



Featured Talk

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 JULY 19 • SUNDAY
 

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1:00pm – 1:40pm

**F F1: Delineating Reward/Avoidance Decision Process in the Impulsive-compulsive Spectrum Disorders through a Probabilistic Reversal Learning Task**

Crowdcast (link TBA)

*Speakers: Xiaoliu Zhang*
**Xiaoliu Zhang, Chao Suo, Amir Dezfouli, Ben J.Harrison, Leah Braganza, Ben Fulcher, Lenardo Fontenelle, Carsten Murawski, Murat Yucel**

Impulsivity and compulsivity are behavioural traits that underlie many aspects of decision-making and form the characteristic symptoms of Obsessive Compulsive Disorder (OCD) and Gambling Disorder (GD). The neural underpinnings of aspects of reward and avoidance learning under the expression of these traits and symptoms are only partially understood.

The present study combined behavioural modelling and neuroimaging technique to examine brain activity associated with critical phases of reward and loss processing in OCD and GD.

Forty-two healthy controls (HC), forty OCD and twenty-three GD participants were recruited in our study to complete a two-session reinforcement learning (RL) task featuring a “probability switch (PS)” with imaging scanning. Finally, 39 HC (20F/19M, 34 yrs  $\pm$ 9.47), 28 OCD (14F/14M, 32.11 yrs  $\pm$ 9.53) and 16 GD (4F/12M, 35.53yrs  $\pm$ 12.20) were included with both behavioural and imaging data available. The functional imaging was conducted by using 3.0-T SIEMENS MAGNETOM Skyra syngo MR D13C at Monash Biomedical Imaging. Each volume comprised 34 coronal slices of 3 mm thickness with 2000 ms TR and 30 ms TE. A total of 479 volumes were acquired for each participant in each session in an interleaved-ascending manner.

The standard Q-learning model was fitted to the observed behavioural data and the Bayesian model was used for the parameter estimation. Imaging analysis was conducted using SPM12 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) in the Matlab (R2015b) environment. The pre-processing commenced with the slice timing, realignment, normalization to MNI space according to T1-weighted image and smoothing with a 8 mm Gaussian kernel.

The frontostriatal brain circuit including the *\_putamen\_* and *\_medial orbitofrontal (\_mOFC\_)\_* were significantly more active in response to receiving reward and avoiding punishment compared to receiving an aversive outcome and missing reward at *\_p < 0.001\_* with FWE correction at cluster level; While the *\_right insula\_* showed greater activation in response to missing rewards and receiving punishment. Compared to healthy participants, GD patients showed significantly lower activation in the *\_left superior frontal\_* and *\_posterior cingulum\_* at *\_p < 0.001\_* for the gain omission.

The reward prediction error (PE) signal was found positively correlated with the activation at several clusters expanding across cortical and subcortical region including *\_the striatum, cingulate, bilateral insula, thalamus and superior frontal\_* at *\_p < 0.001\_* with FWE correction at cluster level. The GD patients showed a trend of decreased reward PE response in the *\_right precentral\_* extending to *\_left posterior cingulate\_* compared to controls at *\_p < 0.05\_* with FWE correction. The aversive PE signal was negatively correlated with brain activity in regions including *\_bilateral thalamus, hippocampus, insula and striatum\_* at *\_p < 0.001\_* with FWE correction. Compared with the control group, GD group showed an increased aversive PE activation in the cluster encompassing *\_right thalamus\_* and *\_right hippocampus\_*, and also the *\_right middle frontal\_* extending to the *\_right anterior cingulum\_* at *\_P < 0.005\_* with FWE correction.

Through the reversal learning task, the study provided a further support of the dissociable brain circuits for distinct phases of reward and avoidance learning. Also, the OCD and GD is characterised by aberrant patterns of reward and avoidance processing.

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*Speakers: Andrea Navas-Olive*

**Andrea Navas-Olive, Liset M de la Prida**

The hippocampus-entorhinal system is critical for learning and memory. Recent cutting-edge single-cell technologies from RNAseq to electrophysiology are disclosing a so far unrecognized heterogeneity within the major cell types [1]. Surprisingly, massive high-throughput recordings of these very same cells identify low dimensional microcircuit dynamics [2,3]. Reconciling both views is critical to understand how the brain operates. The CA1 region is considered high in the hierarchy of the entorhinal- hippocampal system. Traditionally viewed as a single layered structure, recent evidence has disclosed an exquisite laminar organization across deep and superficial pyramidal sublayers at the transcriptional, morphological and functional levels [1,4,5]. Such a low-dimensional segregation may be driven by a combination of intrinsic, biophysical and microcircuit factors but mechanisms are unknown. Here, we exploit evolutionary algorithms to address the effect of single-cell heterogeneity on CA1 microcircuit operation [6]. First, we developed a biophysically realistic model of CA1 pyramidal cells using the Hodgkin-Huxley multi-compartment formalism in the Neuron+Python platform and the morphological database Neuromorpho.org. We adopted genetic algorithms (GA) to identify passive, active and synaptic conductances resulting in realistic electrophysiological neural behavior. We then used the generated models to explore the functional effect of cellular heterogeneity during theta oscillations, a major hippocampal rhythm associated to ensemble representation during encoding. We found that intrinsic and morphological variability determines a low dimensional subset of output features (e.g. phase-locking preference) characterized by a bimodal distribution that matches non-fitted experimental data. By combining results from all simulations in a logistic regression model we derived several predictions on the effect of up/down- regulation of different factors. We tested some of these predictions using cell-type specific chemogenetic approaches. Our work identifies mechanisms operating over intrinsic and synaptic variability to restrict neuronal firing during theta oscillations (Fig. 1). **\*\*Acknowledgments:\*\*** Andrea Navas-Olive is supported by PhD Fellowship FPU17/03268. **\*\*References:\*\***

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Synaptic scaling is a homeostatic normalization mechanism that preserves relative synaptic strengths by adjusting them with a common factor. This multiplicative change is believed to be critical, since synaptic strengths are involved in learning and memory retention. Further, this homeostatic process is thought to be crucial for neuronal stability, playing a stabilizing role in otherwise runaway Hebbian plasticity [1-3]. Synaptic scaling requires a mechanism to sense total neuron activity and globally adjust synapses to achieve some activity set-point [4]. This process is relatively slow, which places limits on its ability to stabilize network activity [5]. Here we show that this slow response is inevitable in realistic neuronal morphologies. Furthermore, we reveal that global scaling can in fact be a source of instability unless responsiveness or scaling accuracy are sacrificed.

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A neuron with tens of thousands of synapses must regulate its own excitability to compensate for changes in input. The time requirement for global feedback can introduce critical phase lags in a neuron's response to perturbation. The severity of phase lag increases with neuron size. Further, a more expansive morphology worsens cell responsiveness and scaling accuracy, especially in distal regions of the neuron. Local pools of reserve receptors improve efficiency, potentiation, and scaling, but this comes at a cost. Trafficking large quantities of receptors requires time, exacerbating the phase lag and instability. Local homeostatic feedback mitigates instability, but this too comes at the cost of reducing scaling accuracy.

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Realization of the phase lag instability requires a unified model of synaptic scaling, regulation, and transport. We present such a model with global and local feedback in realistic neuron morphologies (Fig. 1). This combined model shows that neurons face a tradeoff between stability, accuracy, and efficiency. Global feedback is required for synaptic scaling but favors either system stability or efficiency. Large receptor pools improve scaling accuracy in large morphologies but worsen both stability and efficiency. Local feedback improves the stability-efficiency tradeoff at the cost of scaling accuracy. This project introduces unexplored constraints on neuron size, morphology, and synaptic scaling that are weakened by an interplay between global and local feedback.

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*Speakers: Ioannis Pisokas*

**Ioannis Pisokas, Stanley Heinze, Barbara Webb**

Ants, bees and other insects have the ability to return to their nest or hive using a navigation strategy known as path integration. Similarly, fruit flies employ path integration to return to a previously visited food source. An important component of path integration is the ability of the insect to keep track of its heading relative to salient visual cues. A highly conserved brain region known as the central complex has been identified as being of key importance for the computations required for an insect to keep track of its heading. However, the similarities or differences of the underlying heading tracking circuit between species are not well understood. We sought to address this shortcoming by using reverse engineering techniques to derive the effective underlying neural circuits of two evolutionary distant species, the fruit fly and the locust. Our analysis revealed that regardless of the anatomical differences between the two species the essential circuit structure has not changed. Both effective neural circuits have the structural topology of a ring attractor with an eight-fold radial symmetry (Fig. 1). However, despite the strong similarities between the two ring attractors, there remain differences. Using computational modelling we found that two apparently small anatomical differences have significant functional effect on the ability of the two circuits to track fast rotational movements and to maintain a stable heading signal. In particular, the fruit fly circuit responds faster to abrupt heading changes of the animal while the locust circuit maintains a heading signal that is more robust to inhomogeneities in cell membrane properties and synaptic weights. We suggest that the effects of these differences are consistent with the behavioural ecology of the two species. On the one hand, the faster response of the ring attractor circuit in the fruit fly accommodates the fast body saccades that fruit flies are known to perform. On the other hand, the locust is a migratory species, so its behaviour demands maintenance of a defined heading for a long period of time. Our results highlight that even seemingly small differences in the distribution of dendritic fibres can have a significant effect on the dynamics of the effective ring attractor circuit with consequences for the behavioural capabilities of each species. These differences, emerging from morphologically distinct single neurons highlight the importance of a comparative approach to neuroscience.

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