Barcelona Computational, Cognitive and Systems Neuroscience (BARCCSYN) 2018

Sala Joan i Pere Coromines

Institut d'Estudis Catalans

May 24th and 25th, 2018

Organizers

Matthieu Gilson, Universitat Pompeu Fabra
Belén de Sancristóbal, IDIBAPS
Vicky Puig, Institut Hospital del Mar d'Investigacions Mèdiques
Alex Roxin, Centre de Recerca Matemàtica

Keynote Speakers

Boris Gutkin, École Normale Superieure
William Newsome, Stanford University
Gregor Rainer, University of Fribourg

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2. Abstracts of the Speakers

The neural circuit basis of feature-binding in working memory

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Summary. *Binding* (or *swap*) *errors occur* in working memory tasks when a wrong response is in fact accurate relative to a non-target stimulus [1]. These errors reflect the failure to maintain bundled in memory the conjunction of features that define one object, and the mechanisms implicated remain unknown. Here, we tested the mechanism of synchrony across feature-specific neural assemblies [2]. We built a biophysical neural network model for working memory items defined by one color and one location. The model is composed of two one-dimensional attractor networks for working memory (as in [3]), one representing colors and the other one locations. These two networks are then connected via weak cortico-cortical excitation. Gamma-oscillations were induced during bump attractor activity through the interplay of fast recurrent excitation and slower feedback inhibition [3]. Binding between color and location was accomplished through the synchronization of pairs of bumps across the two networks via weak cortico-cortical excitation. As a result, different memorized items were held at different phases of the network's intrinsic oscillation. In some simulations, *swap errors* arose: "color bumps" abruptly changed their phase relationship with "location bumps". The model makes specific testable predictions that we addressed experimentally. Firstly, a uniform drive pulsating at the natural frequency of the networks stabilizes the bumps and reduces the incidence of swap errors. This was validated in behavioral experiments with oscillating visual placeholders, with a specific swap-reducing effect at theta range. Secondly, swap errors in the model are associated with a lower phase consistency of oscillatory activity in the delay period. We validated this prediction in MEG experiments, finding alpha-band phase changes specific to swap trials in fronto-parietal sensors.

Significance. We propose a plausible mechanism for working memory binding based on neural synchronization in spiking neural networks, and we support it with behavioral and neurophysiological (MEG) experiments in humans.

This is a joint work wit Ainsley Temudo, Vahan Babushkin, Tim Buschman, Kartik K. Sreenivasan, and Albert Compte.

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The influence of motivation onto movement precision: A computational approach

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A foundation of behaviour is reward prospect: we move to attain valuable states. However, moving towards those states implies investing a certain amount of effort and deploying motor strategies that demand specific parameters. Although the relationship between reward, motivation and behaviour has been extensively studied, the specifics of how motivation relates to motor generation, whether and how it considers effort, how this may influence the selection of movement parameters, it all remains largely controversial. For example, it has been often assumed that the activation of motor neurons is unrelated of the intended movement, which is at odds with experimental evidence showing that cortical activity reflects costs associated to intended movements well before movement onset.

To investigate whether and how motor parameters and decisions between movements were influenced by differentially induced motivated states, we performed a decision-making paradigm where healthy human participants, under different movement control conditions, had to make choices between reaching movements. Their goal was to accumulate reward by selecting one of two reaching movements of opposite biomechanical cost, and to perform their selected reaching towards the target. Maximum reward was contingent on the movement entering the centre of the target, and decreased proportionally with error. All trials had fixed duration to prevent the participants from maximizing reward by minimizing temporal discount.

We manipulated the participants' motivated state via social pressure. Each experimental session was composed of six blocks, during which subjects could either play alone or accompanied by another simulated player. Within this illusion, the amount of reward obtained by the participant and by his/her companion was reported at the end of each trial. The previous ten trial ranking for the two players was shown briefly every nine trials. However, no specific mention to competition was ever made to the subjects in the instruction, and any such assumption reported by the player was immediately rejected by the experimenter.

The results show that despite the experimenter's denial on competition, the subjects end-point error diminished proportionally to the skill of the accompanying player, meaning that although not consciously, subjects cared about their own performance. The main behavioural result was an increase of the time to peak velocity and global movement time between the baseline (play alone) condition and any accompanying condition, irrespective of the opponent's skill. This could be viewed as a simple adaptive process of trade-off between precision and time, however, other effects on the movement amplitude became significant when the skill of the companion player was clearly unattainable, such as a reduction of

the amplitude, therefore escaping the traditional context of the speed-accuracy trade-off.

To further investigate the dynamics of adaptation under baseline and motivated conditions, we developed a generative computational model of decision-making and motor control, based on the optimization of the trade-off between the benefits and costs associated to a movement. Remarkably, the predictions of this model show that this optimization depends on the motivational context where the movements and the choices between them are performed. Although further research remains to be performed to understand the specific intricacies of this relationship between motor control theory and motivated states, this suggests that this inter-relation between internal physiological dynamics and motor behaviour is more than a simple modulation of the vigour of movement.

This is a joint work wit Gustavo Deco.

Modelling neural circuit mechanisms of nicotine action in the brain
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Nicotine, a highly addictive substance in tobacco smoke, acts through nicotinic acetylcholine receptors (nAChRs) that are widely expressed throughout the nervous system. I will discuss how we can understand the influence of nicotine on neuronal circuit dynamics acting through the various subtypes of nAChRs that are differentially expressed in the dopaminergic ventral tegmental area and also in the superficial layers of the prefrontal cortex. My talk will be divided into two parts: control over the dopamine circuit dynamics linked to nicotine addiction and control over pre-frontal cortex circuit dynamics linked to schizophrenia.

Dopaminergic (DA) neurons located in the ventral tegmental area (VTA) signal motivational properties of natural reinforcers and addictive drugs. Electrophysiological recordings have demonstrated that transient inputs to the VTA, e.g., glutamatergic (Glu) and cholinergic (ACh), convey salient information about the environment. I will first show how computational modelling can account for in vivo and in vitro data obtained during nicotine exposures and manipulations of VTA input structures. We then show that our model can account for nicotine responses to repeated injections in both wild-type and animals where the a4b2 nAChRs are and how nicotine may change reward signalling in the VTA.

In the second part, I will discuss our on-going work on modelling nicotinic control over resting state activity in the pre-frontal cortex (PFC) and its implications for disorders such as schizophrenia. Notably I will show how computational model of nAChR action can account for the observed changes in the ultra-slow oscillation structure of the resting state in the PFC under pathological mutations linked to schizophrenia and how nicotine appears to remedy this pathology.

In summary, modelling suggests that by its wide ranging action subverting normal cholinergic neuromodulation, nicotine may alter brain computations necessary for higher cognitive functions.

The contribution of evoked variability quenching to working memory reactivations

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Stimulus information maintenance during working memory tasks has traditionally been linked to selective persistent activity in prefrontal cortex neurons. This view has recently been under debate. In novel imaging studies conducted in humans the failure to detect stimulus information during memory periods has been interpreted as evidence for memory storage through activity-silent mechanisms (i.e., in synaptic patterns changes, possibly through short-term synaptic plasticity) (LaRocque *et al.*, 2013). Moreover, these studies have shown that non-specific visual (Wolff *et al.*, 2017; Wolff *et al.*, 2015) or transcranial magnetic (Rose *et al.*, 2016) stimuli could reveal memory-specific information that was otherwise undetected by linear decoders.This increase in decodability following non-specific stimuli is being interpreted as memory reactivations from the so-called "hidden states".

In this study, we argue that stimulus-driven decrease in brain activity variability (Churchland *et al.* 2010) offers an alternative explanation. Intuitively, an increase in signal-to-noise ratio (SNR) can be achieved by an increase in signal, but also by a decrease in noise. We used simulated data to illustrate this effect, and to relate it to single-trial baselining procedures typically used in EEG decoding studies. Our simulations showed that both within-trial and across-trial variability reductions had an impact in decoder accuracy following the stimulus, provided there was stimulus signal at the time of stimulation or at the time taken for single-trial baseline. We next re-analyzed 4 existing datasets (Wolff *et al.*, 2017; Rose *et al.*, 2016; Foster *et al.*, 2016; Wolff *et al.*, 2015) and asked if both visual and magnetic stimuli could decrease the variability of EEG activity experimentally. We found that both stimulus types decreased mostly within-trial variability. Interestingly, this decrease was aligned with decodability increase associated with "memory reactivation" in the original papers. We thus show that quenching of EEG within-trial variability after stimulus onset could partly underlie previous findings: the non-specific evoked activity produced by external impulses could reduce noise measured with EEG, therefore facilitating information decoding, but without any real increase in stimulus-selective signal. We further warn about the importance of baselining procedures for proper interpretation of the results.

This is a joint work wit João Barbosa and Albert Compte.

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High frequency neurons contribute to define effective connectivity in brain networks

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The emergence of flexible information channels in brain networks is a fundamental question in neuroscience. Understanding the mechanisms of dynamic routing of information would have far-reaching implications in a number of disciplines ranging from biology and medicine to information technologies and engineering.

In this presentation, we study how signals transmit in simple bidirectionally-coupled networks. In these networks, each node represents a unit composed of excitatory and inhibitory neurons and all nodes, except one, produce a local oscillation with frequency ν_0 in the gamma range. An inhomogeneity is introduced by placing the remaining node –called source node– to oscillate at a different intrinsic frequency $\nu = \nu_0 + \triangle\nu$. We find that the presence of this particular node leads to reliable transmission of signals and establishes a preferential direction of information flow.

Our results show that slowly varying local signals can better propagate along the network if the receiving node has a higher intrinsic firing rate. Moreover, we find that high frequency units determine the direction of signal propagation, so the effective connectivity in such a network. While structural network connections are bidirectional and symmetric, in the effective network the connections are directed outward from the high frequency node, being highly influential in the activity propagation despite the symmetric homogeneous structure. Thus, by raising the firing rate a low degree node can behave as a functional hub, spreading its activity patterns polysynaptically in the network. Therefore, the firing rate, which might be easily controllable, becomes a tunable parameter that introduces

directionality and enhances the reliability of signal transmission. We find that our results are generic and the same mechanism is observed in networks with more complex topologies.

This is a joint work wit A. Pariz, Z.G. Esfahani, S.S. Parsi, A. Valizadeh, and S. Canals.

Representation of choice bias in the activity of prearcuate gyrus during perceptual decision making

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Optimal decision making often requires integrating current sensory information with prior history of choices, rewards and stimuli. Such biases may be beneficial when sensory information is weak or ambiguous, especially if the task structure is uncertain or when prior history carries relevant information about upcoming stimuli or rewarding actions. Here, we report the existence of history-dependent biases in the behavior of highly-trained monkeys performing a motion direction discrimination task and demonstrate a neuronal representation of the bias in the activity of prearcuate gyrus (PAG) neurons. In our task, stimulus direction and strength varied randomly on a trial-by-trial basis, making previous history irrelevant for the future choice. Despite this fact, monkeys showed small but significant biases that fluctuated at two distinct time scales: slow (tens to hundreds of trials) and fast (previous trial). Fast bias on each trial reflected previous choice and feedback, while slow bias reflected the monkey's choice preference within the neighboring trials. Knowing these biases significantly improved our ability to predict monkeys' upcoming choice on the individual trials. Importantly, the increased prediction accuracy was strongest for trials with weaker motion, suggesting a stronger role of prior history in shaping the choice when sensory information is limited (improved accuracy > 2.5 % for difficult motion coherence with p(correct) < 0.75, compared to a model that predicted choices based only on the stimulus strength).

The pre-stimulus population activity of PAG neurons represented the fast and slow biases, indicating a correlate for both types of bias in the prefrontal cortex. Critically, adding the trial-to-trial variability of these neural representations of bias to our choice prediction model trended toward improving the model accuracy, suggesting that these representations reflected the subjective biases that shaped the behavior. The same activity was also directly predictive about the monkey's upcoming choice but further mediation analyses suggest that this predictive power was a consequence of representing bias signals. Since the same PAG neurons also represented past choices and feedback that shaped the subjective bias, they could offer a compact circuit for the computation of prior history signals and leveraging those signals to guide behavior.

This is a joint work wit Roozbeh Kiani and Rubén Moreno Bote.

Detecting covert cognitive states from neural population recordings in prefrontal cortex

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The neural mechanisms underlying decision-making are typically examined by statistical analysis of large numbers of trials from sequentially recorded single neurons. Averaging across sequential recordings, however, obscures important aspects of decision-making such as variations in confidence and changes of mind' (CoM) that occur at variable times on different trials. I will show that the covert decision variables (DV) can be tracked dynamically on single behavioral trials via simultaneous recording of large neural populations in prefrontal cortex. Vacillations of the neural DV, in turn, identify candidate CoM in monkeys, which closely match the known properties of human CoM. Thus simultaneous population recordings can provide insight into transient, internal cognitive states that are otherwise undetectable.

Maximum entropy models reveal the correlation structure in cortical neural activity during wakefulness and deep sleep

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The macroscopic brain states of wakefulness and sleep emerge from rich interactions within networks of neurons at the microscopic scale. Recent experimental advances, through the recording of spikes of up to 10^2 neurons throughout several hours, have permitted the exploration of these dynamics *in vivo*.

To analyse such complest system, one is interested in searching for the simplest model, able to explain the most of the data statistics. This can be achieved by maximisation of entropy in the system, with constraints imposed by the empirical statistics (Jaynes 1982).

Maximum entropy modelling has been applied to the spiking activity of neuronal networks. While the approach had been demonstrated to accurately predict certain patterns of empirical neural activity, we show that existing models (Schneidman 2006, Okun 2015, Gardella 2016) fail to reproduce the strongly synchronous behaviour of inhibitory neurons during sleep (Nghiem 2017).

By accounting for the interactions between each neuron and the excitatory and inhibitory populations separately, we introduce a model able to overcome this pitfall. We investigate this on multi-electrode array recordings in the cortex of a human and a non-human primate (Peyrache 2012, Dehghani 2016).

Our results suggest that neural dynamics during wakefulness are dominated by pairwise interactions, while neural activity during sleep may be governed by longer-range population- wide interactions. Overall, they highlight inhibitory neurons play a fundamental role in organising coherent dynamics in the cerebral cortex during sleep (Nghiem 2018).

This approach provides a powerful framework to take full advantage of neuron type classification, which is becoming increasingly available in empirical data. More generally, our model may prove useful to constrain bio-physically realistic models of wakefulness and sleep.

This is a joint work wit Bartosz Telenczuk, Olivier Marre, Alain Destexhe, and Ulisse Ferrari.

Dopamine reward prediction errors are modulated by an internal bias during stimulus discrimination

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Under uncertain stimulation conditions dopamine (DA) responses to relevant task cues reflect cortical perceptual decision-making processes, such as the certainty about stimulus detection (de Lafuente and Romo, 2011) and evidence accumulation (Nomoto *et al.*, 2010), in a way compatible with the reward prediction error (RPE) hypothesis (Sarno *et al.*, 2017). This suggests that the midbrain DA system receives information from cortical circuits about decision formation and transforms it into a RPE signal. If so, DA phasic activity should reflect a variety of phenomena, including internally generated biases. This is because biases influence decisions and performance and hence they are expected to modulate the error in the prediction of reward. To test this hypothesis and acquire further insight into how DA neurons behave under uncertainty we used the two-interval, two-alternative forced-choice paradigm. These tasks present a contraction bias whereby the sensory feature of the first stimulus is perceived as if its value were shifted to the center of its range. Specifically:

1. We analyzed the firing rate of DA neurons recorded in monkeys discriminating the frequency of two vibrotactile stimuli.
2. Although naively the response to the first stimulus should only code the predicted average reward, it was modulated (but not tuned) by the value of the frequency in the way expected from the bias.
3. Similarly, the response to the second stimulus depended on the stimulus pair in a way consistent with the bias.
4. The activity during the comparison period was modulated by confidence, defined using a Bayesian model for the choice.
5. The reward prediction error obtained from a reinforcement learning model reproduced the phasic response to the second stimulus and its dependence on confidence.
6. The DA activity was above baseline throughout the delay (memory) period. It was neither tuned nor modulated by the first frequency, pointing to quite different roles of delay and phasic activities.

The results support the notion that the phasic and delay activities of DA neurons have quite different roles. The phasic activity of DA neurons coded RPEs that

were modulated by internal biases. Instead their activity during the delay period was not tuned to the stimulus, did not exhibit bias effects and changed throughout the duration of that period; these properties point to a role in stabilizing working memory in frontal areas.

This is a joint work wit M. Beirán, S. Sarno, R. Rossi-Pool, J. Vergara, and R. Romo

The basal forebrain contributes to default mode network regulation
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The basal forebrain is a collection of nuclei that project to many cortical and subcortical areas, whereby they exert a pronounced influence on brain state and behavior. For example, contributions to attentional functions, as well as wake-sleep regulation have been described for these circuits. I shall present findings suggesting that the basal forebrain also plays an important role in the default mode network (DMN). Accordingly, strong gamma band LFP activations are seen in the basal forebrain when rats in a state of quiet wakefulness that is associated with the default brain state, and these oscillations exhibit functional coupling to the cingulate cortex, a main hub of the DMN in rodents. Effects of electrical BF stimulation on behavior further support the idea that the BF may in fact play a key role in internally directed brain states that have been linked to DMN activation. Preliminary evidence suggests that the DMN related functions of the BF may be due to GABAergic, not cholinergic projections. Our findings highlight a novel and largely unexplored facet of BF function.

Post-inhibitory rebound interacts with preventing or deleting mechanisms to generate thetaspiking resonance in hippocampal CA1 pyramidal cells
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A crucial issue in the understanding of neuronal oscillations is to elucidate the microcircuits that are the substrate to these rhythms in the different brain areas. The question arises whether rhythmic activity results solely from the network properties (e.g., excitation and inhibition, topology) or it involves the interplay of the latter with the intrinsic properties of the participating neurons (e.g., ionic currents). We address this issue theoretically in the context of the hippocampal area CA1 microcircuits, which include excitatory (PYR) and inhibitory (INT) cells. It has been observed in in vitro experiments that PYR exhibit a preferred subthreshold frequency response to oscillatory inputs (subthreshold or membrane potential resonance) at theta (4 - 10 Hz) frequencies (Hu *et al.*, 2002, 2009; Zemankovics *et al.*, 2010). Previous in vivo work (Stark *et al.*, 2013) has shown that, contrary to expectation, these cells do not exhibit spiking resonance in

response to direct oscillatory optogenetic activation, but, surprisingly, spiking resonance in PYR occurs when INT are activated in this way. We explain the underlying mechanisms by combining biophysical modeling, numerical simulations and dynamical systems analysis. The PYR subthreshold resonance fails to be communicated to the spiking regime by direct PYR activation because of the relatively strong effect of the oscillatory input amplitude that causes the spiking activity to spread over a broad range of input frequencies (for which the voltage response is above threshold) as shown theoretically (Rotstein 2017). PYR theta-band resonance through direct INT activation results instead from a combination of (i) rebound spiking, and (ii) a timing mechanism. Rebound spiking is responsible for the "spiking low-pass filter" (generation of spikes for input frequencies that are low enough for the voltage responses of both PYR and INT to be above threshold), but it is not enough to generate spiking resonance since spikes are generated for arbitrary low input frequencies. The timing mechanisms are responsible for either "erasing" the spikes generated by input frequencies lower than theta (deleting mechanisms) or failing to produce spikes for these input frequencies (preventing mechanisms). We identified three such mechanisms: (i) network-mediated inhibition from OLM cells, (ii) synaptic depression of INT synapses, and (iii) subthreshold gamma resonance in INT, which has been shown to be present *in vitro* (Pike *et al.*, 2000). Overall, these results provide a mechanistic understanding of network resonance at theta frequencies and make several predictions. The principles identified in this study are applicable not only to CA1 networks, but also to other systems that exhibit theta resonance such as neocortical networks (Stark *et al.*, 2013). Finally, the results and ideas that emerge from our study are seminal for the construction of a theoretical framework for the investigation of the preferred frequency responses of neuronal networks to oscillatory inputs at a variety of biophysically realistic frequency bands.

This is a joint work wit Takuya Ito and Eran Stark.

Single-neuron interactions in the thalamo-cortical network during somatosensory perception

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Sensory thalamo-cortical interactions are key components of the neuronal circuits associated with stimulus perception, but they are still poorly understood. We addressed this problem by evaluating a directional measure between simultaneously recorded neurons from somatosensory thalamus (VPL) and somatosensory cortex (S1) sharing the same cutaneous receptive field, while monkeys judged the presence or absence of a tactile stimulus. During the stimulus-presence, feedforward (VPL $\rightarrow$ S1) interactions increased, while pure feedback (S1 $\rightarrow$ VPL) interactions were unaffected. Remarkably, bidirectional interactions (VPL $\leftrightarrow$ S1)

emerged with high stimulus amplitude, establishing a functional thalamo-cortical loop. Furthermore, feedforward interactions were modulated by task context and error trials. Additionally, significant stimulus modulations were found on intra-cortical (S1 $\rightarrow$ S1) interactions, but not on intra-thalamic (VPL $\rightarrow$ VPL) interactions. Thus, these results show the directionality of the information flow between the thalamo-cortical circuits during tactile perception. We suggest that these interactions may contribute to stimulus perception during the detection task used here.

This is a joint work wit Yuriria Vázquez, Manuel Álvarez, Antonio Zainos, Román Rossi-Pool, Gustavo Deco, and Ranulfo Romo.

Multimodal characterization of the Tg2576 mice model of AD

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In this talk I will show our latest results in the characterization of the Tg2576 mice model of AD. The Tg2576 is a transgenic strain expressing mutant amyloid precursor proteins (APPs) and constitute an opportunity for exploring the pathophysiology and neurobiology of Alzheimer's disease. Although cognitive function has been extensively characterized in this model, the neurophysiological basis of memory impairment is poorly understood. Here we aim at obtaining a full electrophysiological characterization of this model. To do that, we use systems neuroscience tools (chronic electrophysiological recordings and data analyses) to identify functional domains that could be involved in the progression of the cognitive deficit.

Morris water maze (MWM) and fear conditioning (FC) test were used to assess cognitive deficit in the Tg2576 mice. Then, animals were implanted with ECoG screws on prefrontal cortex together with 6 equally spaced deep electrodes in the hippocampal CA1 region and EMG. After recovery, mice were recorded in a freely moving open field and under physiological sleep. Behavioral states were divided into awake rest, awake movement, slow sleep and REM sleep conditions. Raw signals were inspected for the presence of artifacts and segments containing low quality signals were removed from the analyses. Around 75% of the Tg2576 animals (17) showed paroxysmal activities originated in the dentade gyrus that spread into the CA1 region, mostly under sleep conditions. On the contrary, such activities were not detected in any of the wild type (WT) mice recorded (24). Then power spectrum, cross-frequency coupling and imaginary coherence estimates were obtained and compared across conditions and genotypes. Age effect was investigated by means of covariance analyses and detected significant differences between Tg and WT, mainly during sleep. To finish, electrophysiological parameters were correlated with behavioral (MWM, FC) and histopathological (amyloid and tau deposition) markers.

To the best of our knowledge this is one the most detailed characterizations of the Tg2576 electrophysiology that could serve to guide new investigations devoted to bridge the gap between behavioral deficits and histopathological markers present in this mice model for AD.

This is a joint work wit Sandra Arrieta, A. Ricobaraza, M. Nicolás, and J. Artieda.

3. Abstracts of the Posters

Increased hippocampal oscillatory activity and prefronto-hippocampal functional connectivity in a cognitive impaired mouse model of down syndrome

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Down Syndrome (DS) is the most common genetic cause of intellectual disability and is modeled in Ts65Dn mice by a partial trisomy of the murine equivalent of human chromosome 21. Ts65Dn mice exhibit dendritic and synaptic abnormalities in the Prefrontal Crotex (PFC) and Hippocampus (HPC) and severe cognitive impairments in PFC- and HPC- dependent tasks. However, whether these cellular alterations affect neural network activity and PFC-HPC communication is still unknown.

To tackle this question, we have recorded neural activity in the PFC and HPC of freely-moving Ts65Dn mice via tungsten stereotrodes with the Open Ephys data acquisition system in quiet wakefulness, open field exploration, slow wave sleep, rem sleep and during the performance of the Novel Object Recognition Task.

Results indicate that Ts65Dn mice show alterations in neural network dynamics especially in the HPC and in its functional connectivity with the PFC. Particularly, Ts65Dn mice have increased delta, theta, beta and low gamma activity in the HPC and theta-gamma coupling is also exacerbated specifically in the HPC. Interestingly, Ts65Dn mice show also augmented PFC theta activity and functional hyperconnectivity between the PFC and the HPC specifically in the theta frequency band.

Our findings suggest that exacerbated widespread oscillatory activity in the HPC and increased theta activity in the PFC together with an aberrant augmented PFC-HPC theta connectivity in Ts65Dn mice could be functional markers of cognitive impairment at the network level.

This is a joint work with T. Gener and M.V. Puig.

Open source, high-throughput platform for automatized rodent training

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Modern approaches in neuroscience emphasize the need to scrutinize brain circuits in action and require monitoring the behavior of subjects that are performing finely controlled tasks. The field of decision making has recently incorporated rodent models that have proven to be able to perform complex tasks previously thought to be reserved for primates. Because animal training in cognitive tasks is very time consuming, the main advantage of rodent models is the possibility

to simultaneously train large cohorts of animals using high-throughput behavioral setups. The size of these setups, composed of many behavioral boxes, is usually limited by (1) the cost of commercial equipment and software to control each of these boxes, (2) the degree of automatization of the process such that the bandwidth of a single researcher can be maximized to supervise the training of many animals. Here we present a novel high-throughput platform for rodent training composed of (1) PyBpod, an open software suited for the design and control of behavioral experiments (2) custom made hardware aimed to minimize the cost and physical space of each box while maximizing the temporal precision of the task, the trial number of rats, and the reproducibility of the data. PyBpod inherits some of the features of his older brother Bcontrol but does not rely on MATLAB or other commercial software. It is designed to run with Bpod State Machine (by Sanworks), an Open Arduino-based system for precise measurement of animal behavior. It is composed of an API running on a standard Linux PC and a GUI which provides a tailored interface to run multiple experiments simultaneously using multiple Bpods connected to the PC via USB. Experimental protocols in PyBpod are short Python routines that can be readily programmed by researchers and technicians without strong programming skills. This maximizes the versatility of the software (almost any trial- based experiment can be programmed) while maintaining the simplicity. Protocols, designed as Finite State Machines, are loaded into Bpod which provides an excellent low-latency link between behavioral events (a snout enters a port, a tongue breaks a photogate, etc.), stimuli (different sounds, in our case) and reinforcement (water valves). The hardware features a low cost acoustic isolation chamber (noise isolation $\sim$ 40 dB at 10kHz), lab-made behavioral boxes to perform two alternative forced choice tasks in rats, 3D-printed water ports designed to facilitate water retrieval at minimal head rotation, low cost ultrasound speakers and infrared cameras. We provide quantitative measurements of latencies of the systems under the most demanding conditions as well a break of the costs of each part and a comparison with commercial alternatives. In total, our system provides an inexpensive fully open and highly customizable platform for high-throughput automatic rat behavioral experimentation.

This is a joint work with Simón Serka, Jordi Pastor, Rachid Azizi, Carlos Mão de Ferro, Tíffany Oña, Niccolò Bonacchi, Zach Mainen, Jaime de la Rocha, and Ricardo Ribeiro.

Comparing task-relevant information across different methods of extracting functional connectivity

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The concept of brain states has become popular in neuroscience, but their characterization and the validation of decoding schemes in the literature varies widely.

Our study focuses on whole-brain fMRI signals and aims to investigate which types of functional connectivity (FC) perform well in a five-task classification problem. In particular, we validate the classification procedure using cross-validation, in line with recent methodological recommendations.

We use functional magnetic resonance imaging data of 14 subjects during rest, the nBack task, the Flanker task, a mental rotation task, and an odd-man-out task. For the FC, we compare covariance and correlation across different temporal window lengths, as well as the Hilbert transform. We evaluate which types of FC convey task-dependent information with a multinomial logistic regression decoder. We consider two types of cross-validation schemes, over subjects and across time. Cross-validation across time indicates how stable the structure of tasks is across time, whereas cross-validation over subject indicates how general the structure of tasks is between subjects.

The results of our methodological study emphasize the importance of using cross-validation and show that reducing FC features can lead to a strong increase of accuracy in subject-wise cross-validation. Conceptually, our results indicate that the task-relevant FC signature can differ strongly across FC methods and that the type of FC chosen should be carefully considered with respect to the aim of a study.

Dynamic mean-field of conductance-based networks of AdEx neurons modelling slow oscillations

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The brain is a highly complex system composed of $\sim 10^{11}$ neurons interconnected by $\sim 10^{14}$ synapses and displaying extremely complicated firing patterns. Mean-field approaches aim at simplifying such dynamics by focusing of the collective activity and the correlation patterns of neurons lumped together, in this way bridging microscopic (single-neuron spikes) and macroscopic scales (instantaneous spike rate of a neuronal ensemble). In this framework, a successful theoretical effort has been consolidated in time for network models in which neurons are point-like like integrate-andfire (IF) neurons driven with current-based (CUBA) synaptic input [1, 2]. However, a mean-field description with comparable effectiveness for IF neuron models incorporating conductance-based (COBA) synaptic currents is still lacking, although its relevance in terms of biological plausibility [3]. To fill this gap, here we propose and develop a novel dynamic mean-field theory for networks of COBA adaptive exponential (adEx) IF neurons. The approach consists of taking different approximations for the Fokker-Planck equation describing the population density dynamics in a regime-dependent way. As a result, a stationary current-to-rate gain function is worked out capable to match quantitatively well with simulated single-neuron firing rate (Fig.1A). The predictive power of the mean-field description is also proved for networks of homogeneous excitatory and inhibitory neurons (Fig.1B) [2, 4] both under stationary

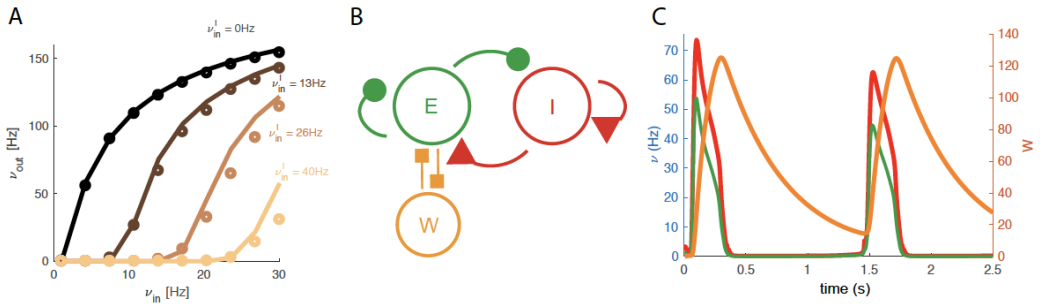

FIGURE 1. **Mean-field dynamics for netoworks of COBA exciatory-inhibitory IF neurons: A.** Comparison beween firing rate evaluated through spiking simulations (circles) and transfer function prediction (lines) as a function of the input firing rates. On x axis excitatory firing rate, while different colors represent different inhibitory firing rates. **B.** Sketch of the structure of E-I network. E is also affected by adaptation W. **C.** Example of slow oscillating activity for the E-I population. (Red and green) average firing rate for excitatory and inhibitory respectivle. (Orange) Adaptation.

conditions (asynchronous state) and for activity regimes displaying slow-fast dynamics like those modeling the slow oscillation observed both in vitro and in vivo experiments (Fig.1C). Intriguingly, when such global oscillations occur, the effect of a statedependent synaptic efficacy, only present in COBA models, allow to reproduce changes in the network dynamics which cannot be captured when CUBA IF neurons are taken into account. We expect that our approach would be a valuable tool to study other phenomena strongly shaped by the effect of conductances, and to describe more complicated (multi-population) systems such as the thalamo-cortical loop or spatially extended structures.

This is a joint work with Matteo di Volo, Alberto Romagnoni, Maurizio Mattia, and Alain Destexhe.

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A new dynamical firing rate model of the parvocellular pathway in V1

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Neurodynamical models based on known circuitry contribute to our understanding of the plausible neural mechanisms underlying visual processing in the human visual system. Few models have addressed color perception taking into account the fine machinery involved in the processing of color information. In this work, we present a new multilayer firing rate computational architecture that models the feedforward mechanisms present in the parvocellular pathway of the primary visual cortex, which is responsible for processing red-green chromatic information. The architecture models layers 4Cβ and 2/3, with their corresponding single- and double-opponent cells, simple and complex cells, and lateral connections.

As a test for the model, we measured the tuning properties of the underlying units and compared them to neurophysiological recordings found in the literature. In particular, we measured the spatial frequency and orientation selectivity, as well as the modulation ratio of the modeled neurons. We found that under some assumptions on unknowns properties of the cells and circuitry of the parvocellular pathway, namely on the type of double-opponent cells that can be found in layer 4Cβ and on the input and connectivity to complex cells, the modeled neurons had properties similar to those described in the literature. Our modeling sheds lights on fundamental unresolved questions regarding the organization early stages of color processing in the human visual system.

This is a joint work with X. Otazu and O. Penacchio.

Mechanisms for anticipated synchronization in neuronal models

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If we have two identical synchronized dynamical systems, coupled unidirectionally in a master-slave configuration, could we predict the master's future? Well, one decade ago Voss [1] proposed what is currently known as Anticipated-Synchronization (AS). AS is a form of synchronization that occurs when the slave system is subject to a negative delayed self-feedback and leads the master in time. Many examples of AS dynamics have been found and where?? showed to be a pure result of the delayed feedback.

The brain, as a dynamical system, can exhibit diverse, global or local, patterns of activity, such as synchrony, oscillations and so on. Also, at a neuronal level, the majority of neurons (excitatory or inhibitory) are coupled via chemical synapses that are highly nonlinear, and can be seen as dynamical systems per se. Given that, Matias *et al.*, have showed that a transition for Delayed-Synchronization (DS) to AS regime is also possible in biologically plausible mod- els of neurons

through chemical synapses: three-neurons- motif [2] and two cortical populations of neurons [3].

Here, as a further step, we investigated other possible mechanisms for which neuronal models could present the DS-AS transition. Indeed the mechanisms for which AS regime can be reached is not only through internal param- eters, it can be also through an external factor.

This is a joint work with A. Santos Neto, F. Matias, P. Carelli, M. Copelli, and C. Mirasso.

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Neural substrates of serotonin and antipsychotic drug action on prefronto-hippocampal networks

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Background: Serotonin receptors 5-HT_{1A}R and 5-HT_{2A}R in the prefrontal cortex (PFC) and hippocampus (HPC) are major targets for antipsychotic drugs useful to treat psychosis in schizophrenia. The contribution of these receptors to the action of antipsychotics on prefronto-hippocampal neural network dynamics and on cognition is unresolved.

Methods: We recorded neural activity in PFC and HPC of freely-moving mice while administering acutely 5-HT_{1A}R and 5-HT_{2A}R agonists and antagonists and antipsychotic drugs risperidone, clozapine and haloperidol.

Results: Pharmacological activation of 5-HT_{1A}R (8-OH-DPAT) and blockade of 5- HT2AR (M100907) reduced multi-unit activity (MUA), the power of theta and gamma oscillations and exacerbated delta waves in both areas. Similar effects were observed following administration of antipsychotic drugs, although the two serotonin receptors contributed differently to the power changes for each drug. Activation of 5-HT2AR (DOI) decreased MUA and enhanced gamma oscillations only in PFC. 5-HT_{1A}R agonism, 5- HT_{2A}R antagonism and antipsychotics weakened PFC-HPC functional connectivity at theta but only 8-OH-DPAT and atypical antipsychotic drugs enhanced connectivity at gamma frequencies.

Conclusions: Serotonin 5-HT_{1A}R and 5-HT_{2A}R exert opposite effects on prefrontal gamma oscillations, a band markedly related to cognitive abilities, and are major contributors to the action of antipsychotic drugs on prefronto-hippocampal neural network dynamics. 5-HT_{1A}R agonism and 5-HT_{2A}R antagonism inhibit neural activity (MUA and oscillations) of prefronto-hippocampal circuits and contribute differently to the action of antipsychotic drugs. 5-HT_{1A}R agonism, but not 5-HT_{2A}R antagonism, could underlie the cognitive enhancing properties of

atypical antipsychotic drugs by boosting prefronto-hippocampal gamma connectivity. These results may be relevant for understanding the actions of psychiatric medication targeting the serotonergic system.

This is a joint work with Thomas Gener, Adrià Tauste-Campo, Maria Alemany-González, Pau Nebot, Jordi Chanovas, and M. Victoria Puig.

Resting state autocorrelation window modulates sensory-evoked response variability

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We show that inter-individual variability of sensory-evoked responses elicited by long- lasting sounds ($\sim$ 3 s) can be explained by a homologous heterogeneity in the brain's intrinsic fluctuations. We combined electroencephalographic (EEG) recordings from human participants while they listened attentively to the stimuli with recordings while resting eyes-closed. Indeed, subjects with a similar temporal structure of the resting state, quantified by its autocorrelation window (ACW), exhibited comparable trial- averaged event-related spectral dynamics. Namely, slower spontaneous resting state fluctuations (i.e., with longer ACW) coincide with larger differences of a subject's response to distinct sounds and, in turn, better correlated with time-varying acoustic intensities. Our results are based on the first principal component extracted from all electrodes and were qualitatively well reproduced by a simple computational model of resting state fluctuations, that allowed us to confirm that changes in ACW alone can cause this variability. ACW's effects were also observed in single-trials in the form of a dynamic bias that forced the sound-triggered power fluctuations to relax back to the mean spontaneous activity. This temporal constrain, rather than time-averaged measures such as mean pre-stimulus activity, limited the amount of information about the nature of the stimulus. These results suggest that neuronal computations needed to extract stimulus-relevant information depend on the endogenous neuronal activity, i.e., the brain dynamics at rest, with inherent time-correlated dynamics.

This is a joint work with F. Ferri, M.G. Perrucci, G. L. Romani, A. Longtin, and G. Northoff.

Fluctuation-driven plasticity allows for flexible rewiring of neuronal assemblies

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Cortical circuitry is shaped through ongoing synaptic plasticity. However, network models in which recurrent synaptic connections change via Hebbian plasticity rules are unstable: synapses become maximally potentiated or depressed, effectively erasing all nontrivial structure in the connectivity. One solution to this

dilemma is to include additional mechanisms to offset Hebbian instabilities [1]. Here we consider an alternative scenario in which, given constant firing rates, the rates of potentiation and depression are equal and opposite. Net potentiation or depression only occurs when the firing rates of neurons covary in time. We show that standard heuristic STDP (spike-timing dependent plasticity) rules can have this property. Furthermore, we show how external time-varying signals can be used to flexibly control the network structure. As an example, neuronal assemblies can be strongly coupled, decoupled, or uni-directionally coupled by driving them with oscillatory signals with distinct phase lags. Alternatively, the connectivity between assemblies driven by stochastic inputs can be flexibly shaped via the covariance matrix of the inputs. Specifically, we consider a system of coupled firing rate equations of the form

$$\tau \dot{\mathbf{r}} = (\mathbf{W} - \mathbf{I})\mathbf{r} + \mathbf{I}(\mathbf{t}) \tag{1}$$

where the connectivity matrix $\mathbf{W}$ is shaped via a pairwise spike-timing dependent plasticity rule (STDP) implemented by generating spikes stochastically in accordance with the underlying rates. In the limit in which plasticity occurs much more slowly than the firing rate dynamics, the evolution of the synaptic weights can be approximated as a continuous process [2]

$$\dot{W}_{ij} = \int_{-\infty}^{\infty} dT K(T) r_j(t) r_i(t+T), \tag{2}$$

where $K(T) = A_+ e^{-T/r_+}$ if $T > 0$ and $K(T) = -A_- e^{T/r_-}$ otherwise. We formalize the slowness of learning by introducing a small parameter ε such that $(A_+, A_-) = \varepsilon(\widetilde{A}_+, \widetilde{A}_-)$ and then define a slow time $t_s = \varepsilon t$. This separation of time scales allows to treat the connectivity W as a constant in Eq.1, solve for the rates exactly, and then calculate the self-consistent ODEs for the connectivity by performing the integral in Eq. 2. In this way we can determine the evolution of the recurrent synaptic weights as a function of the feedforward inputs $\mathbf{I}(\mathbf{t})$.

Recent work [3] shows that model networks with hierarchically organized clusters can fit all relevant connectivity statistics reported in slice experiments from rat cortex [4]. Our work here suggests a mechanism to account for the formation of such a clustered network structure. Namely, when sensory stimuli drive a time-varying response in a network with heterogeneous feature selectivity, the recurrent connectivity will be shaped by the cross-correlation in the firing rates as in Eq. 2. Our analysis indicates that neurons with similar time-varying response (selectivity) will form strongly interconnected clusters, while the connectivity between any pair of clusters will depend on the cross-correlation and time-lag in the sensory drive that each receives. Importantly, this rewiring only occurs due to stimulus-driven fluctuations of the neuronal activity about the baseline rates; constant rates result in no overall plasticity.

This is a joint work with Ernest Montbrió, Marina Vegué, Toni Guillamon, and Alex Roxin.

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An in silico investigation of cannabinoid CB1 receptor activation

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Cannabinoid receptor 1 (CB1) mediates the functional responses of Δ^9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive constituent of marijuana. Although significant progress has been made in understanding cannabinoid binding and receptor activation, the study of the activation mechanism of CB1 has lacked accurate structural data. Here, we use published X-ray crystal structures of CB1 to analyze the transition from inactive to active states of the receptor by performing long-timescale molecular dynamics (MD) simulations, totaling 36 μs, of the CB1 receptor bound to potent and efficacious agonists (CP-55940 and HU-210), as well as evaluating membrane lipid-mediated allosteric interactions. Receptor activation was characterized by the $W356^{6.48}$/$F200^{3.36}$ rotameric switch, the approach of $Y294^{5.58}$ and $Y397^{7.53}$, and the rigid body movement of transmembrane helix 6. These conformational changes allowed Gs protein docking, although fully active-like states of the receptor were not stabilized. Additionally, our data suggest the presence of a weak positive allosteric effect of DOPG membrane lipid on the intracellular loop 3 and the intracellular region of transmembrane helix 6 of the receptor.

This is a joint work with James A. R. Dalton and Jesús Giraldo.

Statistical regularities are explicitly learned within but not between sensory modalities

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Statistical learning (SL) is the human ability to extract statistical regularities from the environment. Most of the previous studies on SL have focused on the regularity extraction mechanisms taking place within sensory modalities but there is little evidence that statistical regularities can be learnt across different modalities. To test whether SL is a domain-general or modality-specific mechanism (Frost *et al.*, 2015), we exposed participants with a stream of visual and auditory abstract stimuli whereas they performed an oddball detection task. Stimuli were grouped into unimodal (V-V or A-A) or crossmodal (A-V or V-A) pairs and the only cue to identify a pair was a higher transitional probability between the paired elements. After 30 minutes of exposure we measured learning using a 2AFC and gathered the participants confidence on their answers. We

found that only the unimodal transitional probabilities could be explicitly reported above chance level. Our prior results favor the hypothesis that SL is a stimulus specific modular system tuned to work within but not between sensory modalities.

This is a joint work with Ruth de Diego-Balaguer and Alexis Pérez-Bellido.

Hippocampal representation of a non-spatial goal-oriented task
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The hippocampus is crucial for the neuronal processing of episodic memory and spatial navigation. Although hippocampal cells coding for place, head direction, velocity and acceleration have been widely described and linked with navigational planning, neural representation of non-spatial information supporting episodic memory processes remain underestimated. To address this, we developed a non-spatial perceptual decision-making task in which rats were trained to press a lever and hold it for at least 300 ms. Valid presses started a trial by triggering the random delivery of a GO or NO-GO stimulus. For GO stimuli, the animal was allowed to obtain an appetitive liquid reward; whereas NO-GO stimuli required behavioral inhibition. Errors were punished with timeout preceding the following the next trial. The electrical activity in CA1 hippocampal neurons was recorded during the task. Our analysis revealed neural populations representing all different phases of the task, namely, lever press, stimulus onset, lever release, choice and conjunctive representations of the previous variables. Moreover, the proportion of neurons encoding the different task variables was significantly correlated with the task performance. Our results suggest that hippocampal neurons might encode a cognitive map of the task, playing a role in the performance improvement and thus, supporting cognitive processing beyond spatial navigation.

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Inhibitory gating in the dentate gyrus
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Electrophysiological recordings have demonstrated a tight inhibitory control of hilar interneurons over Dentate Gyrus granule cells (DGgc) (Bragin *et al.*, 1995; Permía-Andrade *et al.*, 2014). This excitation/inhibition balance is crucial for information transmission (Bartos *et al.*, 2001) and likely relies on inhibitory synaptic plasticity (Vogels *et al.*, 2011).

Our experiments show that LTP induction in perforant pathway, not only potentiate glutamatergic synapses, but unexpectedly decrease feed-forward inhibition in the DG, facilitating activity propagation in the circuit. To investigate this phenomenon we propose a model based on the Izhikevich's neuronal equations. The model contains entorhinal cortex (EC) neurons, DGgc, mossy cells and two populations of hilar interneurons, basket and Hil cells. The results obtained from the numerical integration of the model equations, before and after LTP induction, support the counterintuitive experimental observation of a synaptic depression in the feed-forward inhibitory connection induced by LTP. We show that LTP increases the efficiency of the glutamatergic input to recruit the inhibitory network, resulting in a net inhibition of the basket cell population. The key role of basket cells (parvalbumin+ interneurons) is then confirmed in pharmacogenetic experiments conducted in parvalbumin-cre mice in which the activity of this cell type can be selectively enhanced or depressed. Overall, our findings suggest that LTP of the EC input increases the excitation/inhibition balance and facilitates activity propagation to the next station in the circuit by recruiting an interneuron-interneuron network that inhibits the tight control of basket cells over DGgc firing.

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Response to damage and recovering capability in clustered neuronal networks

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The analysis of the spontaneous activity in cultures derived from embryonic cortical neurons allow us to evaluate changes in dynamics when the structural connections are being perturbed. This study characterizes the degradation process of a cultured neuronal network and its recovery capabilities, to mimic a degenerative disease scenario.

Based on network theory, we focus on the evolution of two properties of the culture, namely modularity and efficiency, that picture their functional organization along degradation. Data analysis is combined with a theoretical model which displays the same behaviour observed in the experiments.

Our goal is to understand in detail how these networks react towards a disturbance, and uncover their mechanisms of recovering, as well as the interplay between the structural and the effective connectivity. In such a way, the identification of resilience methods in neuronal networks displays promising applications for the study of neuronal disorders in vitro.

Expression of the PPM1F gene is regulated by stress and associated with anxiety and depression

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Molecular mechanisms underlying psychological sequelae of exposure to stressful experiences, such as posttraumatic stress disorder (PTSD) and depression, are not well understood. Using convergent evidence from animal and human transcriptomic and genomic studies, we aimed to identify genetic mechanisms underlying depression and anxiety after traumatic experiences. From a transcriptome-wide analysis in mice, we found the Ppm1f gene to be differentially expressed in the amygdala and medial prefrontal cortex (mPFC) a week after immobilization stress. Next, we found that PPM1F messenger RNA levels in human blood were downregulated in patients with symptoms of comorbid PTSD and depression and consistently in patients with anxiety symptoms in a separate human dataset. Furthermore, we showed that a genetic variant of PPM1F, rs17759843, was associated with comorbid PTSD and depression and with PPM1F expression in both human brain and blood. Given prior reported mechanistic links between PPM1F and CAMK2, we examined blood messenger RNA of CAMK2G in humans and found it to be lower in patients with comorbid PTSD and depression. We also found that Ppm1f protein levels and colocalization with CAMK2G were altered in amygdala and mPFC of male mice. Additionally, we found a systemic dose of corticosterone blocked the depressive-like phenotype elicited by stress in female mice. Lastly, corticosterone rescued the anxiety-like phenotype and messenger RNA levels of Ppm1f in amygdala and mPFC in male mice and in mPFC of female mice. Taken together, our data suggest a mechanistic pathway involving PPM1F and CAMK2G in stress and trauma-related manifestation of anxiety and depression across species.

This is a joint work with Aliza P. Wingo, Eric Velasco, Adriana Lori, Dennis C. Choi, Tanja Jovanovic, Kerry J. Ressler, and Raül Andero.

Towards computational principles of theory of mind using cognitive architectures

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A major challenge in cognitive science and AI is to understand how intelligent agents might be able to predict mental states of other agents during complex social interactions. What are the computational principles of such a Theory of Mind (ToM)? Recent work has suggested that deep neural networks implementing pure reinforcement learning (RL) can generate ToM-like behaviors (Rabinowitz *et al.*, 2018). This raises the question whether this is a form of mimicry given the training set or a genuine acquisition of the principles underlying ToM. However, given the black-box nature of deep network approaches, computational principles

of ToM are not readily revealed by such approaches nor can we conclusively verify whether these networks genuinely develop a ToM capable of dealing with the complexity of a social world. Here we consider different hypotheses of how the human brain realizes a ToM. In particular, we propose control-based cognitive architectures to predict the model of other agents in a game-theoretic task (Battle of the Exes). Our multi-layer architecture implements top-down predictions from adaptive to reactive layers of control and bottom-up error feedback from reactive to adaptive layers. We test cooperative and competitive strategies among different agent models, demonstrating that while pure RL leads to reasonable efficiency and fairness in social interactions, there are other architectures that can perform better in specific circumstances while being fully transparent in explaining the operations. In summary, our work sheds light on central principles of ToM and its implications for machine intelligence and Human-Machine Interaction.

This is a joint work with Xerxes D. Arsiwalla, Jordi-Ysard Puigbò, and Paul Verschure.

Intracortical correlates of visually pinging working memory traces in humans

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Decoding analyses from human brain signals are increasingly used to track information stored in working memory. There is growing interest in understanding the brain mechanisms behind the enhanced decodability of working memory contents following high-contrast non-informative visual stimuli (visual pinging). This has been reported for decoding fMRI and EEG/MEG signals ((Wolff *et al.*, 2017; Wolff *et al.*, 2015) (Rose *et al.*, 2016)). In our laboratory, we have identified one intriguing condition in which visual pinging before memory cues induces stronger serial biases caused by memory traces from the previous memory trial. Our EEG decoding studies show that brain signals carry information of the previous trial item right before cue presentation (Stein *et al.*, 2018), but we do not know how visual pinging affects this residual memory trace in electrophysiological signals and how regionally specific this is. To address this question, we are recording intracortical data from intractable epilepsy patients implanted with depth electrodes for clinical monitoring. Participants are asked to perform a single-item delayed response task where they need to hold in mind the angle of a stimulus during a 1s-delay and report it afterwards using a mouse click. In half of the trials a visual stimulation is delivered 500ms before the cue is presented, while the participant keeps fixation. We set out to study the electrophysiological effect of non-specific external visual stimulation during the fixation period prior to stimulus presentation, and its relation to serial biases. Results from a first subject and the methods developed will be presented.

This is a joint work with João Barbosa, Diego Lozano-Soldevilla, Antonio Donaire, Mar Carreño, and Albert Compte.

Gene Set Enrichment Analysis (GSEA) of mouse and human transcriptomes reveals fatty acid oxidation in astrocytes

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The prevalent view in neuroenergetics is that glucose is the main brain fuel, with neurons being mostly oxidative and astrocytes glycolytic. Here we sought to determine what is unique about astrocyte mitochondria defining a mitochondrial functional signature in astrocytes. Using MitoCarta, a compendium of mitochondrial proteins, together with five transcriptomes of mouse neurons and astrocytes, we generated cell- specific databases of nuclear genes of mitochondrial proteins, classified by functional categories. Standard and in-house Gene Set Enrichment Analyses (GSEA) revealed that genes encoding for enzymes involved in fatty acid oxidation (FAO) and amino acid catabolism are consistently more expressed in astrocytes than in neurons. Importantly, FAO and oxidative-metabolism-related genes are also up-regulated in human cortical astrocytes versus the whole cortex, and in adult astrocytes versus fetal astrocytes. Moreover, distribution of genes encoding for components of different organelles with respect to their relative gene expression in adult versus fetal human astrocytes revealed that increased expression during development is a unique feature of mitochondria. In vitro, FAO coexists with glycolysis in astrocytes and is inhibited by conditions resembling in vivo task-elicited excitatory neurotransmission. Altogether, these analyses constitute the first evidence of FAO in human astrocytes, indicate that the metabolism of astrocytes is versatile and complex and reveal mitochondria as specialized organelles in these cells. Our results therefore imply that core tenets in neuroenergetics, such as glucose is the main brain fuel, ought to be revised.

This is a joint work with Abel Eraso-Pichot, Marina Brasó-Vives, Arantxa Golbano, Carmen Menacho, Enrique Claro, and Roser Masgrau.

Long-term spatial memory consolidation during sleep along developmental neuronal circuits maturation

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Sleep following encoding favors the formation of episodic long-term memory (Rasch and Born, 2013). In particular, slow wave sleep appears to support hippocampus-dependent declarative memory consolidation, i.e.; spatial tasks such as object in place recognition (OPR) (Inostroza and Born, 2013). It has been proposed that this process is supported by the phase-locking of three cortical rhythms: neocortical slow oscillations, thalamic spindles, and hippocampal sharp wave-ripples thus sustaining hippocampal-neocortical long-term storage (Sirota *et al.*, 2003; Clemens *et al.*, 2007; Mölle and Born, 2010; Latchoumane, *et al.*, 2017; Staresina *et al.*, 2015).

During postnatal development cortical oscillations related to cognitive functions and synaptic plasticity emerge in the network, such as sharp waves, theta, and gamma rhythms. Ripples begin to emerge at P14 (Lahtinen *et al.*, 2002; Buhl, Buzsaki *et al.*, 2005). Furthermore, allocentric spatial abilities emerge at an early stage, along with rat's sensorimotor repertoire (J. Altman *et al.*, 1975; Tan H. 2017). We are particularly interested in the study of oscillation phase-locking related to memory consolidation during sleep, coupled with allocentric spatial emergence during development. To address this, Long Evans pup's rats were repeatedly trained in a spatial memory task (OPR) during several postnatal days. Our data suggest that animals acquire the task at around P32, after several repetitions. Moreover, we predict that interregional connectivity will be enhanced during that period, reflected in enhanced synchrony in thalamocortical networks during sleep. According to this, we will implant multichannel electrodes in the posterior parietal cortex, somatosensory thalamus, and dorsal hippocampus (CA1) for LFP and single units recording during sleep. We hypothesize that early spatial memory reinforcement following sleep may improve the oscillation phase-locking and in consequence long-term storage.

This is a joint work with G. Valdivia, N. Espinosa, V. Tiznado, and P. Fuentealba.

Keywords: Neurosciences, electrophysiology, behavior, development.

Assessing the role of synchronization in epilepsy and sleep using time series analysis

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Deviations towards hyper-synchronization and hypo-synchronization in neu- ronal dynamics are regarded as potential characteristics of diverse neurological diseases and physiological processes. In epilepsy, these dynamics are altered as result of disturbed coordination between neuronal populations that lead to abnor- mal synchronization patterns. Moreover, sleep-wake cycle has also a strong im- pact on synchronization of brain dynamics. The application of time series analysis techniques to electroencephalographic recordings (EEG) can provide us with an advanced characterization of these underlying brain dynamics. The objective of this study is to investigate the role of synchronization in both epilepsy and sleep. The understanding of this interplay can contribute to the localization of the seizure onset zone, the brain region from which initial seizure discharges can be recorded. For this purpose we analyse all-night recordings from epilepsy patients implanted with intracranial electrodes. These recordings were performed with hybrid depth electrodes, which are a combination of cylindrical macro-contacts with recording surfaces of the order of square millimetres and micro-wires with a diameter of 40 micrometers. We use linear and non-linear as well as uni- and bivariate time series analysis techniques separately on the two different spatial

scales of recording to characterize the synchronization patterns from these recordings and thereby assess the interplay of epilepsy and sleep.

This is a joint work with Johannes Niediek, Florian Mormann, and Ralph G. Andrzejak.

Dorsomedial striatum encodes previous stimulus statistics to guide perceptual choices

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Prior experiences shape the way we perceive the world by creating expectations, a reference frame for future decisions and judgements. Little is known however about how these expectations are adjusted to the environment changing conditions.

We trained rats in an auditory discrimination task, where the probability to repeat the previous stimulus category was varied in blocks of trials. Rats adapted their behavior to the stimulus serial correlations by developing a positive (negative) repeating choice bias after correct repetitions (alternations). The repeating bias built up in series of correct repetitions /alternations but vanished after error trials, independently of the number of previous correct trials. A GLM analysis revealed that this repeating bias was composed of two history-dependent factors: (1) a lateral bias towards (away from) the side of recently rewarded (unrewarded) responses, i.e., a win-stay-lose-switch strategy; (2) a novel transition bias that reinforced recent correct repetitions and alternations. We found that the transition bias was ignored after error trials and recovered after the subsequent correct trial.

We performed bilateral excitotoxic lesions and pharmacological inactivations using muscimol on medial prefrontal cortex (mPFC), dorsomedial striatum (DMS) and posterior parietal cortex (PPC). Lesion on the mPFC significantly increased the win-stay strategy after correct trials. Similarly, lesion on DMS also enhanced the win-stay strategy significantly and diminished the loose-switch strategy and the transition bias after correct trials. These effects were more subtle for DMS muscimol inactivations. Surprisingly, inactivation of the PPC did not cause a significant change in any of the sequential effects.

We also conducted neural population recordings in DMS. Preliminary analyses showed that neurons were selective to rats' present choice, present outcome and previous trial transition type. Together, our results suggest that DMS might be accumulating behaviorally-relevant information from recent trial history in order to guide perceptual choices.

This is a joint work with Alex Hyafil, Pavel E. Rueda-Orozco, Santiago Jaramillo, David Robbe, and Jaime de la Rocha.

Stimulus expectations based on previous trials impact reaction times
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Decisions in animals are not solely grounded on current stimulus information, but previous experiences do also play an essential role in choices by shaping expectations. These expectations modify both, choice biases and reaction times (RTs). However, the mechanisms that govern the generation of prior expectations, modulate decision biases, and frame the distribution of RTs are still unclear.

We trained rats in a two-alternative forced choice auditory discrimination task, in which the probability to repeat the previous stimulus category (go left, go right) was varied in blocks of trials. To improve their performance, rats developed a strategy that exploited stimulus sequence correlations: previous correct repetitions built up a bias to repeat, whereas correct alternations promoted an expectation of stimulus alternation. An error in the immediately previous trial reset this bias, although it could be partially recovered after a correct decision in current trial. Animals mean RT decreased for expected stimuli and rose for unexpected ones with respect to the no prior situation. Finally, the impact on accuracy of the repeating bias decreased as RT increased, consistent with the bias affecting the initial position of a stimulus integrator. However, in the repeating environment, but not in the alternating environment, there was a further effect of the bias that persisted for long RTs suggesting that the bias in this environment impacts the integration throughout the stimulus.

Overall, our findings reflect that expectations modify the process of stimulus integration, allowing animals to respond faster capitalizing on the predictability of the stimulus sequence.

This is a joint work with Ainhoa Hermoso-Mendizabal, Alex Hyafil, and Jaime de la Rocha.

Calcium influx dependent plasticity model
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Hebbian plasticity means that if the firing of two neurons is correlated, then their connection is strengthened. Conversely, uncorrelated firing causes a decrease in synaptic strength. Spike-timing dependent plasticity (STDP) represents one instantiation of Hebbian plasticity, and depends on the relative timing of the pre- and post-synaptic firing. Biophysically, strengthening (long-term potentiation or LTP) or weakening (long-term depression or LTD) of glutamatergic synapses depends on the post-synaptic influx of calcium (Ca^{2+}), which changes the efficacy and the number of AMPA receptors: Weak Ca^{2+} influx leads to LTD, while strong influx causes LTP. The voltage-dependent NMDA channels are the main source of Ca^{2+} influx, but they will only open if a neuron is sufficiently

depolarized. Otherwise they are blocked by Mg^{2+}. Thus, Ca^{2+} influx requires simultaneity between the release of glutamate by the pre-synaptic neuron, and the voltage-dependent elevation of the Mg^{2+} block. This means that a coincidence of pre- and post-synaptic activity is needed for Ca^{2+} influx. Here we present a computational mechanism for Ca^{2+} dependent plasticity in a spiking neuron model. The magnitude of synaptic change depends on Ca^{2+} concentration, and the direction of change (LTD vs. LTP) is determined by the speed of Ca^{2+} influx. This model complies with the classic BCM-theory and STDP results. Furthermore, by adding a short-term depression mechanism, it also reproduces experimental observations that were obtained with triplets of spikes.

This is a joint work with Matthias S. Keil.

Temporal integration is a robust feature of perceptual decisions

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Current theories in human decision-making emphasize the capacity of the brain to integrate information over different time scales to reach best informed decisions. For perceptual decisions, this temporal integration of sensory evidence is conceptualized by the drift-diffusion model (DDM). Nevertheless, the presence of temporal integration has scarcely been tested experimentally. Here we compare how perceptual choices from monkeys performing a motion perception task can be accounted for by a discrete-time DDM model as well as two alternative models that do not rely on temporal integration. In the first alternative model (*extrema detection model*), responses simply report the motion of the first sensory frame that surpasses a certain threshold. In the second model (*snapshot model*), responses correspond to the motion to a randomly selected sensory frame. Strinkingly, both alternative models, despite lacking temporal integration, could account for accuracy level similar to highly trained animals, as well as for the observed primacy effect. However, further analyses clearly rule out that monkeys use either of these strategies. First, while the extrema detection model predicts an exaggerated influence of sensory frames with large net motion onto decisions, we found that the decision weight of sensory frames scaled sublinearly with net motion. Second, the probability of right responses depended on the sum of the net motion in the first samples and the net motion in the late samples, consistently with the DDM model but inconsistently with the snapshot model. Overall, our results show that in fixed-duration settings, even though the timing of decisions cannot be accessed experimentally, psychophysics analyses provide strong support in favor of temporal integration in perceptual decisions.

This is a joint work with Jacob Yates, Leor Katz, Alex Huk, Jonathan Pillow.

Bayesian estimation of effective connectivity
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Large scale effective connectivity is emerging as richer and more robust alternative to correlation-based measures to study the pattern of functional association between brain areas. Multivariate Ornstein-Uhlenbeck (MOU) network model has been used to extract the effective connectivity from human fMRI data and recently achieved almost perfect accuracy in classifying both subjects and cognitive conditions. The estimation method is crucial to obtain reliable network parameters. In particular a Bayesian estimation is potentially favorable because it naturally provide a way to regularize the estimation and to perform statistical inference on the parameters. In this work we compare the accuracy of a Bayesian estimation with a gradient-based optimization method. We show that Bayesian maximum a posteriori (MAP) estimate with uniform prior is equivalent to moments method for MOU. We also show that MAP estimate for connectivity in a MOU model scales poorly with number of nodes in the network as compared to the gradient-based method. In particular when the number of nodes in the network is in the order of those used for whole-brain studies ($\sim$100) the number of time points needed to get a desired accuracy is about one order of magnitude larger for Bayesian compared to gradient-based method. Finally, when used to classify cognitive conditions, the more reliable estimation of connectivity for gradient-based method reflects in much higher classification accuracy compared to Bayesian method.

This is a joint work with John P. Cunnigham, Gustavo Deco, and Matthieu Gilson.

Exploring the multidimensional memory representation of our daily life experience
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A current hallmark in Autobiographical Memory (AM) research is to unravel how individual real-life event episodes are encoded and retrieved from long-term memory. Research has shown that spatial, temporal and semantic features of an encoded event promotes clustered organization and representation of experienced event episodes' details are essential factors for the retrieval of autobiographical events. The aim of the current study is to test whether such organizational perspective can be quantified from brain patterns responses recorded when individual real life event episodes are retrieved from memory. To address this question, we recorded electroencephalographic activity (EEG) while participants retrieved their individual AMs cued by pictures taken automatically by a wearable camera from the past one-week daily life. Simultaneous GPS measures registered during the encoding week and were used to extract

spatial features of the tested memories. Deep learning algorithms were used to automatically construct semantic clusters from the pictures. Neural patterns of EEG activity elicited by each of these cues were related then related to each of these memory organization features and related to memory recollection performance.

This is a joint work with Berta Nicolás, Mariella Dimiccoli, Petia Radeva, and Lluis Fuentemilla.

Assessing perceptual surround suppression in schizophrenia
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Altered perception in the form of hallucinations is a definitory positive clinical symptom of schizophrenia. But, in addition to this type of dramatic perceptual alterations, some studies suggest that early perceptual processing of basic attributes are also affected. For motion, for example, Tadin and colleagues (Tadin *et al.*, 2006) have shown that the typical impairment in motion discriminability that occurs when a brief image increases size (perceptual surround suppression, Tadin *et al.*, 2003) is attenuated in schizophrenia to the point that patients with severe symptoms discriminate motion of large stimuli better than healthy individuals. This type of perceptual alteration is interesting because it implies that the differences in performance between patients and healthy individuals cannot be explained by a generalized behavioral impairment associated with the disease. Given that the study of Tadin included a relative small sample of 16 patients, we decided to try to replicate the study using a larger sample of 50 patients. To facilitate the collection of a large sample in the hospital, we created an iPad application to measure perceptual surround suppression. Using a cohort of 13 healthy individuals, we found estimates of surround suppression on the iPad that quantitatively matched the surround suppression measured using the conventional setting (a CRT monitor running at a high refresh rate connected to a desktop computer), which validates the iPad for assessing surround suppression. We will present preliminary data on surround suppression in patients with schizophrenia and healthy controls. Since abnormal early perceptual processing has been linked to a hypofunction of the glutamatergic system, the use of perceptual alterations as a biomarker could be useful to differentiate subgroups of schizophrenics based on the affectation of the glutamatergic system. This biomarker, thus, may help the diagnosis and follow-up on patients with schizophrenia as well as patients with other diseases in which the glutamate receptors are affected (antibody-mediated synaptopathies, for example). It might also be useful to assess the effect of drugs that target glutamate receptors.

This is a joint work with Silvia Amoretti, Rafael Marín, Josep Dalmau, Miquel Bernardo, and Albert Compte.

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Inference of neuronal connections

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Cultures of neurons provide models for neurodegenerative diseases such as Sanfilippo's, Huntington's and Parkinson's. Our current work within the MesoBrain project focuses on growing three dimensional neuronal circuits *in vitro* by guiding the growth of neurons derived from human induced pluripotent stem cells [1].

Spontaneous firing activity and synchronized bursting regimes of these cortical cultures, can be altered using physical or chemical cues. The activity of hundreds of neurons can be recorded using calcium fluorescence imaging with high spatiotemporal resolution.

In order to show the effects of mutations or drugs we study variations in the network structure formed by connections between individual neurons. We infer the direction and relative weight of connections using an algorithm based on Transfer Entropy. Simulations of neuronal activity on known network topology allow us to compare inferred networks of various algorithms. This has shown that Transfer Entropy provides a good reconstruction of the ground truth topology[2].

Local properties such as degree and clustering coefficient of given nodes can be used to study development of the network, for which we show results on rat primary cortical cultures of varying degree of aggregation [3].

This is a joint work with J. Soriano.

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Detection of interaction between brain regions: influence of sleep

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The detection of connectivity between brain regions is a well-studied problem in neuroscience. In recent years, the increased availability of multi-unit recordings of neuronal spike trains [1] helped to advance the understanding of interrelations at the level of single neurons.

In this study we analyze spiking data of intracranial recordings from epilepsy patients. We consider signals from different parts of the medial temporal lobe recorded during the awake state and different sleep stages of the patient. Our aim is to characterize interactions between these brain regions and assess their dependence on sleep stages.

In order to detect distinct types of dependence between the signals we use both linear and non- linear techniques [2-4]. We furthermore combine nonlinear interdependence measures with surrogates to test our results against different null hypotheses.

We also highlight some problems that can arise in such analyses. These include nonstationarity in the firing rate of the neurons, correlation in their temporal modulation or an insufficient number of spikes. We illustrate that these problems can hinder a reliable detection of connectivity.

This is a joint work with Thomas Kreuz, Johannes Niediek, Florian Mormann, and Ralph G. Andrzejak.

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Clinical interface for seizure-onset identification in epileptic patients

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Over 50 million people worldwide suffer from epilepsy, a disease characterized by abnormalities in brain's electrical activity. Drug-resistant epilepsy patients are potential candidates for surgery. Stereoencephalography (SEEG) is a pre-surgical technique that permits the evaluation of the epileptogenic zone by the analysis of depth electrode EEG signals placed in subcortical and cortical regions. This project builds up from a previous work by Vila-Vidal and Tauste Campo [1] in 2017, which provides an analytical framework to identify the seizure onset zone (SOZ) channels.

Medical software has become ubiquitous in healthcare applications to improve patients' assistance. In particular, computer-aided applications have started to

emerge to improve post-surgical outcomes. In this context, the aim of this work is to develop a novel medical interface that integrates the framework mentioned above to complement the standard pre- surgical diagnosis of drug-resistant epileptic patients. Specifically, the use of this interface will help clinicians' apply advanced analytical tools in a semi-automatic fashion to identify the most likely SOZ channels per patient and contrast these data with additional sources of clinical information.

The interface is run sequentially following a number of steps, which include reading the (input) seizure files per patient, computing functions on the EEG signals (such as spectrograms, multiple-channel time varying plots and channel-specific activations during a seizure event) and is customized to be user friendly and make an optimal use of time and space resources. The design of the overall application was performed through PyQt, a technology that links both Python programming language and Qt, a software used for the development of user interfaces. Overall, the interface carries out a patient-specific analysis that meets the demands of individualized treatments in nowadays personalized medicine.

This is a joint work with Manel Vila-Vidal, Adrià Tauste Campo.

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Modulating serial biases in spatial working memory with transcranial magnetic stimulation in inter-trial intervals

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Working memory is a cornerstone of cognition, accounting for our ability to maintain stable representations of stimulus properties across noise-induced temporal and spatial changes. An emerging body of evidence suggests that our mental representations of spatial cues are systematically biased towards previous information in a spatial working memory task. Modeling studies have suggested that this may be mediated by activity-dependent subthreshold mechanisms that maintain stimulus information between trials of the task. This information may thus still be accessible despite having ceased to be maintained at a neuronal spiking level. Indeed, previous studies show that memories that are not detected in electrophysiological activity can be reactivated through use of a non-specific external input such as targeted transcranial magnetic stimulation. Here, we use single-pulse transcranial magnetic stimulation to investigate the validity of current computational models of serial biases in spatial working memory. The study will examine the effect of external input during the intertrial interval of a spatial working memory task on the serial biases observed in behavioral responses. According to computational models, unspecific external input prior to the memory

cue should reactivate previous memories from synaptic traces and increase their impact on the newly memorized item, thus increasing serial biases. Our study examines serial bias through a randomized trial delayed response task where participants report with a mouse click the location of a briefly displayed dot following a short delay interval (1 s). Due to the critical role played by the dorsolateral prefrontal cortex and posterior parietal cortex in spatial working memory, we counterbalance blocks with a single TMS pulse specifically targeted to these locations. Inspired by the computational model, we hypothesize that during trials involving TMS, participants will exhibit a heightened serial bias compared to controls.

This is a joint work with João Barbosa, Josep Valls, and Albert Compte.

Information transmission in a modular neuronal network
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Despite intensive research, the mechanisms by which neurons encode information in spike trains remain poorly understood. Recent work has focused on how a FitzHugh-Nagumo neuron encodes a weak (subthreshold) sinusoidal signal, in a noisy environment [1], and on the impact of a second neuron, which does not perceive the signal [2]. By applying a symbolic time-series analysis method to the sequence of inter-spike-intervals (ISIs), preferred and infrequent spike patterns were detected, whose probabilities encode information of both, the amplitude and the frequency of the weak signal. Here we investigate whether this symbolic information-encoding mechanism is robust when the neurons are coupled in a small modular network (motivated by the modular structure of the brain). We assume that the weak signal is perceived by the neurons in only one of the modules, and the information is transmitted to the other modules in the form of more expressed and less expressed spike patterns. We analyse how the coupling parameters, the network size and its modular structure impact the encoding of weak periodic or aperiodic signals.

This is a joint work with Cristina Masoller.

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Synthesizing realistic neural population activity patterns using generative adversarial networks

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The ability to synthesize realistic patterns of neural activity is crucial for studying neural information processing. Here we used the Generative Adversarial Networks (GANs) framework to simulate the concerted activity of a population of neurons. We adapted the Wasserstein-GAN variant to facilitate the generation of unconstrained neural population activity patterns while still benefiting from parameter sharing in the temporal domain. We demonstrate that our proposed GAN, which we termed Spike-GAN, generates spike trains that match accurately the first- and second-order statistics of datasets of tens of neurons and also approximates well their higher-order statistics. We applied Spike-GAN to a real dataset recorded from salamander retina and showed that it performs as well as state-of-the-art approaches based on the maximum entropy and the dichotomized Gaussian frameworks. Importantly, Spike-GAN does not require to specify a priori the statistics to be matched by the model, and so constitutes a more flexible method than these alternative approaches. Finally, we show how to exploit a trained Spike-GAN to construct 'importance maps' to detect the most relevant statistical structures present in a spike train. Spike-GAN provides a powerful, easy-to-use technique for generating realis- tic spiking neural activity and for describing the most relevant features of the large-scale neural population recordings studied in modern systems neuroscience.

This is a joint work with Arno Onken, Eugenio Piasini, and Stefano Panzeri.

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A novel behavioural task to study the neuronal representation of long-term spatial memories

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We developed a fully automated spatial navigation task that serves as a long-term memory test to quantify recall. The task consists of a daily training session (15-20 min) where mice search for a rewarded water port from eight possible port locations, eliciting large number of correct trials (up to 60 per day). Trials are self-initiated every time the animal finds a hidden trigger zone that varies randomly from trial to trial. After trial onset, animals have 6 sec to find the rewarded port. Transient inactivation by infusion of muscimol, confirmed the hippocampal dependency to solve the task by a drastic decrease in performance

($p < 0.05$). Higher number of visits to the rewarded port compared to the non-rewarded ones ($p < 0.05$) on a recall non-rewarded session, confirms 2 and 24 hrs long-term memory. Summarizing, this novel hippocampal dependent navigation task yields a large number of trials per session with a uniform coverage of the arena. This will allow a detailed characterization of the changes in hippocampal neuronal activity during spatial learning and retrieval, once it is combined with population calcium imaging or electrophysiology.

This is a joint work with Jaime de la Rocha, Josep Dalmau, and Pablo Jercog.

Singular location and signaling profile of adenosine A_2A-cannabinoid CB_1 receptor heteromers in the dorsal striatum

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The dorsal striatum is a key node for many neurobiological processes such as motor activity, cognitive functions, and affective processes. The proper functioning of striatal neurons relies critically on metabotropic receptors. Specifically, the main adenosine and endocannabinoid receptors present in the striatum, i.e., adenosine A_{2A} receptor ($A_{2A}R$) and cannabinoid CB_1 receptor (CB_1R), are of pivotal importance in the control of neuronal excitability. Facilitatory and inhibitory functional interactions between striatal $A_{2A}R$ and CB_1R have been reported, and evidence supports that this cross-talk may rely, at least in part, on the formation of $A_{2A}R$-CB_1R heteromeric complexes. However, the specific location and properties of these heteromers have remained largely unknown. Here, by using techniques that allowed a precise visualization of the heteromers in situ in combination with sophisticated genetically modified animal models, together with biochemical and pharmacological approaches, we provide a high-resolution expression map and a detailed functional characterization of A2AR-CB1R heteromers in the dorsal striatum. Specifically, our data unveil that the A2AR-CB1R heteromer (i) is essentially absent from corticostriatal projections and striatonigral neurons, and, instead, is largely present in striatopallidal neurons, (ii) displays a striking G protein-coupled signaling profile, where co-stimulation of both receptors leads to strongly reduced downstream signaling, and (iii) undergoes an unprecedented dysfunction in Huntington's disease, an archetypal disease that affects striatal neurons. Altogether, our findings may open a new conceptual framework to understand the role of coordinated adenosine endocannabinoid signaling in the indirect striatal pathway, which may be relevant in motor function and neurodegenerative diseases.

This is a joint work with A. Chiarlone, M. Medrano, E. Resel, I. Galve-Roperh, F. Ciruela, Beat Lutz, Krisztina Monory, C. Lluís, V. Casadó, P.J. McCormick, M. Guzmán, and E.I. Canela.

Keywords: GPCR heteromerization, cannabinoid CB_1 receptor, adenosine A_{2A} receptor.

Using reinforcement learning to extract cognitive representational maps

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Setting goals and making the optimal decisions to reach those goals is a crucial part of human survival. Decision-making in complex environments requires an agent to form appropriate representations of the world based on unique experiences. The agent must do so in spite of changing goals and rewards. It is therefore critical to study how such transient and labile experiences allow us to form hierarchical representations of the environment and how we use these maps to make optimal decisions. We asked participants to find optimal paths that linked sequences of fractal pictures to a reward. Critically, these picture sequences and paths coalesced around clusters or communities' of mutually predicting stimuli, thereby eliciting the emergence of hierarchical event memory representations of the explored space, also known as 'cognitive maps'. Reinforcement learning algorithms such as SARSA were used to model the task and the participant's behavior. We found that this model was sensitive to the hierarchical representational model depicted by the task, and it was able to well explain individual learning performance throughout the task. Our findings suggest that hierarchical memory representations can be successfully extracted throughout reinforcement learning mechanisms and doing so coincides with optimal decision-making strategies.

This is a joint work with Josep Marco Pallarés and Lluís Fuentemilla.

Machine learning for neuroimaging applied to functional connectivity data

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During last years, large neuroimaging datasets have been made publicly available. These datasets, in particular fMRI scans, allow for the study of whole-brain connectivity using different multivariate approaches, and are a tool to reach better understanding of both cognition and clinical condition of the brain. In this context, statistical machine learning methods are increasingly applied to deal with this kind of high-dimensional data. Supervised and unsupervised classification techniques can be used to discriminate between populations and to make predictions of connectivity patterns for unseen data. Resting state BOLD time series are traditionally transformed into connectivity matrices, constructing in this way a new space, where a better separation between classes could be achieved. In this work, we obtained functional connectivity matrices from fMRI data of different datasets, calculated through pairwise Pearson correlation of BOLD time series. The main goal is to study the impact of different common machine learning pipelines, parameters and techniques on classification performance of both

subjects and conditions, which is of paramount importance in the new era of personalized medicine.

Characterization of grey matter connectivity changes in patients with multiple sclerosis after a neurorehabilitation program

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Aim: The aim of this study was to assess the grey matter connectivity (GM CONN) changes in patients with multiple sclerosis (MS) after a 5 weeks neurorehabilitation program (NRP), by using a graph theory approach. The final goal was to assess whether those changes were related with the clinical variables of the patients and the cognitive improvement. In addition, an exploratory study was performed in the regions where significant changes in functional CONN (assessed with resting-state) were found.

Material and methods: 15 MS patients and 5 controls were scanned before and after the NRP on a 1.5T MRI system. The protocol included 3D-T1 MPRAGE and 2D-FLAIR sequences. Brain lesion volume (LV) was determined from the FLAIR image by using the Lesion Segmentation Toolbox. From the segmented GM images, single subject networks were extracted and the size (S), degree (D), connectivity density (CD), clustering (C), path length (PL), betweenness centrality (BC), lambda (L), gamma (G) and small world (SW) parameters were quantified. Differences between groups and time points were assessed by using a univariate general lineal model with age, gender and GM volume as covariates. The baseline association between GM CONN metrics and clinical variables was assessed with partial correlations (controlling for age, gender and GM volume). The relationship between changes in GM CONN metrics and changes in cognition was also assessed with controlled partial correlations. At a regional level, changes in GM CONN were assessed with the Automatic Anatomical Labelling template at the right (R) inferior and middle temporal (TMP), left superior TMP, R superior parietal and R frontal middle orbital gyrus (Pareto *et al.*, J Neuroimaging. 2018 Feb 5. doi:10.1111/jon.12500.).

Results: GM CONN at baseline showed that betweenness centrality was decreased in MS patients compared to controls (15%, $p = 0.022$). At baseline, the LV showed a negative association with BC (-0.68; p=0.02) and L (-0.65; $p = 0.03$). After CRP, a significant decrease ($p < 0.05$) was measured in MS patients in CD, C, PL, BC and L. No differences were found between the two time points in controls. Disease duration showed a positive association with changes in the PL (0.60; p=0.04), BC (0.60; $p = 0.04$) and L (0.068; $p = 0.01$); while the LV showed a negative association with changes in G (- 0.62; p=0.04) and SW (-0.64; $p = 0.03$). No significant associations were found between global GM CNN changes and cognitive improvement after CRP. At a regional level, cognitive improvement

was associated with changes in L in the R mid TMP (-0.69; p = 0.012); and a trend was found for BC changes at the R frontal middle orbital (0.55; p = 0.06).

Conclusions: Results suggest that a NRP of 5 weeks duration induces changes at a global level in GM CONN metrics, which seem to be modulated by the disease burden. Those global changes do not seem to be related with the cognitive improvement after CRP in MS patients. At a regional level, changes in GM CONN seem to be related with cognitive improvement in MS patients after NRP in some of the explored regions. Further analysis at a regional level are needed.

Disclosure: DP, AG, JA, IG have nothing to disclosure. JSG has received compensation for consulting services and speaking honoraria from Merck-Serono, Biogen-Idec, Teva, Sanofi-Aventis and Novartis. MJA has received receipts of grants and contracts by Biogen, Novartis and Excemed. MR has received receipts of grants and contracts by Excemed. XM has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Pharmaceuticals and Almirall. AR serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, and has received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, OLEA Medical, Stendhal, Novartis and Biogen Idec.

This is a joint work with A. Garcia, B. Tijms, J. Alonso, I. Galán, M.J. Arévalo, M. Renom, X. Montalban, J. Sastre-Garriga, and À. Rovira.

Modifying the magnitude of stimulus noise can distinguish between neural mechanisms of evidence integration

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Our brains interpret ambiguous streams of information to take decisions and guide our behavior. The canonical approaches to model this cognitive function are based on diffusion processes that assume bounded or unbounded perfect integration of the stimulus. Here we study the integration process in neurobiological models with winner take all dynamics that can be reduced to a diffusion process. To show the key mechanisms that differentiate this model from the canonical ones, we characterized the integration process by quantifying the shape and magnitude of the Psychophysical Kernel. With this approach, we found that increasing the magnitude of the fluctuations of the stimulus, a new integration regime emerged, named flexible categorization, in which the attractor dynamics of the system were balanced by the stimulus fluctuation. The existence of this regime, specific of the neurobiological models, gave rise to a non-monotonic dependence of the accuracy and the response consistency on the stimulus fluctuations. The existence of

a flexible categorization regime, a signature of winner take all dynamics, could therefore be demonstrated by testing these novel predictions in a psychophysical experiment.

This is a joint work with K. Wimmer, N. Wilming, T.H. Donner, A. Roxin, and J. de la Rocha.

Towards a neural model of prediction and uncertainty
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The fact that the brain performs some kind of inference to make predictions and understand the world is a theory that has been growing in the latest years. Nonetheless, these functional theories fail to address how predictions could actually be implemented in biological brains. We derive here a mathematical implementation of such predictions that can be easily implemented as a neural network. By using gradient descent optimization methods, we derive the mathematical formulation to train a graphical model to perform statistical inference. The derivation of our model can be interpreted as a network of neurons and leads to local learning rules that can be derived from and compared to classical Hebbian learning rules. This model provides a biologically plausible implementation of statistical inference, that allows the computation of expected values and standard deviations in a neural circuit. Moreover, the uncertainty or confidence on such predictions can be extracted from the model with minimal extensions. We test the capabilities of the model in continuous function estimation and discrete classification tasks. Interestingly, our framework draws resemblance to the cortical microcircuitry, promoting a reinterpretation of the role of inhibitory interneurons and neuromodulators such as acetylcholine. All together, our model is a first step towards bridging the gap between functions and mechanisms for prediction in the brain.

This is a joint work with P. Verschure.

Basins of attraction in neural networks: A computational study
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The study of memory storage and retrieval with models of attractor neural networks dates back to the 1980's [5]. In such models memory is defined as a persistent state of the dynamics of the network, which is stored in the synaptic weight matrix [4]. Introduction of tools inherited from statistical physics, in particular the spin glass theory created for the study of magnets, allowed analytical study of the models [1]. In particular the capacity, defined as the maximum number of fixed points that the network is able to store, is still one of the main questions in the field [2, 7]. However, little is known about the basins of attraction of these fixed points.

Here we present a computational study of the basins of attraction in a network of sparse binary synapses with continuous on-line learning, similar to the Amit-Fusi model [3]. We introduce an asymmetric learning rule which is both biologically plausible and beneficial for performance. We study the connectivity of the network once the steady state is reached, and compare its properties with experimental data. We study the stability of the attractors under an homogeneous external input, which we use as a bifurcation parameter. To measure the basin of attraction, we test initial conditions increasingly perturbed from the attractor, measuring the hamming distance between initial condition and intended attractor. We also study the stability of the fixed points under increasing synaptic noise, and the ability of the system to visit different attractors when drived by noise. Finally, synaptic depression dynamics are introduced to recreate hippocampal replay situations [6].

We find that the asymmetric rule increases the resilience of the model against different depression probabilities, and that the resulting connectivity has, when parameters are in their optimal values, similar properties to real hippocampal tissue. Basins of attraction can be tuned using both external input and depression probability. Noise driven dynamics show stable attractors unreachable from random initial conditions. The use of synaptic depression allows the system to visit those attractors, to the point of overcoming capacity of the system when no noise or synaptic depression is applied.

This is a joint work with A. Roxin.

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Whole-brain synchronization after in vivo *stimulation of D1 and D2 receptor-expressing neurons*

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Whole-brain dynamics in the resting brain is phenomenon that is currently under scrupulous research (Deco *et al.*, 2016; Hindriks *et al.*, 2016). However, the effect that local neural activity has on these large-scale dynamics is not well understood. Here, I?m presenting results showing that local *in vivo* stimulation of D1 and D2

receptor-expressing neurons in the basal ganglia in mice (Lee *et al.*, 2016) create a global synchronization characterized by a coherent global functional topology (as measured by fMRI), which is consistently present in all animals. Interestingly, this large-scale hypersynchronization is only present during stimulation periods while returning back to baseline within periods of no stimulation (Figure 1). As also seen in Figure 1, similarity of connectivity matrices over time (see methods summary) is greater during stimulation periods in both protocols and this result is consistently present across all animals.

Methods summary: fMRI while in vivo periodic optogenetical stimulation in the basal ganglia was performed in 10 lightly anesthetized mice (Lee *et al.*, 2016). In total, 6 stimu- lation (on-off) periods were present in each animal. Whole-brain images were transformed into time series after motion correction, normalization and signal filtering. The brain was later parcellated into 96 regions. After applying the Hilbert transform to the time series across all regions, a whole-brain connectiv- ity matrix (CM) was constructed by computing the cosine difference between the instantaneous phase of each node pair at each time point t (Cabral *et al.*, 2017). This allowed to construct a CM at each time point in each animal, which let us explore dynamical properties at a whole-brain scale with a good temporal resolution. Later, the similarity between all CM pairs (across time) was com- puted by the correlating the lower triangular part. This information is resumed as a dynamic functional connectivity matrix or dFC (Deco *et al.*, 2016). This matrix was used to compute similarity and whole-brain synchronization scores during and after stimulation.

Conclusion: These results shed light into the intricate relationship between local neuronal activity and its effect with global dynamics. Even more interesting is the fact that these observations showed a clear periodic behavior, closely linking the effect of neuronal activity with fMRI.

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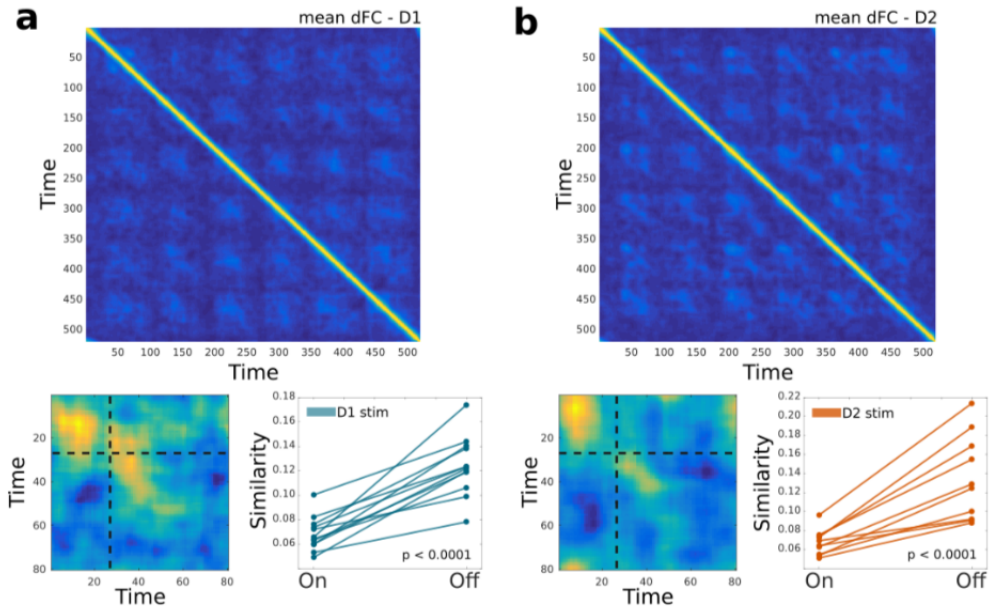

FIGURE 2. Global functional synchronization after optogenetic stimulation of the basal ganglia. a) Mean dynamic functional connectivity after D1 stimulation. Entries represent similarity between two given functional connectivity matrices over time. Lower matrix represents an extract of one stimulation period. Dotted lines depict the end of stimulation. Paired plot represents global similarity within off and on periods. b) Results for stimulation of D2-expressing neurons. p-values are generated after a paired t-test.

Hippocampal state representations supporting imagination-based and habitual decision making systems: a large-scale computational model

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Several recent experimental findings have shed light on the functional anatomy of the mammalian brain's multiple decision making systems, particularly the deliberative internal simulation- (or imagination-) based system and the more automatic habitual system. At the same time, a wealth of theoretical and computational studies in the field of Reinforcement Learning have provided understanding about the relative merits and practical pitfalls of each approach, known as model-based and model-free decision making, respectively. Despite these advances, however, the interplay between these two systems is little known, and in particular, the inevitable competition and trade-off between them has been poorly studied. In this computational study, we model these decision making

systems following our current knowledge of their large-scale functional anatomy and investigate the above questions in the context of a navigation task. To successfully solve the task, the simulated animal first has to learn to recognize its current state by integrating information from multiple noisy sensory sources, visual stimuli and proprioceptive feedback, mimicking the function of hippocampal place cells. An accurate enough model of the navigation environment allows the agent to mentally simulate the outcome of samples of potential action sequences, according to the experimentally observed imagination-based planning behaviour of rats during such tasks. Concurrently, a model of the dorsomedial striatum learns habitual state-action responses based on the outcomes of actions in each recognized states, and with learning gradually overtakes control from the deliberative systems. Competition between the two systems is induced by introducing non-stationarities to the environment, and the interplay between the systems is modelled based on a process tracking the animal's internal prediction error. This process allow the animal to fall back from a quick but inflexible habitual to a slow but flexible deliberative mode whenever the animal experiences surprise relative to its own expectations.

Unravelling episodic memory structure in a lifelike continuous experience using Hidden Markov Models

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Perception and memory have been widely studied in the context of discrete pictures or words. However, in real-life, we are faced with a continuous stream of perceptual input that arrive on a wide range of timescales. Previous studies have shown that our brain can segment this continuous stream into events that not only reveal a hierarchy from coarse to fine time-scales, but also integrate them differently throughout the cortex, with processing timescales increasing from tens of milliseconds in early sensory regions up to hundreds of seconds in higher-order regions. However, the neural mechanisms that support such event segmentation process during online encoding of a naturalistic and continuous experience remain unknown. To address this issue, we tested whether the formation of meaningful event models could be expressed by specific patterns of electrophysiological activity recorded from healthy humans elicited during the online encoding of a 50 minutes movie. A Hidden Markov Model based algorithm was used to identify latent variables in the EEG and relate them to participant?s later memory recall of the encoded events.

This is a joint work with Lluís Fuentemilla and Christopher Baldassano.

Keywords: Events, processing timescales, Hidden Markov Model

Glutamatergic modulation of working memory precision and serial biases

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Continuity of mnemonic contents in time contributes to integrating information into coherent memory representations. Recently, attractive response biases towards previously memorized locations in visuospatial delayed response tasks have been reported as evidence for continuous integration of memory contents between trials. These serial attractive biases emerge specifically during working memory (WM) delay. Assuming a beneficial role of attractive biases for the coherence of memory representations, psychiatric and neurological disorders could be characterized by atypical serial memory biases, along with impairments in memory maintenance and precision. We tested a unique population of patients recovering from anti-NMDAR encephalitis to study possible synaptic mechanisms of memory maintenance and continuous memory integration. These patients still have a decreased NMDAR mediated neurotransmission and reportedly suffer from long-term and WM deficits. We collected behavioral and electroencephalography (EEG) data from anti-NMDAR encephalitis patients and healthy control subjects performing a visuospatial delayed response task. While healthy controls' responses were significantly biased towards previous memoranda, serial attractive biases were absent in patients with reduced glutamatergic synaptic transmission. Moreover, encephalitis patients reported memorized spatial positions with lower precision than healthy controls. Both serial biases and WM precision normalized with recovery from the synaptopathy. In EEG data, we analyzed task-related changes in alpha-band power during WM delay and prior to stimulus onset. Both during WM encoding and delay, encephalitis patients showed reduced decodability of the stimulus, compared to healthy controls. Similarly, past stimulus locations could be decoded just before the onset of the new stimulus in healthy controls, but not in encephalitis patients. Persisting target-specific neural activity during delay and in the inter-trial interval might play a role in explaining behavioral differences between anti-NMDAR encephalitis patients and controls. Taken together, our findings suggest a fundamental role of the NMDAR in the within- and between-trial maintenance of short-term memory traces, potentially leading to deficits in the continuous integration of memory contents in NMDAR synaptopathies.

This is a joint work with Diego Lozano-Soldevilla, Josep Dalmau, and Albert Compte.

Differential connectivity gradient along the human hippocampal longitudinal axis with resting state networks

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The hippocampus (HPC) can evoke large-scale influences on cortical activity as it it receives convergent information from sensory and limbic cortices before sending reciprocal divergent projections back to a wide range of distributed cortical areas. However, HPC play a differential pivotal role in several cognitive processes along the longitudinal axis. For instance, the Anterior HPC (aHPC) supports the memory retrieval of global representations, pattern completion and motivational processing, while the Posterior HPC (pHPC) is associated with local representations and pattern separation.

Here, we examined whether differential functional connectivity existed along the longitudinal axes of the HPC in healthy humans with two brain-wide cortico-cortical resting state networks known to correlate to sensory, memory, and learning task performance: the Default Mode and the Salience network. These networks were identified by using Independent Component analysis and the strength of connectivity within the network was calculated voxel-wise. The results show a gradient in the strength of connectivity along the longitudinal axis, being more positive in the pHPC than the aHPC. These findings indicat the existence of differential hippocampo-cortical connectivity patterns during resting state. Functional implications of these graded connectivity are discussed

This is a joint work with Lluís Fuentemilla and Estela Cámara.

Network resilience in clustered neuronal cultures
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The understanding of the key mechanisms behind neuronal network resilience is a highly active field of research. To shed light on this study, we introduce a new experimental paradigm using *clustered* neuronal cultures upon a local physical damage. These neuronal cultures are constituted by islands of hundreds of neurons termed *clusters* and are formed through a self-organizing process. A remarkable feature of these cultures is that they display a rich spatiotemporal spontaneous activity, with assortative connectivity and a rich club core [1], features that have been related to network resilience [2, 3].

Here, we present the results of the experiments carried out in collaboration with the Institute of Photonics Sciences (ICFO), in which a single cluster of the network is silenced by a laser beam. The changes in spontaneous dynamics of these clustered networks after the physical attack allow us to study the resilience of these networks and their recovery mechanisms. In particular, our results show that local damage does not initiate a cascade of failure, but rather activates global network response to boost up recovery.

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How spaced learning affects stability of hippocampal neural correlates of memory

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In this work we assessed how the turnover of hippocampal CA1 neurons activity over days is modulated by two different spaced learning regimes.

Hippocampal CA1 neurons are of critical importance in learning and memory. As such, extensive research has been directed to elucidate the cellular mechanisms of synaptic memory consolidation, characterizing plasticity and stability of neural response as correlates of memory. Recently, by using miniaturized calcium-imaging neuronal recording systems, scientists have gained the ability to both: i) record a large number of cells with individual resolution and ii) to track these ensembles across several days, in order to understand the mechanisms of what is called system's memory consolidation. With these novel tools, (Ziv *et al.*, 2013) have demonstrated that the neuronal ensemble that participates during the activation elicited by a known event is not constant or rigid over time, but instead there is replacement rate of activation over days, called turnover. They have hypothesized that this turnover could be related to either an intrinsic physiological turnover of cell process like synaptic spines turnover, or to neural population activity dynamics dictated by cognitive processes related to memory formation and recall. We repeated this experiment changing the frequency of exposition to the same spatial task and measured how space learning influences the turnover rate of hippocampal CA1 neurons activity over days. We found indeed that the rate of turnover changes with the frequency of training. Our results shed light into how memory is encoded and recalled over long-term time scales (days to weeks) and how this information is modulated by the frequency of learning.

This is a joint work with Pablo Jercog.

Attractor dynamics of cortical assemblies underlying the transition from deep to light anesthesia

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Cortical slow oscillations (<1 Hz) are a universal hallmark of slow-wave sleep and deep anesthesia (Steriade *et al.*, 1993; Sanchez-Vives and Mattia, 2014). These slow oscillations are characterized by periods of neuronal activity (Up states) and periods of silence (Down states) showing a low degree of complexity that opens a window on understanding the brain multiscale organization, on top of which cognitive functions emerge during wakefulness. Understanding the transition

across different levels of vigilance might shed light on the emergence of the rich repertoire of neuronal dynamics underlying brain computations.

Here we investigated the dynamics of the transition from deep anesthesia towards wake-fulness by recording from neuronal assemblies of layer 5 in the primary visual cortex of the ketamine/medetomidine anesthetized rat. Our results indicate that, far from being a continuum, the transition from deep anesthesia to wakefulness is characterized by both gradual and abrupt changes in the local field potential and multi-unit activity. Crucially, we found that the sleep-like rhythms fade out when wakefulness is approached not only through the destabilization of Down states, but also through the appearance of a novel activity pattern which consists in a slow ($\sim$ 0.2 Hz) alternation between highly regular slow oscillations and short periods of awake-like activity or micro-arousals. Interestingly, the appearance of this activity pattern is accompanied by an increase in the power of beta and gamma frequency bands, associated during wakefulness to increased attentiveness and arousal (Steriade, 2005).

We reproduced these transition in a mean-field computational model of a cortical net-work (Mattia and Sanchez-Vives, 2012) by modulating the excitability and the fatigue level of the modeled network, and we identified a competition between two metaestable attractor states underlying the transition. Our model suggests that the micro-arousal pe-riods could be explained by a Hopf-like transition from a limit cycle to a stable fixed point at a high level of activity, where the slow alternation between periods of slow oscillations and micro-arousals is led by a slowly oscillating ($\sim$ 0.2Hz) excitatory input of extracortical origin. We tested our model predictions as the anesthesia faded out, finding a remarkable evidence of the proposed dynamical framework.

This is a joint work with Cristiano Capone, Maurizio Mattia, María V. Sanchez-Vives.

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Bimodality of cortical Up states and thalamic modulation of Up state duration: an experimental and computational study

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The dynamics of cortical activity during deep stages of sleep and anesthesia consists in a slow alternation of high and low firing rate states of activity

(Up and Down states, respectively) (Steriade *et al.*, 1993; Sanchez-Vives and Mattia, 2014). Although this oscillating activity observed in the cortex is also known to be present in the thalamus with a high degree of correlation (Timofeev and Steriade, 1996; Sheroziya and Timofeev, 2014), it is not clear how the two elements of the thalamo-cortical system coordinate to produce such pattern. Here, we investigate the cortical dynamics in the primary visual cortex of ketamine-medetomidine anesthetized rats, in the presence and absence of thalamic activity, in order to separate the contributions of the two elements of the thalamo-cortical system. We found that the statistics of cortical Up state duration change significantly between the two conditions. When the cortex is not receiving input from the thalamus the distribution of Up state duration is unimodal. On the contrary, when the thalamus is active the distribution becomes bimodal, suggesting the presence of two qualitatively different types of Up states. To investigate the possible mechanisms underlying the experimental observations, we used a computational model of a thalamo-cortical network of spiking neurons (Destexhe, 2009). We found that the hyperpolarization-activated Ih current in thalamic cells can account for the bimodal distribution of cortical Up state duration. Indeed, the activation of this current leads to a calcium spike in thalamocortical cells which project to the cortex, occasionally allowing for an elongation of the Up state duration. Such result further supports the hypothesis that the thalamus is not only a relay station of sensory information, as it plays a state-dependent modulatory role of the cortical persistent activity eventually affecting how information is processed and maintained as it has been described for working memory (Guo *et al.*, 2017).

This is a joint work with Cristiano Capone, Maurizio Mattia, María V. Sanchez-Vives, and Alain Destexhe.

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The role of sleep in the organization of spatial representations during memory formation

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The development in the study of place cells discovered by O'Keefe (1971) has put the focus on the study of spatial representation of the environment in the processes and functions lead by the hippocampus. Among these functions, the hippocampus plays a preponderant role in the establishment of spatial memory, in which sleep is fundamental, suggesting a possible relationship between sleep and the establishment of spatial representations by place cells.

In this line, there is a query if sleep participates in the consolidation and configuration of spatial representations. One possibility is that sleep affect the configuration of place fields in a post-sleep exploration when place cells are reactivated during slow wave oscillations in a post-learning sleep.

In this study we will evaluate the influence of sleep on the variations in the configuration of a spatial map given by changes in spatial context during a spatial memory task. Specifically, we will analyze the features of place cells recorded in hippocampal CA1 in terms of firing rate and localization of place fields of adult Long Evans rats during object in place recognition (OPR) task performance and the reactivation and temporal coupling of place cell activity with the slow wave oscillations during the post-learning sleep phase.

Here we will present our preliminary results showing that post-learning sleep enhances performance in the OPR task. We expect to find that the coupling of place cells activity with hippocampal oscillatory activity during sleep helps to establish spatial representations that allow to improve the performance of spatial memory.

The study of sleep's influence on spatial representations given by place cells in the hippocampus will allow us to understand the importance of this process in the performance of a cognitive function such as memory.

This is a joint work with Alexandra García, Vicente Tiznado, Nelson Espinosa, and Pablo Fuentealba.

Rapid memory replay of life-like episodic sequence of events precedes their verbal recall from-long term memory

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Memories of past experiences (episodic memories) are thought to be organized in a manner that preserves the temporal structure of the experience. It is unclear, however, whether their recollection involves replay of the specific sequence of events in temporal order and whether this precedes their verbal recall. In real life, events occur in a temporal succession and it has been revealed that brain can segment the information in different timescales depending of the brain

regions involved [1]. The event boundaries generated by long-timescale cortical regions are triggering hippocampal activity in order to encode information about the just-concluded event into episodic memory. Moreover, semantic congruence has already been related with an enhancement of episodic memory association and the acceleration of the onset signals of those items successfully encoded in memory [2]. In the current study, we recorded electrophysiological (EEG) activity while participants encoded life-like sequences of pictures into an episodic narrative, and in a subsequent memory test, asked them to verbally recall each sequence upon presentation of a cue (the first picture of the sequence). We have tested congruent and incongruent series of information in order to further study the impact of this conditioning factor in neural similarity and also in the event boundary formation. Behaviourally, we found that participants? verbal recall preserved the temporal order of the encoded sequence but accuracy decreased as a function of the picture?s temporal distance from the cue. Neural similarity analysis on spatio-temporal EEG patterns elicited during picture encoding and by the memory cue revealed an increase in similarity at fronto-central scalp regions within 600-1000 ms of cue onset, thereby suggesting the existence of a rapid memory replay of the encoded picture sequence triggered by the memory cue. In addition, the degree of neural similarity associated with each picture within the sequence decreased linearly, was correlated with sequence recall accuracy across participants, and varied according to whether specific items from the episodic sequence would be later recalled at the within-subject level. These findings indicate the existence of a very rapid replay of event sequences upon presentation of a memory cue preceding, and therefore possibly determining, their later verbal recall from long-term memory.

This is a joint work with Iria Rodríguez, Ignasi Sols-Balcells, Aya Ben-Yakov, and Lluís Fuentemilla.

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Neuronal dynamics underlying stable population-level working memory representations in prefrontal cortex

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Neurophysiological experiments in primates have found that during the delay period of working memory tasks, a fraction of neurons in the prefrontal cortex carries information about the stimulus as sustained activity, therefore supporting

a stable code during the whole delay period. However, many neurons show strong temporal dynamics, which has given rise to the dynamic coding model for working memory. This model proposes that due to the time-varying dynamics of single neurons, a stable memory representation can only be achieved at the population level through a linear combination of individual neural responses of a sufficiently large population of neurons.

Here we set out to investigate how prefrontal neurons with different delay-period dynamics contribute to population dynamics during an oculomotor delayed response task [1]. We first characterized the delay dynamics of single neurons based on their firing rate autocorrelation. Autocorrelation decays were heterogeneous, ranging from persistent neurons with slow decay to dynamic neurons with more transient delay activity autocorrelation. We extended the result of Murray *et al.*, [2] by analyzing how different neurons contribute to the principal components of the pseudo-population responses and found that the persistent neurons, but not the dynamic neurons, span a stable, low- dimensional mnemonic subspace.

We then used linear decoders on single neurons and compared stimulus information during different time points throughout the whole trial period. Persistent neurons carried more information than dynamic neurons on any tested time point during the delay. Moreover, by combining single neuron recordings to pseudo-population responses we found that $\sim$10% of neurons with the highest individual cue and delay selectivity provide a stable representation throughout the trial, as accurate as the whole population of 541 neurons.

In sum, we conclude that persistent neurons are the main drivers of memory-selective delay period dynamics in our data.

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An operational model for GPCR homodimers and its application in the analysis of biased signaling

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G protein-coupled receptors (GPCRs) are among the most important protein superfamilies as drug targets in drug discovery programs. Their interactions

with ligands are influenced by their homomerization. In this study, we propose an operational model for receptor homodimers, which includes constitutive receptor activity. Distinct functional response curves can be obtained from this model, which can satisfactorily depict typical complex experimental data as biphasic and bell-shaped curves. Operational parameters in the model may provide mechanistic explanations for observed functional complexity associated with the cooperativity and intrinsic efficacy of ligands. Because the herein presented model is derived within the conceptual framework of operational models, it takes advantage of the body of knowledge coming from the widespread use of this type of modeling. The operational homodimer model can also explain the biased signaling dependent on ligand concentration. In conclusion, this operational homodimer model has a wide range of applications in pharmacological research.

This is a joint work with Jesús Giraldo.

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