether to stay with the current option or leave and search for a better one. Typically, when making such foraging-style choices, both staying and leaving requires effort, but effort costs have received little attention in prior work. We developed a novel foraging task in which human participants invested physical effort into foraging from a patch or leaving it. Patches varied in their starting richness, but depleted over time. Participants had to infer the patch richness from received outcomes and decide when to leave. Patches also varied in the amount of button presses required for foraging. Moreover, the proportion of rich patches and the travel time to the next patch varied across blocks. A large online sample of participants (N = 461) completed this task as well as a battery of psychiatric questionnaires. Overall, participants adjusted their stay/leave choices to the benefits (patch and block richness) and costs (foraging and traveling effort) imposed by the task. However, they also generally overstayed and took seemingly irrelevant factors into account, such as the effort (number of button presses) they had invested on the previous trial. Button presses regularly exceeded response requirements and were themselves adjusted in response to outcomes and environmental richness, suggesting effort investments might partially mediate the effect of rewards on stay/leave choices. This effect was particularly strong in individuals with high scores on depressive symptoms, specifically in those reporting negative cognitions (self-criticism, worthlessness). Individuals with higher scores on depressive symptoms also showed less overstaying, resulting in overall better performance on the task. This work sheds light on how effort both influences and reflects valuation in foraging decisions.

Studying the neural and neurochemical basis of flexible decision making in changing environments using continuous decision paradigms

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To study the sub-components of decision-making and their neurochemical basis, previous research has mostly employed trial-based choice paradigms, where participants choose between two options, the value of which remains fixed within trials. However, in everyday life we do not make decisions in confined trials and between two options. Instead, we continuously accumulate information about multiple decision options whose value might be changing over time.

Here, we present data from two novel continuous decision paradigms (CDP), paired with a convolutional GLM analysis of EEG data, to study decision-making in dynamic and temporally extended choice settings and across different domains. Instead of emitting one choice per trial, in our tasks, participants are presented with a continuous stream of evidence for several minutes and need to continuously integrate evidence over time to decide when to commit to a choice. In a within-subjects, placebo-controlled design (N=30), we test the effect of the NMDA receptor antagonist ketamine on evidence integration in the value (task 1) and emotional (task 2) domain.

In a planned intermediate data review (N=12), we find that participants flexibly adjust their weighting of recent evidence to changes in both environmental volatility and stimulus noise. This is true for perceptual information as well as for integrating facial emotion expressions over time to judge emotional valence or arousal. Our tasks allow us to study sub-components of decision making in dynamic environments, across different domains (value, emotion), and make better use of experimental time and data. Characterising the effects of NMDA receptor antagonist ketamine on decision computations during both value and emotional processing will help us understand the drug's dual role as a model of psychosis and as a rapid acting antidepressant.

Algorithmic schema representations in human 7T fMRI

Svenja Küchenhoff, Mohamady El-Gabay, Jacob Bakermans, Alon Baram and Timothy E. J. Behrens

We use regularities to understand the world. To behave in a meaningful way, our brain builds on the structure of the environment and of our own actions. Structural knowledge about the world is stored in cellular representations in the entorhinal cortex and hippocampus, for example in place cells and grid cells. Additionally, recent single-cell recordings in rodents have provided a novel mechanism of how populations of cells in the prefrontal cortex support one's own schematic behaviour. We propose that the brain makes use of the structural representations in the medial temporal lobe to then construct representations for current and future schematic behaviour in the prefrontal cortex. Here, we conducted an experiment which serves as a direct mirror to a rodent experiment which first extracted this algorithmic code. Using high-field neuroimaging in humans, we attempt to detect structural coding principles across the whole brain and their interaction when humans are solving a spatial schema task or are told to spontaneously adapt to a changed schema. To bridge from rodent electrophysiology to human neuroimaging, we are making use of a computational model that has been validated in rodent single-cell data. By using representational similarity analysis, we are showing that medial prefrontal cortex represents algorithmic activations for future actions, analogous to the rodent results. We furthermore find orbitofrontal cortex to be particularly sensitive to actions relating to future rewards within the schema task. Our findings suggest that prefrontal cortex capitalises on structural building blocks represented in the medial temporal lobe, and combined with task progress tracking, supports complex schematic behaviour with action plans.

Orbitofrontal Noradrenaline as a Facilitator of Behavioral Flexibility

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Effective decision-making in dynamic environments requires continuous monitoring and updating of internal representations. The Orbitofrontal cortex (OFC) is believed to represent structural information about tasks or the environment which must be updated to promote behavioral change. Emerging findings point to the Locus Coeruleus (LC), the main source of Noradrenaline (NA) in the brain, as a potential modulator of the OFC, to enable behavioral flexibility. In the current work, we aim to dissect how the OFC and LC:OFC projections promote adaptability using a sequential probabilistic reversal learning task. The stochastic nature of this task allows us to investigate how animals integrate information over multiple trials, offering insights into trial-by-trial adaptation based on choice-outcome history. Using a combination of anatomical tracing, causal interventions, and correlative approaches, we investigate the mechanisms that underlie LC-OFC-dependent modulation of behavioral flexibility. First, we found that chemogenetic inhibition of the OFC resulted in an impaired ability to shift from a previously unrewarded lever. Subsequently, employing a genetically encoded fluorescent sensor, GRAB_NE1m, coupled with fiber photometry for rapid and specific detection of NA in vivo, we recorded NA release within the OFC. We found that NA release was modulated by trials' outcomes and choice-outcome history. Additionally, these NA dynamics following unrewarded trials correlated with an increased shifting behavior at the time of reversals. Finally, we assessed the impact of chemogenetic modulation of the LC:OFC projections in reversal learning by employing a pair of CaV2 viruses enabling the expression of either excitatory (hM3Dq) or inhibitory (hM4Di) DREADDs under a PRS promoter specifically targeting NA neurons. While LC:OFC inhibition impaired rats' ability to shift from the Low-probability lever following unrewarded trials, specifically at the time of reversal of contingencies, LC:OFC excitation yielded the opposite effect. Altogether, these results indicate that NA inputs to the OFC might be required to facilitate abandoning a formerly profitable option to explore new ones upon violation of prior expectations to promote adaptation.

Linking Causes and Consequences: The Role Orbitofrontal Cortex in Model-Based Credit Assignment

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Humans are remarkably adept at pursuing goal-directed behavior in complex and dynamic environments. Adaptive behavior in these contexts requires the ability to link causal actions to outcomes by leveraging knowledge of the underlying task structure, a process known as model-based credit assignment (MBCA). However, the neural mechanisms supporting MBCA remain largely unclear. One possibility is that orbitofrontal cortex (OFC) represents information about causal actions when their consequences are observed, allowing the brain to forge links between actions and outcomes. Here, we test whether the OFC contains representations of previous choices when outcomes are observed, and whether these credit assignment signals follow the task's causal structure. Participants completed a learning task that required tracking of choice-outcome contingencies in one of two conditions. In the "direct transition" condition, participants saw the outcome of a choice after a short delay. In the "indirect transition" condition participants saw the outcome of a choice only after making the next choice, meaning that credit assignment for that action must be kept pending until the correct outcome is observed. Using multivoxel pattern analysis, we show that MBCA in both conditions is supported by a network of regions including OFC (pTFCE < .05 ROI corrected) and hippocampus (pTFCE < .05 ROI corrected) which reinstated representations of the causal choice identity at feedback. Importantly, we show that in "indirect transitions", the frontal pole maintains information about the causal

choice in a pending state during the interim feedback period (pTFCE < .05 ROI corrected). Moreover, the fidelity of these representations predicts MBCA in the OFC at feedback (pTFCE < 0.05 ROI corrected). These results highlight the importance of the OFC in creating relational knowledge about states in the environment and present novel evidence of coordination between neuro-cognitive systems during learning.

Listen to yourself: How motivational interviewing shifts food choices and craving-related brain responses to healthier options

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Background: Changing dietary patterns is challenging and Motivational interviewing (MI) has been proposed to overcome this challenge. MI seeks to strengthen motivation to a specific goal by eliciting statements for change, i.e. change talk (CT), and handling reasons against change, i.e., sustain talk (ST). Despite prior evidence of the influence of change talk (CT) on neural responses, the implications of this neurocognitive shift at both behavioural and neural levels remain unclear. This study explores value-based decision-making and the neurobiological craving signature (NCS) in relation to talk type. Methods: Women (BMI<30kg/m2) were invited to participate in two visits one-week apart: visit 1 to undergo a MI session from which five change and sustain talk statements were selected; and visit 2 to undergo a fMRI session focused on a dietary decision-making task. At the behavioural level, linear mixed-effects models tested whether food valuation differed as a function of the type of talk and food attribute, and a general linear model studied how food attributes were weighted during dietary choices. At the brain level, multilevel general linear models (GLM) were fit to fMRI time series to detect the encoding of: 1) food valuation, and 2) healthiness as a function of the type of talk. Additionally, NCS responses were measured in relation to healthy food valuation. Results: We found that following CT, compared to ST, participants' food choices and activity in the ventromedial prefrontal cortex were more driven by the healthiness and less by the tastiness of food (behaviour: $p<0.001$, Cohen's $d=0.7$; brain: MNIpeak: =-8, 46, -8, small volume correction, $pFWE<0.05$). These findings were paralleled by lower NCS responses to tasty food after CT compared to ST ($p=0.03$, Cohen's d =-0.35). Conclusions and implications: These results show that MI can shift value-based decision-making and reduce craving-related brain marker responses to highly palatable food items.

Neural representations of flexible cognitive maps in the Orbitofrontal Cortex and Hippocampus

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The concept of 'cognitive maps' is a useful framework to think about how the brain may form neural representations of everyday experiences. Cognitive maps are posited to represent the possible options or 'states' currently available (e.g. the distribution of cards and players in a boardgame), as well as the possible transitions from one state to another (e.g. the rules of the game). This knowledge about available states and transitions can then be used for inference, to form predictions about the future, to generalize, and guide decision making. In recent years, both the Hippocampus (HPC) and the Orbitofrontal Cortex (OFC) have been posited to be part of the network supporting such cognitive maps. Many parallels have been drawn in the content of said cognitive maps in the two regions: from purely sensory associations (e.g. spatial relations, sensory preconditioning) to more abstract representations (e.g. reward coding, nonspatial task states). We hypothesize that the two regions likely operate in a feedback loop to keep the right balance between a representation of the sensory specificities of the environment and a sensory-independent representation of the rules guiding said environment, including hidden or partially observable states (e.g. past choices). This balance is then shifted by experience and task demands, supporting flexible cognitive maps and decision making. To gather evidence for our hypothesis, we designed a task during which previously behaviorally irrelevant stimuli suddenly gate outcome magnitude in an odor-discrimination task. We recorded extracellular signal in the HPC and OFC of rats before, during and after this change. We predict that the content of cognitive maps in the HPC and OFC is updated to incorporate this feature as the rats learn about the behavioral relevance of this stimulus. We expect to see increased synchronization between the OFC and HPC during learning and the reorganization of the cognitive map, but not steady-state behavior.

Study OFC Function in Irritability Using a New Mouse Frustrative Nonreward Paradigm

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Irritability, defined as a proneness to anger upon little provocation, is a core feature of Disruptive Mood Dysregulation Disorder and cuts across several psychiatric disorders. It causes long-lasting adverse outcomes in youths. Limited clinical tools are available to manage irritability and the underlying brain science is in its infancy. This study interrogated the brain regions and neural circuits mediating irritability-like behavior in mice. We first developed a mouse behavioral paradigm for irritability using frustrative nonreward (FNR), a pathophysiological model for irritability, as the conceptual framework. This paradigm induces frustration by withholding expected rewards. It is quickly learned and easily performed by young mice. We then cleared and stained the brain for cFos to identify brain regions responsive to FNR. After the frustration session, both male and female mice increase locomotion and aggression. Anxiety- and depression-like behaviors, however, are unchanged. Of the 562 analyzed brain regions, 43 including the orbitofrontal cortex (OFC) are activated by FNR. Many of them are involved in negative emotions, aggression, and motor impulsivity. The imaging data are consistent with the human fMRI studies. We further recorded local field potentials in OFC before, during, and after the FNR session to study its role in FNR-induced behavioral changes. Our study demonstrates that our frustration paradigm induces hyperactivity and aggression escalation, the behavior associated with irritability in humans, and recapitulates some human fMRI findings. Further investigations with this paradigm can facilitate the search for neural mechanisms and novel treatments for irritability.

Adolescent neurodevelopment supports the emergence of adaptive generalization during value-based decision-making

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Adolescence provides a window of opportunity for learning. As adolescents encounter new experiences, they develop a richer understanding of the world around them. How do adolescents integrate this expanding knowledge to make good and bad decisions? To test this, we tasked participants (N=83) aged 11-25 with making value-based decisions while undergoing fMRI scanning. Participants chose between pairs of objects for the chance to receive a monetary reward. Objects were sampled from 32 distinct categories which were, on average, worth different amounts of reward, allowing participants to learn a latent category value structure. We tested whether individuals generalized category value to guide decisions when they were presented with novel objects from previously learned categories. To index explicit awareness of the category value structure, participants reported category values after learning. Because retrieving and updating category knowledge relies on cortical systems that continue to mature during adolescence, we hypothesized that flexible category generalization would emerge with age. We found that younger adolescents were less likely to use category value to guide decision making. However, generalization increased with age, and older adolescents and adults were more likely to generalize category value. Although younger adolescents did not apply category value to guide decisions, they still reported explicit awareness of the category values following the task. For adults, vmPFC activity parametrically tracked choice value, but this was not the case for adolescents. Together, these findings demonstrate that younger adolescents experience a knowledge-behavior gap: they can explicitly express value knowledge but don't apply it to guide value-based decision making. This developmental difference may reflect the late maturation of cortical circuitry, which supports the emergence of adaptive decision-making during adolescence.

Selective Disruption of Target Value and Target Location Signals in Primate Orbitofrontal Cortex: Effects on Binary Choice

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During economic decision-making, the primate orbitofrontal cortex (OFC) encodes multiple variables, including the value and location of decision targets. While the role of value signals is well-characterized, the role of target location signals is unclear. Here, we compared the role of these signals by selectively disrupting them with the electrical microstimulation of the OFC.One monkey performed a two-alternative value-based decision task (Lupkin and McGinty, 2023, eLife) while brief stimulation trains were delivered to the left posterior OFC. The aim was to disrupt neural activity concurrent with the encoding of target value or location in separate sessions. To disrupt value signals, stimulation was delivered 200ms after the monkey viewed either the first or second target in each trial. Likewise, to disrupt target location signals, we stimulated 65ms after the first target was initially shown.Consistent with previous studies, stimulation following fixation onto the first target (when its value was encoded) decreased the monkey's probability of choosing the first target, consistent with a decrease in its subjective value (Ballesta, Conen, and Padoa-Schioppa, 2020). Interestingly, stimulation disrupting the target location signal increased the probability of choosing the first target, consistent with an increase in subjective value - showing the opposite effect as stimulation during the value-encoding epoch. This was unexpected, given that in this epoch value signals were not yet evident in OFC. In a follow-up analysis of OFC neural recordings, we found that target location signals did not predict variability in the monkey's choices (unlike value signals measured from the same data, McGinty and Lupkin, 2023, Nat. Neuro.) These preliminary results suggest the possibility of a causal role for offer location signals in OFC in economic choice; however, the nature of the downstream read-out of these location signals remains unclear.

Roles of the orbitofrontal cortex in human emotion, depression, and memory

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The human orbitofrontal cortex is a key brain region in emotion (Rolls 2023) and depression (Zhang, Rolls et al 2024). The human orbitofrontal cortex is also important in episodic memory, with its effective and functional connectivity showing how it introduces reward value inputs into the hippocampal memory system (Rolls et al 2023). During recall, this value component involving the orbitofrontal cortex is likely to be important in memory consolidation by representing the reward value of the recalled memory (Rolls 2022). The human orbitofrontal cortex also has connectivity to the cholinergic neurons in the basal forebrain and septal region, and this route is also implicated in the control of memory consolidation by the orbitofrontal cortex (Rolls 2022). New fMRI findings will also be described showing how the human orbitofrontal cortex and hippocampus communicate during the storage and recall of reward-spatial location episodic memory, which is fundamental to remembering where rewards are in the world.

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Midbrain signaling of identity prediction errors depends on orbitofrontal cortex networks

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Previous work has shown that the lateral orbitofrontal cortex (OFC) represents expectations about the identity of rewards and that the dopaminergic midbrain responds to reward identity prediction errors (iPE, i.e., value-matched violations of identity expectations). We hypothesized that the lateral OFC directly contributes to the computation of iPEs in the midbrain by signaling reward expectations. To test this, we used network-targeted transcranial magnetic stimulation (TMS) to modulate activity in the lateral OFC network. Healthy human subjects (N=31, 11 males) performed a trans-reinforcer reversal learning task during functional magnetic resonance imaging (fMRI) in two sessions (order counterbalanced); once after sham stimulation and once after continuous theta burst stimulation (cTBS). Stimulation coordinates in the lateral prefrontal cortex (LPFC) were individually selected based on maximal resting-state fMRI connectivity with the lateral OFC. Subjects learned associations between visual cues and equally-valued food odor rewards. Unpredictably, these associations were reversed multiple times, eliciting iPEs. Functional connectivity between the lateral OFC and the rest of the brain was significantly reduced after cTBS relative to sham in the first block of the experiment. Relative to sham, cTBS impaired behavioral performance in the first block of the task and disrupted expected reward identity representations in the lateral OFC. Importantly, fMRI responses to iPEs in the midbrain were significantly modulated by OFC-network targeted cTBS relative to sham. These results suggest that neural representations of expected outcome identity in the lateral OFC directly contribute to signaling of iPEs in the midbrain, presumably by providing the predictions necessary for computing the error signal. Taken together, our findings support a model in which midbrain iPEs are generated by comparing incoming sensory information with identity expectations represented in the OFC.

The encoding of economic decision variables in OFC is longitudinally stable and varies by cortical layer

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Economic choices entail computing the values of different options; a decision is then made by comparing values. Work in primates and rodents has shown that these mental processes rely on the orbitofrontal cortex (OFC). Neurophysiology studies identified distinct groups of neurons encoding the value of individual options, the binary choice outcome, and the chosen value. These variables capture both the input and the output of the choice process, suggesting that the cell groups identified in OFC constitute the building blocks of a decision circuit. A primary challenge is to assess the structure and mechanisms governing this circuit. One aspect of this broad issue is whether the circuit is longitudinally stable. Another aspect is whether different cell groups are differentially distributed across cortical layers. We addressed these questions using two-photon calcium imaging. Head-fixed mice chose between two juice types (represented by different odors) offered in variable quantities. Confirming neurophysiology results, different groups of cells encoded individual offer values, the spatial configuration, the choice outcome, and the chosen value. We recorded from individual neurons for up to 20 weeks. For each cell and each pair of sessions, we compared the activity profiles and the encoded variables. We found a high degree of stability in the activity profiles and in the functional properties of individual cells. For each cell, we also identified the cortical layer (L2/3 or L5; OFC lacks L4). Notably, L2/3 is the primary input layer, while output from OFC originates from L2/3 and L5. Remarkably, L2/3 and L5 differed for the distribution of encoded variables. Cells encoding the offer values were over-represented in L2/3, while cells encoding the choice outcome were over-represented in L5. Thus the anatomical distribution across layers concords with computational considerations. These results lay the ground to further dissect the mechanisms underlying economic decisions.

Cracking and packing information about the features of expected rewards in the orbitofrontal cortex

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The orbitofrontal cortex (OFC) is important for tracking features of expected outcomes, including their size, timing, and unique sensory features. This information plays a role in guiding our choices and also supports learning when actual outcomes diverge from these expectations through its influence on dopaminergic prediction errors. Previously we have reported that the effects of reward timing and size on activity in single units in OFC were dissociable, with largely separable populations of neurons responding to one or the other variable, in an odor-guided choice task in which they were manipulated independently (Roesch et al, Neuron, 2006). Here we asked a similar question with regard to information about the timing and identity of an expected reward, in the same choice task however under conditions in which changes in timing were sometimes confounded with changes in identity. Specifically in some blocks, when the timing of the reward changed, its flavor also changed, as if a different reward was being delivered, where as in other blocks, the timing changed but the flavor remained the same, as if a single reward was being moved. We again found significant numbers of OFC neurons that fired differentially to immediate versus delayed reward and also to the different reward flavors. However, in contrast to prior findings, under these conditions we found that encoding of reward timing was strongly correlated with selectivity for reward identity. That is, when reward features are correlated, OFC tends to "pack" them into unitary constructs, whereas when they are independent, OFC tends to "crack" them into separate constructs. In addition to this result, we also found that when both reward timing and identity changed, some OFC neurons initially showed unique activity leading up to and during the missing reward, differences that were not evident when only timing changed. Notably these patterns were complementary to differences in dopaminergic error signaling at

The common root of creativity-related preferences across domains.

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Decision-making is a daily and necessary practice for human beings, and creative decision-making is one of them. Previous research on creativity has proposed a breakdown of creative ideation into two main processes: a generative phase for spontaneous idea associations and an evaluative phase for monitoring these ideas. During the evaluation stage, ideas are judged based on their adequacy and originality, two defining dimensions of creativity. Recent findings decompose the evaluation phase into monitoring and valuation. The subjective value of ideas (valuation) was found to be computed based on their adequacy and originality (monitoring). The aim of the current study is to ascertain the consistency of preferences across diverse creativity domains. To achieve this, seventy-three participants engaged in free-generation tasks across three creativity domains: semantic associations, alternative uses, and drawings. Subsequently, they rated their responses based on likability (subjective value measurement) and perceived adequacy and originality. Participants tended to provide ideas more rapidly when they liked them more across all three domains. This result emphasizes the motivational role of valuation in the creative process. Furthermore, across these domains, the likability of ideas stemmed from a combination of their adequacy and originality. Through computational modelling, we established that a similar non-linear value function, with consistent weighting and convexity parameters across domains, governed ideas' judgments. These findings reflect both the inherent nature of the valuation process observed in value-based decisions and contribute to consolidating our understanding of creative ideation.

Opposite gradients of mental imagery and perception in human orbitofrontal and occipitotemporal cortex

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How do distinct domain-preferring cortical regions contribute to the subjective experience of visual mental imagery and visual perception? We systematically examined the role of face- and color-preferring cortical patches using millimeter-scale 7T fMRI. We identified bilateral face- and color-preferring patches, adjacent to each other and distributed along a posterior-anterior axis from occipitotemporal to orbitofrontal cortex, where the face patches were always located lateral to color patches. From posterior to anterior patches, imagery and perception recruited similar increasing gradients of domain-selectivity and representation which correlated with subjective ratings of face identities, face shapes, and visual colors, but opposite gradients of activity amplitude and functional connectivity, with orbitofrontal patches located near the peak of top-down processes. Aphantasic individuals reporting no imagery experience showed decreased imagery representations in orbitofrontal cortex, and reduced amplitude of orbitofrontal activity and orbitofrontal-temporal connectivity in both modalities. Thus, perceptual and imagery processes share similar representations in domain-preferring cortical patches, but exhibit opposite caudo-rostral gradients of activity. Activity of the orbitofrontal cortex contributes to conscious visual experience.

Impairments in orbitofrontal function caused by hippocampal perineuronal net degradation can be ameliorated with orbitofrontal dopamine manipulation

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Human neuroimaging, and rodent models of Schizophrenia implicate both anterior hippocampus (aHipp) overactivity and prefrontal dysfunction in cognitive symptoms which are poorly treated with current antipsychotics. In rodents, hippocampal perineuronal net (PNN) degradation induces subcortical schizophrenia-like changes leading to the hypothesis that degrading aHipp PNNs in marmoset monkeys will allow us to probe associated prefrontal changes, bridging the gap between rodent and human studies. Following aHipp PNN degradation (deg), marmosets are impaired at probabilistic discrimination learning (known to depend on orbitofrontal-striatal circuitry) and microdialysis of the OFC reveals significant increases in dopamine (DA) and noradrenaline (NA), and a reduction in glutamate (Glu). To identify how these individual neurochemical changes contributed to the behavioural impairment we used a daily probabilistic (80:20) reversal task consisting of one discrimination and one reversal stage to probe OFC function following aHipp PNN deg alongside chemical challenges to the OFC (area 11) targeting DA (Quinpirole [1 and 3ug]; SCH23390 [0.1 and 1ug]), NA (Prazosin [0.3 and 1ug]; Yohimbine [0.3 and 1ug]) and Glu (CGP52432/LY341495 both 1ng) systems. Preliminary data reveals aHipp PNN deg caused an impairment on the reversal component of the task that was ameliorated by the actions of OFC DA, but not NA or Glu, manipulation. Specifically, OFC Quinpirole (D2/3 agonist), but not SCH23390 (D1 antagonist) reverses the impact of aHipp PNN deg on reversal performance. The finding that a D2 agonist improves behaviour is interesting given most current antipsychotics are D2 antagonists, suggesting a potential mechanism for why they fail to treat the cognitive symptoms. Overall, marmoset aHipp PNN deg causes behavioural and neurochemical changes relevant to schizophrenia and provides a translational model for understanding how individual changes can be therapeutically targeted.

Task space revisited: human medial OFC's role in performance monitoring

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Orbitofrontal cortex is well known for its involvement in decision making and goal-directed behavior, mostly tested in reinforcement learning (RL) settings. OFC's role in executive functioning is less well understood. Here we investigated how human OFC contributes to performance monitoring of internal error signals and externally cued task switches in a visual attention paradigm. 33 human participants performed a color-orientation-interference task while undergoing functional magnetic resonance imaging (fMRI). The task required speeded button presses corresponding to either the color of a filled circle or to the orientation of an overlayed compass needle. In each run, 75% of trials matched the previously cued dimension whereas 25% per run were task switches. No incentive for nor feedback about correct task responses were provided. We still found increased medial OFC activity for errors and correct task switches compared to correct trials. Moreover, medial OFC activity was significantly more enhanced after errors than after correct switches indicating specific upregulation when incorrect performance was detected. In conclusion, human OFC seems to encode task space not only in the context of RL-based cue-outcome associations but to monitor the outcomes of behavior more broadly.

Advantage Race Diffusion mechanism to study the dissociated roles of Orbitofrontal Cortex subregions in instrumental learning

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The orbitofrontal cortex (OFC) is found to be one of the crucial regions in the prefrontal cortex (PFC) involved in decision-making and instrumental learning, influencing the downstream processes in the subcortical regions. However, the exact mechanisms through which the OFC encodes, or processes information related to decision-making and learning are unclear. Specifically, several lesion studies have shown that two sub-regions of the OFC – lateral OFC and the medial OFC (ventromedial PFC) – have differential roles in the process of instrumental learning in the context of multi-alternative choice. Here, we propose a multi-alternative decision-making model with reward-based learning using evidence accumulation models (EAMs) of decision making and reinforcement learning (RL) models of error-driven learning. More specifically, we use a variation of drift diffusion models (DDM) based on an Advantage Race Diffusion (ARD) framework for choices among two or more options, that captures stimulus difficulty, speed-accuracy trade-off, and stimulus-response-mapping reversal effects (RL-ARD). It is specifically on these aspects of instrumental learning that lateral and medial OFC have been shown to play complementary roles. Unlike DDMs which strongly depend on the accumulation of the evidence difference alone, the ARD based accumulators are driven by both difference and sum of the mean reward expectancies. We studied if the differential contribution of sum and difference of reward expectancies in the RL-ARD model can help explain the roles of lateral and medial OFC in the process of decision-making and learning. We tested the model on a 3-arm bandit task with varying reward probabilities. We simulated lesions of lateral and medial OFC structures in the model and showed differential effects in performance depending on the value difference of the presented options, thus accounting for recent experimental findings about the dissociate functional roles of both the sub-regions.

Do glitches in the OFC neural code explain irrational choices? A neuro-computational approach to value synthesis

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The orbitofrontal cortex (OFC) is known to play a key role in integrating environmental features and signaling value. However, the functional contribution of OFC neurons to value-related computations is still unclear. For example, the OFC may be operating the comparison of options' values for decision making. But another possibility is that OFC neurons are integrating value-relevant features into value estimates, leaving their comparison for downstream decision circuits. This distinction is important, because imperfections in the underlying neural system architectures would yield different forms of irrational behavior. We trained recurrent neural networks (RNNs) to perform either value construction or value comparison, under the constraint that options' features are sampled progressively in time. For both scenarii, we considered different value coding frames, in terms of options spatial position (left/right), temporal order (first/second) or attentional focus (attended/unattended). We then compared their neural signatures to electrophysiological data recorded by Hunt et al. (2018) in the OFC of two macaque monkeys during a binary decision task. We found that key OFC representational geometry properties could emerge under both functional scenarii, but only in specific value coding frames. Furthermore, when disrupting the RNNs' feedback connections to explain monkeys' irrational choices, the representational geometry of RNNs becomes even more similar to that of OFC neurons. Interestingly, the ensuing sparsity of neural representations increases, while the amount of energy used by the units decreases. This suggests that some forms of irrational behavior may result from sparsity and energy budget constraints on the OFC neural code.

Frontal Theta signals Contextual Switches during Flexible Human Tactile Learning

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Adapting one's decisions to changing contexts is a critical component of flexible behaviour. We recently identified that the orbitofrontal cortex plays an important role in signalling contextual switches in human tactile reversal learning. However, the neurobiological mechanisms that underlie such signals during behavioural flexibility remain unclear. To investigate this, we designed a probabilistic tactile 'Go/No-go' reversal learning task and simultaneously recorded brain-wide EEG responses from healthy participants. Participants first learned to associate specific braille stimuli with 'Go' or 'No-go' responses and re-leant the task following a rule-switch. To understand the distinct strategies subjects employ to learn the task, we constructed a Bayesian evidence accumulation model. The rule-switch caused an increase in the 'win-stay' strategy following 'false' rewards (rewards from incorrect decisions), whereas the 'lose-shift' strategy following 'true' errors' decreased. Additionally, participants used 'win-stay' strategy more following immediately preceding 'true' rewards compared to accumulated 'true' rewards in recent history. We used event-related potential (ERP) analysis of the EEG responses to investigate rule-specific neural responses and employed imaginary phase locking value (IPLV) analysis to assess context-dependent connectivity changes across brain areas. We observed significant differences in the ERP of 'false' and 'true' rewards preceding a 'win-stay' decision, evidencing context-tracking mechanisms in frontal areas. IPLV analysis revealed dissociated changes in reward- and error-trial-related theta synchronisation between frontal (the dorsolateral prefrontal cortex), parietal, and lateral sensory areas following a rule-switch. These results suggest that frontal areas differentially use theta signals following reward and error feedback to broadcast contextual switches to downstream brain areas.

Orbitofrontal cortical contributions to behavioural strategies during tactile reversal learning

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Animals continuously evaluate past and current sensory and contextual information to make appropriate decisions during behaviour. How animals employ specific behavioural strategies while learning a task and how the orbitofrontal cortex (OFC) contributes to such strategy-based learning remains understudied. To investigate this, we trained mice on a tactile reversal learning task and implemented a trial-resolution Bayesian evidence accumulation model to measure the probability of the strategies used. We analysed multiple exploratory strategies across key task-learning phases and subsequently after rule reversal. During initial task learning, mice gradually switched from choice-driven strategies (e.g., 'hit-stay-choice') to cue-driven strategies (e.g., 'hit-stay-cue'). Following the rule switch, mice reused a cue-driven strategy for reward-guided exploration. Mice did not rely on one exclusive strategy but adjusted the use of relevant strategies dependent on task phases. Silencing lateral OFC (lOFC) resulted in delayed choice-to-cue transition and impairments in behavioural flexibility. To study the contributions of orbitofrontal signalling in updating behavioural strategy representations to relevant sensory areas, we additionally measured functional responses from excitatory layer 2/3 neurons in the primary somatosensory cortex (S1) using two-photon Ca2+ imaging. Using tensor component analysis and a novel method of temporal decoding, we revealed that history-dependent processes for cue-driven strategies were decoded during learning across mice. lOFC silencing resulted in a reduction of encoding, highlighting its critical contribution to guiding behaviour. Our study revealed how animals employ distinct exploratory strategies during flexible behaviour and highlighted the role of lOFC in leveraging prior knowledge supporting reward and error-guided learning.

Impact of the sulcal pattern variability on the distribution of cytoarchitectonic areas in the medial prefrontal cortex in macaques

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The Medial Prefrontal Cortex (mPFC) plays an important role in reward and error monitoring and in behavioural adaption. This heterogenous region is composed of multiple cortical areas, but their specific functions remain debated. As the structural properties of a brain region constrain the computations it could support, it is crucial to understand its organization. We hypothesize that a better grasp on the impact of the interindividual structural variability in the mPFC on the distribution of cytoarchitectonic areas will help interpreting results of MRI and electrophysiological studies in rhesus macaques. Based on recent studies on the sulcal pattern variability of the mPFC (Amiez et al. 2019; Lopez-Persem et al. 2019), we investigated the link between 4 different sulci, namely the Dorsal Extension (CGS-DE) or a Ventral Extension (CGS-VE) of the cingulate sulcus, the Rostral Sulcus (ROS-S) and the Accessory Supraorbital Sulcus (ASOS) to better understand the link between cytoarchitecture and sulci. Preliminary results have shown that i) ROS-S is not a boundary between areas 14m and 32 as previously suggested ii) CGS-DE is limiting between the area 10 and the area 9 and iii) The Accessory Supra Orbital Sulcus (ASOS) is an axial sulcus of area 10.

Friend Request Accepted: Fundamental Features of Social Environments Determine Rate of Social Affiliation

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Humans start new friendships and social connections throughout their lives, and it has been consistently found that such relationships lead to mental and physical well-being. In the present study, we investigate the behavioural and neural mechanisms governing our decisions to initiate friendships with other people. We examine whether such decisions are influenced by the friendliness, i.e., the social reward rate, and the density, i.e., the rate of opportunities, afforded by the environment. In a computer based online task (n=783), we found that people were more likely to send friend requests in friendly and sparse environments in comparison to hostile and dense environments. Further, we found task-related measures like overall friend requests correlate with personality-related factors like social thriving. Next, in a 7T fMRI study (n=24), we found that subcortical regions like the dorsal raphe nucleus and the hypothalamus represent density and outcome effects whereas the lateral habenula represents friendliness effects. We also found cortical regions like the anterior insula/posterior orbitofrontal cortex and dorsomedial prefrontal cortex represent both friendliness and density effects. Taken together, these findings suggest that the human brain takes background statistics of an environment into account while making social decisions and such decisions can be explained by personality or psychiatric factors.

Deep Transcranial Ultrasonic Brain Stimulation During Decision-Making in Changing Social-Emotional Environments

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Humans show incredible flexibility in responding to social-emotional cues. For example, depending on circumstances, they can overwrite automatic response tendencies (e.g., to approach and talk to a grumpy teenager) or adjust to changes in response demands (e.g., leave them alone when needed). Work using correlational techniques suggests that these two processes require interactions between cortical and subcortical regions, specifically the frontal pole and OFC, respectively, and amygdala. However, the causal role of these interactions remains unclear.

In this project, we aimed to provide causal evidence for the role of subcortical-cortical interactions, in particular the influence of the amygdala, in guiding flexible social-emotional responses. We used a novel non-invasive neurostimulation technique, transcranial ultrasonic stimulation (TUS), to causally modulate activity in the amygdala in healthy human participants.

Participants (n=12, data collection ongoing) underwent three TUS-fMRI sessions where they received offline TUS targeting bilateral amygdala, insula (control), or sham (counterbalanced). Based on prior work, offline TUS effects are expected to last 60 minutes. During this time, participants performed a cognitive task probing social-emotional flexibility in learning and overwriting automatic responses while we recorded 7T-fMRI.

Preliminary findings suggest that amygdala TUS influenced choice flexibility, as evidenced by higher switch rates to negative feedback, compared to sham. Additionally, amygdala TUS slowed responses for all trial types. Task fMRI analyses will examine BOLD responses in automatic (congruent) and controlled (incongruent) trials following amygdala vs sham sonication in the amygdala and its connected regions such as frontal pole and OFC.

In conclusion, by employing TUS, we provide causal evidence for the role of amygdala - prefrontal circuits in guiding flexible behaviour in response to emotional cues.

Neural timescales reflect functional processing in human cortico-subcortical networks

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Recent research has uncovered a structured hierarchy in the brain's intrinsic neural timescales (INTs), which measure the extent of autocorrelation in neural activity over time. This hierarchy is marked by shorter INTs in unimodal sensory areas and progressively longer INTs in higher-order transmodal regions, a pattern consistently observed across different imaging techniques and animal species. The hierarchical nature of INTs hints at an intrinsic organising principle central to brain function and is accompanied by evidence that their relevance extends beyond basic mechanistic function to potential implications in mental health. Yet, the precise role of varying INTs in neural processing remains to be fully understood.

Here, we use data from n=400 healthy participants from the Human Connectome Project (HCP) to explore a potential link between INTs and functional cognitive processes. We focus on INTs not only in cortical regions which have been the focus of previous investigations on neural timescales, but also consider INTs in sub-cortical regions given their important role in in healthy as well as dysfunctional cognitive processing in psychiatric illness.

We extracted INTs from cortical and subcortical regions of interest (ROIs) using resting-state functional magnetic resonance imaging (fMRI) data. Additionally, we applied factor analysis to questionnaire data and cognitive task performance scores of the same people to extract latent behavioural variables capturing functionally distinct dimensions, such as emotion regulation, somatic and sleep functions, and processing speed. Preliminary analyses indicate that autocorrelation timescales in distinct anatomical circuits, including the OFC, relate to specific functional processes across individuals. This suggests that intrinsic organising principles of neural circuits in functionally specialised networks may contribute towards normal and abnormal cognitive function.

Differential Contributions of Anterior Cingulate and Orbito-Frontal Cortex to action timing and its self-monitoring in rats

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Performance monitoring is a hallmark of cognition, typically studied in paradigms involving processing of external stimuli. However, whether and how animals monitor performance that originate from internal processing, such as temporally precise self-generated actions, remains unknown. To address that gap, we developed a task allowing to study inference of their own timing errors in rats. We then sought to understand which frontal cortical areas carry computations relevant to performance monitoring of internally-generated timing behavior. Rats self-reported temporal errors in their time production (TP) without any external feedback. They produced precise time intervals (>2.4s) by holding a lever and reporter their errors by betting on reward access in Short Error (SE) or Long Error (LE) ports, demonstrating error monitoring of self-generated actions. To investigate the neural bases underlying this ability, we inhibited either the orbitofrontal cortex (OFC), which carries confidence signals, or the anterior cingulate cortex (ACC), which carries error-dependent signals. Rats underwent training until they reached consistent error monitoring behavior. On alternating days, muscimol (GABAergic agonist) or saline was infused in OFC (n=11) and ACC group (n=10). Inhibiting the OFC impaired their ability to produce accurate time intervals. Conversely, for rats in the ACC group, timing performance was not impaired. Fitting the behavioral model showed an overestimation bias to judge their TP as longer under muscimol, suggesting a disruption of temporal error monitoring in ACC. In addition, we fitted several models investigating utilization of history of previous outcomes and learning from negative feedback, thereby uncovering a multitude of performance monitoring aspects inherent in the ACC. The finding of hierarchical and independent from time-keeping inference of temporal errors in the ACC offers valuable insight into timing and performance monitoring architectures.

Orbitofrontal noradrenaline acts as an early gate for reversal learning

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In a dynamic environment, organisms must continuously monitor the ongoing relationship between actions (A) and their specific outcomes (O) to guide their decision-making processes. Such flexible, goal-directed behavior is believed to rely on key neurotransmitters, like dopamine (DA) and noradrenaline (NA), and to be supported by the prefrontal cortex, with a high functional parcellation existing within different prefrontal subregions in rodents. For instance, we recently demonstrated that NA projections from the locus coeruleus (LC) to the ventral and lateral parts of the orbitofrontal cortex (OFC) are specifically required to update A-O contingencies following reversal in rats, with manipulation of DA transmission within the area or NA transmission in other prefrontal subregions (e.g. the medial prefrontal cortex) yielding no effect (Cerpa, Piccin et al. 2023). In here, we decided to investigate the spatiotemporal dynamics of OFC-NA during instrumental reversal learning using fiber photometry and a NA-specific sensor. We monitored OFC-NA activity during specific days of our task and observed increased NA transmission exclusively following unexpected reward deliveries on day 1 of reversal learning. Notably, the magnitude of such OFC-NA release acted as a positive predictor of the rats' performance, with faster learners displaying strong NA responses to reversal and slower learners clearly lacking this specific signaling. Next, we employed chemogenetics coupled with a NA-specific retrograde viral approach to test if inhibiting this predictive OFC-NA response at reward affected the pace of the behavioral adaptation. We found that silencing LC:OFC projections on day 1 of reversal learning indeed delayed the update of reversed A-O contingencies, thereby confirming the hypothesis of causality raised by fiber photometry recordings. Overall, the present results deepen our understanding of how NA signals uncertainty and point at the OFC as a key player integrating this messages to drive flexible behaviors.