Fourth Quadrennial Meeting on OFC Function

13-15 Nov 2019

Institute for Brain and Spine (ICM), Paris, France

Provisory Program

Wednesday, November 13, 2019

TIME	EVENT
09:10 - 09:30	Geoffrey Schoenbaum: Welcome and opening remarks
09:30 - 12:30	Session I - Chair: Mathias Pessiglione
09:30 - 09:50	Camillo Padoa-Schioppa - *Causal links between OFC activity and economic decisions*
09:50 - 10:10	Peter Rudebeck - *Reward identity and probability encoding in prefrontal-striatal-amygdala circuits*
10:10 - 10:30	Susanne Ahmari - T.B.A.
10:30 - 11:00	Coffee break (Poster room)
11:00 - 11:20	Lesley Fellows - *OFC contributions to discovering value*
11:20 - 11:40	Stephanie Groman - *Orbitofrontal circuits control multiple reinforcement-learning and addiction-relevant processes*
11:40 - 12:00	Mathias Pessiglione - T.B.A.
12:00 - 12:30	Discussion
12:30 - 15:00	Lunch out in Paris
15:00 - 18:00	Session II - Chair: Betsy Murray
15:00 - 15:20	Erin Rich - *Stable and dynamic representations of value in orbitofrontal cortex*
15:20 - 15:40	Christina Gremel - *Thalamic mechanisms supporting OFC-based value updating*
15:40 - 16:00	Vincent McGinty - *A population approach to choice prediction in the OFC*
16:00 - 16:30	Coffee break (Poster room)
16:30 - 16:50	Thorsten Kahnt - *Inference-based behavior depends on outcome-specific expectations in orbitofrontal cortex*
16:50 - 17:10	Erie Boorman - *Map Making: Constructing, Combining, and Navigating Abstract Cognitive Maps in the OFC*
17:10 - 17:30	Tianming Yang - *Orbitofrontal Cortex Plays A Limited Role in Value Computation During Decision Making*
17:30 - 18:00	Discussion
19:00 - 22:00	Social event (Zamansky Tower)

Thursday, November 14, 2019

TIME	EVENT
08:30 - 11:30	Session III - Chair: Jay Gottfried
08:30 - 08:50	John O'Doherty - *The construction of value: attribute-based value integration in orbital and medial prefrontal cortices.*
08:50 - 09:10	Alicia Izquierdo - *Orbitofrontal cortex in adjusting to changes in reward delay and probability*
09:10 - 09:30	Shauna Parkes - T.B.A.
09:30 - 10:00	Coffee break (Poster room)
10:00 - 10:20	Kate Wassum - *Corticolimbic circuitry in reward learning and pursuit*
10:20 - 10:40	Catharine Winstanley - *Cue-biased risky choice and the orbitofrontal cortex*
10:40 - 11:00	Miriam Klein-Flügge - *Multiple neural mechanisms of knowledge acquisition*
11:00 - 11:30	Discussion
11:30 - 14:00	Lunch and Posters (Poster room)
14:00 - 19:00	Free afternoon in Paris

Friday, November 15, 2019

TIME	EVENT
09:30 - 12:30	Session IV - Chair: Mehdi Khamassi
09:30 - 09:50	Steve Kennerley - T.B.A.
09:50 - 10:10	Lauren Atlas - *Orbitofrontal contributions to expectancy, learning, and pain*
10:10 - 10:30	Jay Gottfried - *What Tim Hath Wrought: Following Your Nose to Find Your Way*
10:30 - 11:00	Coffee break (Poster room)
11:00 - 11:20	Daniela Schiller - T.B.A.
11:20 - 11:40	Masayuki Matsumoto - *Value-to-choice signal transformation in midbrain dopamine neurons and orbitofrontal neurons during economic decision-making in monkeys*
11:40 - 12:00	Mehdi Khamassi - *Hippocampal replay and preplay through the lenses of model-based reinforcement learning*
12:00 - 12:30	Discussion
12:30 - 15:00	Lunch out in Paris
15:00 - 18:00	Session V - Chair: Matthew Shapiro
15:00 - 15:20	Matthew Shapiro - T.B.A.
15:20 - 15:40	Betsy Murray - T.B.A.
15:40 - 16:00	Joni Wallis - *Orbitofrontal-hippocampal interactions during reward-guided learning*
16:00 - 16:30	Coffee break (Poster room)
16:30 - 16:50	Alison Preston - *Hippocampal-prefrontal interactions support formation of cognitive maps that generalize across experiences*
16:50 - 17:10	Tim Behrens - *The Tolman-Eichenbaum Machine*
17:10 - 17:30	Yael Niv - T.B.A.
17:30 - 18:00	Discussion
18:00 - 18:05	Geoffrey Schoenbaum: Closing remarks

Speaker Abstracts

Camillo Padoa-Schioppa

Causal links between OFC activity and economic decisions

I will present the results of two experiments that established causal links between neuronal activity in OFC and economic decisions.

Peter Rudebeck

Reward identity and probability encoding in prefrontal-striatal-amygdala circuits

Optimal decision-making requires an understanding of the identity of the outcome, good or bad, big or small, that will follow a particular choice. It also requires an understanding of the probability of receiving that outcome. Both orbitofrontal (OFC) and ventrolateral prefrontal cortex (PFC) have been implicated in these decision processes, but their precise roles and the neural mechanisms engaged are unclear. Here I will describe experiments designed to provide mechanistic and circuit level understanding of how OFC and VLPFC represent outcome identity and probability information. We recorded neural activity within OFC, VLPFC and amygdala as well as parts of the striatum while monkeys chose between different visual stimuli predicted different outcomes, distinct fruit juices, at different probabilities. We show that VLPFC preferentially encodes reward probability, whereas outcome identity is encoded in to a similar degree in both OFC and VLPFC especially when monkeys exhibit a preference for a specific outcome. Recordings in amygdala suggest that VLPFC and amygdala form a functional circuit for computing reward probability during decision-making. Thus, our data provide mechanistic insight in how separate parts of ventral PFC represent different decision-related information, both of which are required for optimal decision-making.

Lesley Fellows

OFC contributions to discovering value

Even apparently simple choices, like selecting from a breakfast buffet, involve options characterized by multiple attributes. Orbitofrontal cortex (OFC) has been implicated in making optimal choices in the face of this complexity. However, the mechanisms involved remain unclear. I will present evidence from studies of people with focal damage affecting the OFC. These findings support the claim that OFC makes a necessary contribution to attending to and learning about potentially reward-predicting attributes of the environment, particularly under conditions of complexity: i.e. when the environment contains multiple candidate predictors, or when the reward contingencies are probabilistic. This region is also critical for making value judgments and value-based choices of complex, multi-attribute objects, notably when value is conferred by the relationships between attributes. Together, these findings point to a nuanced role for OFC in discovering and recognizing value under

conditions of environmental complexity. How these results might relate to object recognition in the ventral visual stream and relational mapping hippocampus will also be discussed.

Stephanie Groman

Orbitofrontal circuits control multiple reinforcement-learning and addiction-relevant processes

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2. Department of Neuroscience, Yale University
3. Department of Neuroscience, Johns Hopkins University

Introduction: There is evidence that some individuals are more susceptible to developing substance abuse disorder, which may be linked to neurobiological differences that are present prior to drug use. The identity of these differences, however, remains unknown because most investigations into addiction susceptibility mechanisms have been conducted in humans and/or animals exposed to drugs of abuse, which result in robust neurochemical alterations that likely overshadow the subtle, pre-existing variation mediating susceptibility. Our recent work, using computational approaches, has found that individual differences in reward-mediated updating of decisions are uniquely associated with future drug-taking behaviors, whereas decision-making deficits following drug self-administration are due to selective disruptions in the updating of choices following no reward outcome (Groman et al., 2019a). These data suggest that the neural circuits mediating addiction susceptibility may differ from those that are affected by chronic drug use. Here, we used a viral approach to investigate the function of anatomically-defined orbitofrontal circuits in reinforcement-learning and addiction-relevant behaviors in rats.

Methods: Adult, male rats (N=80) were trained to make decisions in a three-choice, probabilistically reinforced, reversal-learning task. Anatomically distinct orbitofrontal cortical (OFC) circuits were targeted by combining a floxed diphtheria toxin (DT) receptor virus with a retrograde Cre virus to selectively express DT receptors either in OFC neurons projecting to the nucleus accumbens (N=40) or amygdala neurons projecting to the OFC (N=40). Individual circuits were ablated by systemic administration of DT (30 ug/kg; i.p.). Decision making was reassessed in a subset of rats (N=40) to investigate the role of OFC circuits in computationally distinct reinforcement-learning processes. The remaining rats (N=40) were trained to self-administer methamphetamine (0.05 mg/kg/infusion) in 5 h, daily sessions for 30 days. Drug self-administration behaviors were then examined under probabilistically delivery of electric foot shocks and followed by tests of motivation and relapse-like behaviors.

Results: Ablation of OFC neurons projecting to the nucleus accumbens impaired decision-making processes by disrupting the use of negative outcomes to guide

subsequent choices ($p<0.001$) and lead to greater self-administration of methamphetamine only under punishment ($p<0.01$). Ablation of amygdala neurons projecting to the OFC also impaired decision-making, but this was due to a disruption in the use of positive outcomes to guide subsequent choices ($p<0.001$). Moreover, ablation of amygdala neurons projecting to the OFC resulted in greater levels of cue-induced reinstatement and responding under a progressive ratio schedule ($p<0.05$)

Conclusions: These data demonstrate that anatomically-defined OFC circuits – that are linked to different computational steps – are involved in distinct aspects of addiction-relevant behaviors. Our ongoing work is using viral approaches to investigate the circuit-specific signaling mechanisms that are linked to drug-taking behaviors in order to identify novel molecular targets for the prevention and treatment of addiction.

Erin Rich

Stable and dynamic representations of value in orbitofrontal cortex

The ability to associate positive and negative outcomes with predictive stimuli allows us to make optimal decisions. These stimulus-value associations are kept up to date by comparing an expected value with the experienced outcome, so that expected values must be held in mind when a stimulus and its outcome are separated by a delay. Little is known about the neural mechanisms that hold value representations online across delays, but temporarily remembering task-relevant information has been extensively studied in the context of item-specific working memory. Different hypotheses have suggested this ability requires either persistent or transient neuronal activity, with stable or dynamic representations respectively. To test these different hypotheses in the context of value representations, we analyzed the spiking activity of neurons in the orbitofrontal cortex while monkeys performed a task in which cues predicted rewards delivered after a short delay. Features of all hypotheses were simultaneously present in prefrontal activity. Thus, mixed dynamics supported robust, time invariant value representations while also encoding the information in a temporally specific manner. We posit that this hybrid coding might be a critical mechanism supporting flexible cognitive abilities.

Christina Gremel

Thalamic mechanisms supporting OFC-based value updating

The orbitofrontal cortex (OFC) supports the ability to update the value our decisions, however, the cell-type and circuit mechanisms supporting this computation are not clear. Thalamic projections to cortex have been hypothesized to support cortical computations, as well as provide sensory, and perhaps motivational, information. I will present findings from our investigations into the contribution of mediodorsal thalamic (MdT) inputs to OFC.

Previous works have shown OFC supports incentive learning, or the process through which motivational states assign value to the goals of our actions. We found chemogenetic attenuation of MdTOFC projections disrupts both the updating and inference of a value change. In vivo photometry of OFC projection neurons shows calcium transients increases during epochs of decision-making, but a notable decrease during consummatory processes. In contrast, calcium photometry of MdT terminals in OFC shows marked calcium transient increases reflecting learned associations or decisions predictive of reward proximity. Intriguingly, we also see increased calcium activity of MdT terminals in OFC during consummatory processes. This contrast between MdT terminal activity in OFC and OFC projection neuron activity led us to examine the functional role of MdT on OFC activity. Using whole-cell physiology, we found that MdT inputs into OFC support a disynaptic inhibitory gating of OFC projection neuron firing rate. The magnitude of this disynaptic inhibition appears greater in food-restricted than sated mice. This raises the hypothesis that MdT input into OFC may enforce precise spiking timing important for value-based computations. In support of this, optogenetic activation of MdT terminals in OFC specifically during consummatory processes necessary for value updating, increased the magnitude of incentive learning. Together, our data suggests a mechanism through with motivational state gates thalamic support of an OFC-based computation.

Vincent McGinty

A population approach to choice prediction in the OFC

A fundamental goal in neuroeconomics is to identify how neural representations of value relate to value-based decisions. Although the value-coding neurons of the primate orbitofrontal cortex (OFC) have long been scrutinized in this role, we still lack a complete understanding of their contribution to behavior. In particular, we do not fully understand choice prediction in the OFC: how variability in the neural representation of value co-varies with choice behavior on a trial-by-trial basis. In this talk, I will describe a population approach to choice prediction, leveraging the simultaneous activity of many OFC neurons recorded during the performance of a sequential two-alternative economic choice task. One key question that I will address is the predictive leverage afforded by the representations of economic goods per se, in comparison to other potential reference frames, such as the sequence of stimulus presentation.

Thorsten Kahnt

Inference-based behavior depends on outcome-specific expectations in orbitofrontal cortex

Research across species has shown that the orbitofrontal cortex (OFC) is critical for decision making. However, it is less clear what computations are carried out in this region that make it so important for this function. Recent work from our lab and others has suggested that the OFC signals expectations about specific outcomes. Here we present

evidence that these expectations are critical for behavior that is based on inferred or simulated outcomes, as opposed to behavior that can be based on direct experience alone. Specifically, we show that disrupting OFC activity using targeted transcranial magnetic stimulation selectively disrupts choices that require inference, without affecting value-based choices that can be based on direct experiences. Together these findings suggest that the OFC contributes to adaptive decision making by representing a model or cognitive map of the task environment that allows individuals to infer or simulate the value of future outcomes when direct experience is lacking.

Tianming Yang

Orbitofrontal Cortex Plays A Limited Role in Value Computation During Decision Making

During value-based decision making, the value associated with each option is computed and compared. It has been suggested that the orbitofrontal cortex (OFC) plays important roles in this process and produces decisions. We examined the representation of reward value in the OFC during decision making in macaque monkeys with a probabilistic reasoning task. In this task, the monkeys had to make decisions by computing the reward probability associated with each option by accumulating evidence from sequentially presented visual stimuli. We found that the OFC neurons encoded the reward probability associated with individual visual stimuli. However, this representation of reward probability in the OFC was transient and disappeared with the offset of each visual stimulus. The OFC neuronal activity did not reflect the process of reward information accumulation during decision making. Our results indicated that the OFC plays a more limited role in value-based decision making than previously suggested.

John P. O'Doherty

The construction of value: attribute-based value integration in orbital and medial prefrontal cortices.

A core notion in economics and psychology is that animals and humans assign value to stimuli in the world and use this information to guide their behavior. Over the past 15 years, we have obtained evidence from numerous neuroeconomics studies that value is encoded in the brain, for diverse kinds of stimuli, tasks and contexts. Value signals have been found in medial orbital, adjacent medial prefrontal cortex and elsewhere in the human brain not only for the prospect or receipt of monetary rewards, but also for food, prospective romantic partners, attractive faces, and even for the aesthetic appreciation of art. However, a fundamental question remains: how are these value signals actually constructed by the brain? Here I will review a series of studies aimed at addressing how value signals are constructed by integrating over underlying attributes from which a given stimulus is composed. I will show that across multiple stimulus types, including food stimuli, art, good bundles and even strategies for exploration, integration of attributes occurs leading to an overall value computation in the medial prefrontal cortex. These findings suggest a

hierarchical process of value-integration in which features of increasing complexity are combined as one transitions from feature-space into value-space.

Alicia Izquierdo

Orbitofrontal cortex in adjusting to changes in reward delay and probability

Neural activity in rodent or nonhuman primate orbitofrontal cortex (OFC) signals both stimulus value and an expected range of possibilities for reward, or risk. These neural responses update following changes in value and are modulated by reward history. Previously we found that rat ventromedial OFC is causally involved in building expectations about the range of expected delays-to-reward acquired over longitudinal experience (Stolyarova & Izquierdo, 2017). Intriguingly, recent studies show that monkey OFC may not integrate different reward attributes (i.e. delay, probability), but may instead maintain orthogonal representations of these attributes (Yang and Murray, 2018) for integration elsewhere. Inspired by this evidence, we ask the following questions: i) are there common mechanisms by which OFC learns/adjusts to changes in probability vs. delay attributes? and ii) is there specialization for this in rat OFC, or does another region in rat frontal cortex (i.e. anterior cingulate cortex, ACC) perform a similar function? In this talk I will review results from different experiments in our lab aimed at understanding the role of OFC in learning under different forms of reward uncertainty. Rats were trained to first discriminate visual stimuli and then adjust to changes in probabilities-of-reward or delays-to-reward associated with those stimuli following inhibitory (hM4Di, Gi) DREADDs in ventral OFC. We found that rats need an intact OFC to adjust to changes in either delay or probability attribute. Furthermore, across both attributes, OFC-inhibition resulted in a pattern of "confirmation bias:" animals learn more from expected than unexpected feedback, and engage in more WinStay and less LoseShift strategies overall. Our parallel experiments with ACC DREADDs inhibition suggest substantial overlap with OFC in adjusting to changes in both attributes, with ACC as more specialized for learning about better-than-expected changes and OFC serving a more general function in learning about both better- and worse-than-expected changes in reward. Collectively, these results support the notion that OFC may encode essential information for generating representations about expected delays and probabilities. This information may then be used by ACC to mediate adjustments when meaningful changes occur. I will end with a discussion of ongoing experiments in which we are imaging, recording, and disconnecting ACC and OFC during these tasks.

Kate Wassum

Corticolimbic circuitry in reward learning and pursuit

To make adaptive decisions we must cast ourselves into the future and consider the outcomes of our potential choices. This prospective consideration is informed by our memories. I will discuss our lab's recent work investigating the neural circuits responsible for encoding, updating, and retrieving reward memories for use in the considerations underlying decision making. We have taken a multifaceted approach to these investigations, combining recording, circuit dissection, and behavioral tools. Our results are indicating that the orbitofrontal cortex and basolateral amygdala work in a circuit to regulate the encoding and retrieval of reward memories to ensure adaptive reward pursuit. The cognitive symptoms underlying addiction can result from a failure to appropriately learn about and/or anticipate potential future events, making these basic science data relevant to the understanding and potential treatment of addiction to drugs or alcohol.

Miriam Klein-Flügge

Multiple neural mechanisms of knowledge acquisition

Humans and animals learn from reward but they also learn by observing statistical relationships in the world. It is the coalescence of these learning mechanisms that shapes our ability to produce complex goal-directed behaviours. While much is known about the neural encoding of updating signals during learning, there is relatively little knowledge on where and how learnt representations are stored. The first study I will present explores the neural representations or 'associative structures' created by multiple different learning mechanisms using human fMRI. We find that knowledge encoded via model-free RL is dissociable, neurally, from the encoding of statistically learnt relationships. One advantage of acquiring relational knowledge is that it allows us to behave adaptively in new situations and make inferences about never previously experienced options. In the second study I will examine whether macaque monkeys can make inferences about novel choice options and show that they recruit a hexagonal map-like coding scheme to represent relationships in an abstract option space.

Lauren Atlas

Orbitofrontal contributions to expectancy, learning, and pain

The orbitofrontal cortex is implicated in value-based learning for both appetitive and aversive outcomes. In this talk, I will review the role of the OFC/VMPFC in expectancy-based modulation of pain and aversive learning. We find that value-based signals in the OFC update with instruction during aversive reversal learning, whereas the amygdala seems to respond to aversive outcomes irrespective of instructions. I will also present new work measuring causal influences of OFC/VMPFC on expectancy effects on pain. We find that human patients with OFC/VMPFC lesions show larger expectancy effects on pain, and reduced pain-related autonomic activity. I will discuss implications of these

findings for our understanding of the role of the OFC in value-based learning, higher order knowledge, aversive experience, and subjective pain.

Jay Gottfried

What Tim Hath Wrought: Following Your Nose to Find Your Way

A singular aspect of odors is their ability to travel through the air over long distances. In this manner, the sense of smell can gather valuable predictive information about an odorous object, enabling animals to navigate either toward or away from an odor source as needed. Notably, in contrast to the “what” questions of olfaction, the role of the olfactory system in spatial navigation is less well studied, though no less important. Elegant neurobiological studies on odor navigation have been conducted in insects and birds, but there are very limited neural data available in mammals, including humans. In this presentation, I will discuss our recent work showing that human subjects can orient within a 2-D abstract space defined by odor mixtures varying in perceived intensity. Intriguingly, even though subjects were not actively navigating through a physical environment, “grid-like” neural representations of this odor intensity space emerged in human ventromedial prefrontal cortex, entorhinal cortex, and piriform cortex, highlighting a novel mechanism by which the human brain can construct an olfactory cognitive map. I will also present new preliminary data suggesting that subjects can learn to navigate a virtual reality (VR) arena in which the only informative sensory cues are olfactory. These studies bring fundamental understanding to the capacities and constraints of human olfactory navigation, and highlight neural mechanisms by which the olfactory system tracks and locates odor sources in odiferous environments.

Masayuki Matsumoto

Value-to-choice signal transformation in midbrain dopamine neurons and orbitofrontal neurons during economic decision-making in monkeys

In economic decision-making, we first evaluate the value of offered options and then decide whether or not to choose them using the value information. To uncover the neural basis of economic decision-making, it is critical to understand how the brain transforms value information into choice commands. Although previous studies have focused on the roles of prefrontal regions (e.g., the orbitofrontal cortex, OFC) in the value-to-choice transformation, the whole picture of the neural network underlying this process remains elusive. Here, we investigated whether and how midbrain dopamine neurons, a subcortical center for reward processing, contribute to the value-to-choice transformation. We designed an economic decision-making task in which monkeys were required to decide to choose or not to choose an option based on its value immediately after the option was offered, and recorded single-unit activities from dopamine neurons as well as OFC neurons, for comparison, in

the animal performing the task. We found that dopamine neurons represented diverse signals related not only to the option's value but also to the animal's choice behavior; some dopamine neurons represented the value of the offered option, some represented whether the animal would choose or not choose the option, and some represented the combination of the value and choice behavior, i.e., these neurons represented the value only when the monkey decided to choose the option (we henceforth call this signal "choice-dependent value"). We next analyzed the time course of these dopamine signals, and found that these signals were observed at different timing. Shortly after the onset of the option, the value signal rapidly appeared, followed by the choice-dependent signal. The choice signal arose at last. This time course of the three signals is well consistent with the time course of the value-to-choice transformation, and we also observed the same time course in the OFC. Notably, the last choice signal appeared before the monkey executed a motor action to choose the option in both dopamine neurons and the OFC. Our findings show that dopamine neurons and OFC neurons share the same signal dynamics corresponding to the value-to-choice transformation, and provide evidence suggesting that not only prefrontal regions but also the subcortical dopamine system regulates the value-based choice formation.

Mehdi Khamassi

Hippocampal replay and preplay through the lenses of model-based reinforcement learning

Apology - I would like to apologize since my talk will be mostly about the hippocampus, but will nevertheless include some OFC data. I think these can contribute to the study of how the hippocampus and the orbitofrontal cortex may interact during offline inference processes to update stimulus values.

Abstract - Hippocampal offline reactivations during reward-based learning, usually categorized as replay and preplay events, have been found to be important for performance improvement over time and for memory consolidation. Recent computational work has linked these phenomena to the need to transform reward information into state-action values for decision-making and to propagate it over time and space. Nevertheless, it is still unclear whether an integrated reinforcement learning mechanism could account for the variety of hippocampal reactivations, including variety in order (forward and reverse reactivated trajectories) and in the places within the environment where they occur (reward site or decision-point). I will present a new model-based bidirectional planning model which accounts for a variety of hippocampal reactivations. The model combines forward trajectory sampling from current position and backward sampling through prioritized sweeping from reward location until the two trajectories connect. This is repeated until stabilization of state-action values (convergence), which could explain why hippocampal reactivations drastically diminish when the animal's performance stabilize. Forward reactivations are prominently found at decision-points while backward reactivations are exclusively generated at reward sites. Moreover, the model can generate imaginary trajectories that are not allowed to the agent during task performance. I will finish the presentation by briefly discussing how an extended version of the model can represent Hpc-OFC communication

during offline preplay/inference, and how this can be related to experimental data in rodents.

Joni Wallis

Orbitofrontal-hippocampal interactions during reward-guided learning

Neuronal oscillations in frontal cortex have been hypothesized to play a role in the organization of high-level cognition. Within orbitofrontal cortex (OFC), there is a prominent oscillation in the theta frequency (4-8 Hz) during reward-guided behavior, but it is unclear whether this oscillation has causal significance. One methodological challenge is that it is difficult to manipulate theta without affecting other neural signals, such as single neuron firing rates. A potential solution is to use closed-loop control to record theta in real-time and use this signal to control the application of electrical microstimulation to OFC. Using this method, we show that theta oscillations in OFC are critically important for reward-guided learning and that they are driven by theta oscillations in hippocampus. The ability to disrupt OFC computations via spatially localized and temporally precise stimulation, could lead to novel treatment strategies for neuropsychiatric disorders involving OFC dysfunction.

Tim Behrens

The Tolman-Eichenbaum Machine

Apology - I realise that this is not strictly about OFC, and apologise, but I feel vindicated for 2 reasons. First, the meeting is dedicated to Howard. Second, with the recent demonstrations of OFC being involved in representing state space locations, many of the things that we say about entorhinal cortex should be relevant to the OFC folk. Actually there is a chance, I will be able to present an example of this at the end of the talk.

Abstract - The hippocampal-entorhinal system is important for spatial and relational memory tasks. We formally link these domains; provide a mechanistic understanding of the hippocampal role in generalisation; and offer unifying principles underlying many entorhinal and hippocampal cell-types. We propose medial entorhinal cells form a basis describing structural knowledge, and hippocampal cells link this basis with sensory representations. Adopting these principles, we introduce the Tolman-Eichenbaum machine (TEM). After learning, TEM entorhinal cells include grid, band, border and object-vector cells. Hippocampal cells include place and landmark cells, remapping between environments. Crucially, TEM also predicts empirically recorded representations in complex non-spatial tasks. TEM predicts hippocampal remapping is not random as previously believed. Rather structural knowledge is preserved across environments. We confirm this in simultaneously recorded place and grid cells. I realise that the this is not about OFC, and apologise, but I feel vindicated for 2 reasons. First, the meeting is dedicated to Howard. Second, with the

recent demonstrations of OFC being involved in representing state spaces, many of the things that we say about entorhinal cortex should be relevant.