bordeaux neurocampus

BORDEAUX NEUROCAMPUS CONFERENCES

bordeaux neurocampus BRAIN

Probing Neuronal Circuits During Behavior

Bordeaux - September 28th-30th, 2016

Domaine du Haut-Carré (Talence)

Scientific Organizers

Frédéric Gambino
Cyril Herry
Yann Humeau

Invited Speakers

Karim Benchenane, FR
Edward Callaway, US
Ricardo Chavarriaga, CH
Rosa Cossart, FR
David Dupret, UK
Joshua Gordon, US
Anthony Holtmaat, CH
Bruce Hope, US
Thomas Klausberger, AT
Bo Li, US
Andreas Luthi, CH
Rony Paz, IL
Carl Petersen, CH
James Poulet, DE
Ryan Remedios, US
Kay Tye, US
Patrik Vuilleumier, CH
Claire Wyart, FR
Ofer Yizhar, IL

brainconf.u-bordeaux.fr

Travel grants for students available

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Linking activity of complex neuronal circuits with behavior is a key to understand how we store information, acquire new skills, and process sensory perception with cognition to initiate an optimal action in a changing environment. This critical question of Neuroscience has long been limited mostly because specific neural circuits and the computations they perform have to be identified, probed, and modulated in living animals during quantitative behaviors that engage these circuits. However, recent technical innovation from single-cell to large-scale recordings as well as modulation of neuronal spiking has brought out modern neuroscience by providing exciting toolboxes for neuroscientists.
For the first time, studying the causal relation between neural dynamics and behaviors becomes possible.

Entitled "**Probing neuronal circuits during behavior**", this unique 3rd Bordeaux Neurocampus Conference aims to gather world-leader experts in optical microscopy, electrophysiology, optogenetic, and computations for measuring and manipulating synapses, neurons and neuronal circuits at the cutting edge of brain investigation in freely behaving animals.

The Invited Speakers are:

Karim BENCHENANE, Lab. Plasticité du cerveau Paris - FR

Edward CALLAWAY, Salk Institute La Jolla - US

Ricardo CHAVARRIAGA, EPFL Lausanne - CH

Rosa COSSART, INMED Marseille - FR

David DUPRET, Université d'Oxford - UK

Joshua GORDON, NIMH Bethesda - US

Anthony HOLTMAAT, Université de Genève - CH

Bruce HOPE, NIH Baltimore - US

Thomas KLAUSBERGER, Medical University of Vienna - AT

Bo LI, Cold Spring Harbor Lab. - US

Andreas LUTHI, FMI Basel - CH

Rony PAZ, WIS Rehovot - IL

Carl PETERSEN, EPFL Lausanne - CH

James POULET, MDC Berlin - DE

Ryan REMEDIOS, Caltech Pasadena - US

Kay TYE, MIT Cambridge - US

Patrik VUILLEUMIER, Université de Genève - CH

Claire WYART, ICM Paris - FR

Ofer YIZHAR, WIS Rehovot - IL

Scientific Committee in Bordeaux:

Frédéric GAMBINO, Interdisciplinary Institute for Neuroscience (IINS) - FR

Cyril HERRY, NeuroCentre Magendie (NCM) - FR

Yann Humeau, Interdisciplinary Institute for Neuroscience (IINS) - FR

The Organizing Committee thanks the institutional and academic partners:

* Signature provisoire : le nom de la Région sera fixé par décret en Conseil d'État avant le 1er octobre 2016 suite à l'avis du Conseil régional

as well as the partners which supported the conference:

PROGRAMME AT A GLANCE

Wednesday, September 28th

08:15 - 09:15	**REGISTRATION**		
09:15-09:30	Welcome remarks by Daniel CHOQUET		
Session a.m. chaired by Andreas LUTHI			
09:30-10:05	Thomas KLAUSBERGER	-	IS 001
10:05-10:40	David DUPRET	-	IS 002
10:40-11:00	*Coffee break*		
11:00-11:35	Bruce HOPE	-	IS 003
11:35-12:10	Karim BENCHENANE	-	IS 004
12:10-12:45	Yann HUMEAU	-	IS 005
12:45-13:45	*Lunch break*		
13:45-15:00	Poster session		
Session p.m. chaired by Carl PETERSEN			
15:00-15:35	Edward CALLAWAY	-	IS 006
15:35-15:55	Charles BOURQUE	-	ST1
15:55-16:30	Rosa COSSART	-	IS 007
16:30-16:50	*Coffee break*		
16:50-17:25	Claire WYART	-	IS 008
17:25-17:45	Antoine ADAMANTIDIS	-	ST2
17:45-18:20	Kay TYE	-	IS 009

Thursday, September 29th

Session a.m. chaired by Yann HUMEAU

09:00-09:35	Frédéric GAMBINO	-	IS 010
09:35-10:10	Robert ROZESKE	-	IS 011
10:10-10:30	Joana DUARTE	-	ST3
10:30-10:50	*Coffee break*		
10:50-11:25	Patrik VUILLEUMIER	-	IS 012
11:25-12:00	Ricardo CHAVARRIAGA	-	IS 013
12:00-13:00	*Lunch break*		
13:00-14:45	Poster session		

Session p.m. chaired by Frederic GAMBINO

14:45-15:20	Carl PETERSEN	-	IS 014
15:20-15:55	Anthony HOLTMAAT	-	IS 015
15:55-16:30	James POULET	-	IS 016
16:30-16:50	*Coffee break*		
16:50-17:10	Balázs RÓZSA	-	ST4
17:10-17:45	Ryan REMEDIOS	-	IS 017

Only participants registered to the gala dinner are expected in the bus near the Agora:

18:15 = bus departure to the Château Luchey-Halde

19:00 -23:15 *Gala dinner at Château Luchey Halde* (Mérignac)*

Return will be ~ 23:15 from the Château with a first stop at the **Haut-Carré**, and a second stop Bordeaux downtown 'Allée de Munich', near the Quinconces tram station.

* 17 avenue du Maréchal Joffre
Tel: +33(0)5 56 45 97 19 - GPS. 44.820650, -0.630599

Friday, September 30th

Session a.m. chaired by Cyril HERRY

08:45-09:20	Andreas LUTHI	-	IS 018
09:20-09:55	Bo LI	-	IS 019
09:55-10:30	Rony PAZ	-	IS 020
10:30-10:50	*Coffee break*		
10:50-11:25	Joshua GORDON	-	IS 021
11:25-12:00	Ofer YIZHAR	-	IS 022
12:00-12:20	Closing remarks by Cyril HERRY		
12:20	*Departure: Lunch box*		

PROGRAMME

Wednesday, September 28th

08:15 - 09:15	**REGISTRATION**
09:15-09:30	Welcome remarks by **Daniel CHOQUET**

Session a.m. chaired by Andreas LUTHI

09:30-10:05	**Thomas KLAUSBERGER**, Medical University of Vienna (AT) *Prefrontal networks for working memory and decision making*
10:05-10:40	**David DUPRET**, Université d'Oxford (UK) *Interfering with neuronal dynamics associated with a memory of space in the hippocampus*
10:40-11:00	*Coffee break*
11:00-11:35	**Bruce HOPE**, NIH Baltimore (US) *Fos-expressing neuronal ensembles in addiction research*
11:35-12:10	**Karim BENCHENANE**, Lab. Plasticité du cerveau Paris (FR) *From necessity to sufficiency in memory research: When sleep helps to understand wake experiences*
12:10-12:45	**Yann HUMEAU**, IINS Bordeaux (FR) *Perturbing synaptic function to understand animal behavior: lessons from ID gene models*
12:45-13:45	*Lunch break*
13:45-15:00	Poster session

Session p.m. chaired by Carl PETERSEN

15:00-15:35	**Edward CALLAWAY**, Salk Institute La Jolla (US) *Genetically parsing cell types, connections and function in layer 5 of mouse visual cortex*
15:35-15:55	**Charles BOURQUE**, Montreal (CA) - *Selected talk 1* *Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep*
15:55-16:30	**Rosa COSSART**, INMED Marseille (FR) *A developmental backbone supporting adult hippocampal function?*
16:30-16:50	*Coffee break*

16:50-17:25	**Claire WYART**, ICM Paris (FR) *Light on an ancestral sensory pathway modulating posture and locomotion in vertebrates*
17:25-17:45	**Antoine ADAMANTIDIS**, Bern (CH) - *Selected talk 2* *Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation.*
17:45-18:20	**Kay TYE**, MIT Cambridge (US) *Neural circuits underlying positive and negative valence*

Thursday, September 29th

Session a.m. chaired by Yann HUMEAU

09:00-09:35	**Frédéric GAMBINO**, IINS Bordeaux (FR) *Dynamic coding of fear and safety signals in the dorsal prefrontal cortex*
09:35-10:10	**Robert ROZESKE**, NCM Bordeaux (FR) *Prefrontal-periaqueductal gray circuit controls context fear discrimination*
10:10-10:30	**Joana DUARTE**, Coimbra (PT) - *Selected talk 3* *Dimorphic brain region regulation of microglia morphology by adenosine A_{2A} receptors: uncoupling anxiety and cognition*
10:30-10:50	*Coffee break*
10:50-11:25	**Patrik VUILLEUMIER**, Université de Genève (CH) *Emotions, network dynamics, and brain states*
11:25-12:00	**Ricardo CHAVARRIAGA**, EPFL Lausanne (CH) *Brain-machine interfaces as a tool for probing motor and cognitive processes*
12:00-13:00	*Lunch break*
13:00-14:45	Poster session

Session p.m. chaired by Frederic GAMBINO

14:45-15:20	**Carl PETERSEN**, EPFL Lausanne (CH) *Neural circuits for goal-directed sensorimotor transformation*
15:20-15:55	**Anthony HOLTMAAT**, Université de Genève (CH) *Mechanisms for synaptic plasticity in the mouse somatosensory cortex*

15:55-16:30 **James POULET**, MDC Berlin (DE)
Sensory integration in the mouse forepaw system

16:30-16:50 *Coffee break*

16:50-17:10 **Balázs RÓZSA**, Budapest (HU) - *Selected talk 4*
Fast 3D imaging of spine, dendritic, and neuronal assemblies in behaving animals

17:10-17:45 **Ryan REMEDIOS**, Caltech Pasadena (US)
Deep-brain dynamics during social behaviors

18:15 => bus departure to the **Château Luchey-Halde** only for participants registered to the gala dinner

19:00 - 23:15 Gala dinner at Château Luchey Halde (Mérignac)

Friday, September 30th

Session a.m. chaired by Cyril HERRY

08:45-09:20 **Andreas LUTHI**, FMI Basel (CH)
Deconstructing fear

09:20-09:55 **Bo LI**, Cold Spring Harbor Lab. (US)
Dissecting the role of the habenula-projecting globus pallidus in reinforcement learning

09:55-10:30 **Rony PAZ**, WIS Rehovot (IL)
Adaptive rule learning in the primate brain

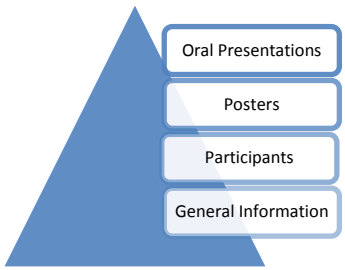
10:30-10:50 *Coffee break*

10:50-11:25 **Joshua GORDON**, NIMH Bethesda (US)
The complex contributions of a simple circuit: the role of hippocampal inputs to the prefrontal cortex

11:25-12:00 **Ofer YIZHAR**, WIS Rehovot (IL)
Understanding the role of amygdala-prefrontal projections through optogenetic perturbation

12:00-12:20 Closing remarks by **Cyril HERRY**

12:20 *Departure: Lunch box*



INVITED SPEAKERS - IS

IS 001 **Thomas KLAUSBERGER** - *Prefrontal networks for working memory and decision making*

IS 002 **David DUPRET** - *Interfering with neuronal dynamics associated with a memory of space in the hippocampus*

IS 003 **Bruce HOPE** - *Fos-expressing neuronal ensembles in addiction research*

IS 004 **Karim BENCHENANE** - *From necessity to sufficiency in memory research: When sleep helps to understand wake experiences*

IS 005 **Yann HUMEAU** - *Perturbing synaptic function to understand animal behavior: lessons from ID gene models*

IS 006 **Edward CALLAWAY** - *Genetically parsing cell types, connections and function in layer 5 of mouse visual cortex*

IS 007 **Rosa COSSART** - *A developmental backbone supporting adult hippocampal function?*

IS 008 **Claire WYART** - *Light on an ancestral sensory pathway modulating posture and locomotion in vertebrates*

IS 009 **Kay TYE** - *Neural circuits underlying positive and negative valence*

IS 010 **Frédéric GAMBINO** - *Dynamic coding of fear and safety signals in the dorsal prefrontal cortex*

IS 011 **Robert ROZESKE** - *Prefrontal-periaqueductal gray circuit controls context fear discrimination*

IS 012 **Patrik VUILLEUMIER** - *Emotions, network dynamics, and brain states*

IS 013 **Ricardo CHAVARRIAGA** - *Brain-machine interfaces as a tool for probing motor and cognitive processes*

IS 014 **Carl PETERSEN** - *Neural circuits for goal-directed sensorimotor transformation*

IS 015 **Anthony HOLTMAAT** - *Mechanisms for synaptic plasticity in the mouse somatosensory cortex*

IS 016 **James POULET** - *Sensory integration in the mouse forepaw system*

IS 017 **Ryan REMEDIOS** - *Deep-brain dynamics during social behaviors*

IS 018 **Andreas LUTHI** - *Deconstructing fear*

IS 019 **Bo LI** - *Dissecting the role of the habenula-projecting globus pallidus in reinforcement learning*

IS 020 **Rony PAZ** - *Adaptive rule learning in the primate brain*

IS 021 **Joshua GORDON** - *The complex contributions of a simple circuit: the role of hippocampal inputs to the prefrontal cortex*

IS 022 **Ofer YIZHAR** - *Understanding the role of amygdala-prefrontal projections through optogenetic perturbation*

SELECTED TALKS - ST

ST 1 **Charles BOURQUE** - *Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep*

ST 2 **Antoine ADAMANTIDIS** - *Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation*

ST 3 **Joana DUARTE** - *Dimorphic brain region regulation of microglia morphology by adenosine A_{2A} receptors: uncoupling anxiety and cognition*

ST 4 **Balázs RÓZSA** - *Fast 3D imaging of spine, dendritic, and neuronal assemblies in behaving animals*

ABSTRACTS

INVITED SPEAKERS - IS

IS 001

Prefrontal networks for working memory and decision making

Thomas KLAUSBERGER

Center for Brain Research, Dept. for Cognitive Neurobiology, Med. Univ. of Vienna, Austria

The distributed temporal activity in neuronal circuits of the prefrontal cortex combines emotional information with episodic and spatial memory to guide behavioural action. Single neurons of often unknown identity have been shown to exhibit specific firing patterns during spatial navigation and decision-making tasks. The cerebral cortex consists of highly diverse neuronal types with distinct synaptic connectivity, molecular expression profile and contribution to network activity. Neurons can be divided into excitatory pyramidal cells, which use glutamate as a neurotransmitter and give both local and long-range axonal projections, and inhibitory interneurons, which are GABAergic and control the activity and timing of pyramidal cells mainly through local axons. These neurons can be further subdivided on the basis of their distinct axo-dendritic arborisations, subcellular post-synaptic targets, and by their differential expression of signalling molecules, including receptors, ion channels, neuropeptides, transcription factors and Ca^{2+} binding proteins. We aim to determine how distinct types of neuron support the executive functions of the prefrontal cortex.

We have recorded from identified GABAergic interneurons and pyramidal cells in the prefrontal cortex of freely-moving rats using the juxtacellular recording and labelling technique. We investigated their contribution to network oscillations and a delayed cue-matching-to-place task involving working memory and decision making. The neuronal identity was determined with post-hoc histochemical analysis. We observed pyramidal neurons which showed task-related firing patterns: neurons that represented the future goal and neurons that fired preferentially during distinct periods of the task. These firing patterns were modulated by the activity of distinct types of interneuron.

We have developed a novel technique that allows the recording of unequivocally identified neurons and show how distinct types of neuron contribute to prefrontal network operations and executive behavior. Our results indicate that GABAergic interneurons release GABA at distinct times to different domains of pyramidal cells contributing to the formation of cell assemblies and representations in the prefrontal cortex.

IS 002

Interfering with neuronal dynamics associated with a memory of space in the hippocampus

David DUPRET

MRC Brain Network Dynamics Unit at the University of Oxford, Mansfield Road, Oxford OX1 3TH, United Kingdom

How does the brain support the emergence of new internal representations of the external world and what are the mechanisms underlying the strengthening of those that finally persist? In this talk I will present a series of experiments addressing these questions by monitoring and manipulating neuronal activity in the hippocampus, a circuit that provides a map-like representation of space. First, I will present recently published work establishing how optogenetic interventions in behaving mice allow the emergence of alternative representation of space to influence a drug-place memory. I will then present ongoing experiments demonstrating a central role of reverberating activity during sleep/rest behaviour in the consolidation of newly-acquired place representations. Finally, I will present preliminary data revealing a possible network mechanism underlying the behavioural translation of neural representation of space in hippocampal-accumbens axis. Overall, these findings highlight how short-timescale neuronal dynamics can support the expression of internal representation of space and their translation into actions.

IS 003

Fos-expressing neuronal ensembles in addiction research

Bruce HOPE

Neuronal Ensembles in Addiction Section, National Institute on Drug Abuse Intramural Research Program, NIH

Learned associations between drugs and environment play an important role in addiction and are thought to be encoded within specific patterns of sparsely distributed neurons called neuronal ensembles. This hypothesis is supported by correlational data from *in vivo* electrophysiology and cellular imaging studies in relapse models in rodents. In particular, cellular imaging with the immediate early gene *c-fos* and its protein product Fos has been used to identify sparsely distributed neurons that were strongly activated during conditioned drug behaviors such as drug self-administration and context- and cue-induced reinstatement of drug seeking. We have used Fos and the *c-fos* promoter to demonstrate causal roles for Fos-expressing neuronal ensembles in prefrontal cortex and nucleus accumbens in conditioned drug behaviors. I will be describing work using our Daun02 inactivation procedure to ablate

specific neuronal ensembles and selective disruption of their associated memories. We have used fluorescence-activated cell sorting (FACS) of Fos-expressing neurons to identify unique molecular alterations that are induced only within behaviorally activated neuronal ensembles and not in the surrounding less activated neurons. We have used transgenic Fos-GFP rats and mice to demonstrate that unique electrophysiological alterations are induced only in behaviorally activated neurons and not in the surrounding less activated neurons. In general, we observe alterations only in the 1% of neurons within neuronal ensembles that were strongly activated and shown to mediate conditioned drug behaviors, with little or no alterations in the surrounding less activated neurons. We will also describe our recent Fos-Tet-Cre transgenic rats that induce Cre recombinase only in strongly activated neurons within a 6-hour time window following systemic injections of tetracycline. We have used these rats to demonstrate reactivation of similar ventromedial prefrontal cortex neuronal ensembles activated on two different days, along with optogenetic inhibition of these ensembles to demonstrate their roles in context-induced reinstatement of cocaine seeking. We now use these rats to assess the roles of our previously described molecular and cellular alterations in Fos-expressing neuronal ensembles.

IS 004

From necessity to sufficiency in memory research: When sleep helps to understand wake experiences

Karim BENCHENANE

Brain Plasticity Unit, UMR 8249 CNRS ESPCI-ParisTech

Memory is the ability to adapt our behavior by using a stored information that has been previously encoded. Sleep is known to be crucial for memory consolidation and its beneficial effect are though to rely on reactivation during sleep of activity patterns encoded during wake. The first investigations of the neuronal bases of the memory trace concerned its properties (location, cellular and molecular mechanisms, among others). However, to understand how memory processes are achieved at the scale of neurons, we must provide evidence about the necessity of a neuronal subpopulation to support the memory trace, but also its sufficiency.

This question can be addressed by studying hippocampal neurons in spatial memory tasks. These neurons called "place cells" fire when animals are in a particular location of the environment, called "place field". Accordingly, hippocampal place cells assemblies are believed to support the cognitive map that is used to drive spatial behavior. Moreover, it has been show that place cells' activity observed during waking is replayed during subsequent sleep, and it has been proposed that these reactivations are involved in memory consolidation.

To test the causal relationship between place cell firing and the location in physical space, we developed a brain machine interface allowing the identification of a single place cell in real time that triggered automatically electrical stimulations of medial forebrain bundle known to induce

reward in rodent. Using this BCI during sleep allowed us to use the activity of a place cells when its firing is decorated from the true position of the animal in the environment. By triggering intracranial rewarding stimulations by place cell spikes during sleep, we induced an explicit memory trace, leading to a goal-directed behavior toward the place field. In addition to the evidence of a creation of memory during sleep, this demonstrates that place cells' activity during sleep still conveys relevant spatial information and that this activity is functionally significant for navigation.

IS 005

Perturbing synaptic function to understand animal behavior: lessons from ID gene models

Chun-Lei ZHANG[1], Mattia AIME[1], Emilie LAHERANNE[1], Xander HOUBAERt[1], Christelle MARTIN[1], Marilyn LEPLEUX[1], Elisabeth NORMAND[2], Jamel CHELLY[3,4], Etienne HERZOG[1], Pierre BILLUART[3] and **Yann HUMEAU**[1§]

[1] *Team synapse in cognition, Institut Interdisciplinaire de Neurosciences, Centre National de la Recherche Scientifique CNRS UMR5297, Université de Bordeaux, Bordeaux, France.*

[2] *Pole in vivo, Institut Interdisciplinaire de Neurosciences, Centre National de la Recherche Scientifique CNRS UMR5297, Université de Bordeaux, Bordeaux, France.*

[3] *Centre National de la Recherche Scientifique, Université Paris Descartes, Institut National de la Santé et de la Recherche Médicale, UMR8104, Institut Cochin, 75014 Paris, France.*

[4] *Team médecine « translationnelle et neurogénétique » IGBMC - CNRS UMR 7104 - Inserm U 964, Université de Strasbourg, Illkirch, France.*

Synaptic function and plasticity are thought to be crucial for learning and memory, More than 400 genes have been identified as causing intellectual disability, and a big proportion of them are coding for synaptic proteins for which functional roles has not yet been clarified. We profit from animal models bearing homologous ID gene mutations to 1) characterize eventual synaptic deficits associated with the absence of the ID gene product, 2) identify behavioral phenotypes that would involve discrete and precise neuronal circuits, and 3) to establish a formal link between synaptic and behavioral phenotypes by tempting phenotypic correction at the behavioral level by optogenetic and pharmacological in vivo manipulations.
Here we will present recent data on *Ophn1* deficient mice suggesting that the absence of oligophrenin1 generate perseverative behaviors due to a secondary increase of PKA activity within the mPFC.

IS 006

Genetically parsing cell types, connections and function in layer 5 of mouse visual cortex

Edward CALLAWAY

The Salk Institute for Biological Studies, La Jolla, California, USA

Cortical layer 5 (L5) pyramidal neurons integrate inputs from many sources and distribute outputs to cortical and subcortical structures. Previous studies demonstrate two L5 pyramid types: cortico-cortical (CC) and cortico-subcortical (CS). We use Cre-expressing mouse lines to characterize connectivity and function of these cell types in mouse primary visual cortex and reveal a new subtype. Unlike previously described L5 CC and CS neurons, this new subtype does not project to striatum [cortico-cortical, non-striatal (CC-NS)] and has distinct morphology, physiology and visual responses. Monosynaptic rabies tracing reveals that CC neurons preferentially receive input from higher visual areas, while CS neurons receive more input from structures implicated in top-down modulation of brain states. CS neurons are also more direction-selective and prefer faster stimuli than CC neurons. These differences suggest distinct roles as specialized output channels, with CS neurons integrating information and generating responses more relevant to movement control and CC neurons being more important in visual perception.

The studies described above utilized a newly engineered rabies virus glycoprotein (oG) to facilitate monosynaptic rabies tracing. Current methods utilize complementation of glycoprotein gene-deleted rabies of the SAD B19 strain with its glycoprotein, B19G, to mediate retrograde trans-synaptic spread across a single synaptic step. In most conditions this method labels only a fraction of input neurons and would thus benefit from improved efficiency of trans-synaptic spread. Here we report newly engineered glycoprotein variants to improve trans-synaptic efficiency. Among them, oG (optimized Glycoprotein) is a codon-optimized version of a chimeric glycoprotein consisting of the transmembrane/cytoplasmic domain of B19G and the extracellular domain of rabies Pasteur virus strain glycoprotein. We demonstrate that oG increases the tracing efficiency for long-distance input neurons up to 20-fold compared to B19G. oG-mediated rabies tracing will therefore allow identification and study of more complete monosynaptic input neural networks.

IS 007

A developmental backbone supporting adult hippocampal function?

Susanne REICHINNEK, Arnaud MALVACHE, Vincent VILLETTE, Caroline HAIMERL and **Rosa COSSART**

INMED Marseille - FR

Most adult cortical dynamics are dominated by a minority of highly active neurons distributed within a silent neuronal mass. If cortical spikes are sparse, spiking of single distinct neurons can impact on network dynamics and drive an animal's behavior. It is thus essential to understand whether this active and powerful minority is predetermined and if true to uncover the rules by which it is set during development. In this talk, I will present data supporting the possibility that birthdate is a critical determinant of neuronal network function into adulthood. More specifically, we reason that neurons that are born the earliest are primed to participate into adult network dynamics. This hypothesis is considerably fed by our past work aiming at understanding how cortical networks function and assemble during development. To test the hypothesis that early born cells are primed to be recruited in the active minority of neurons in the adult hippocampus, we needed to probe microcircuit function in vivo, where the extensive and long-range connectivity of these cells is preserved. I will show how we have translated from the in vitro to the in vivo situation, our multidisciplinary method to investigate structure-dynamics relationship in cortical networks.

IS 008

Light on an ancestral sensory pathway modulating posture and locomotion in vertebrates

Urs Böhm[1], Lydia Djenoune[1], Kevin Fidelin[1], Jeff Hubbard[1], Andrew Prendergast[1], Jenna Sternberg[1], **Claire WYART**[1]

[1] *Institut du Cerveau et de la Moelle épinière (ICM), Inserm U1127, CNRS UMR 7225 UPMC Paris-6 Sorbonne Universités, Campus Hospitalier Pitié-Salpêtrière, Paris, France*

The cerebrospinal fluid (CSF) is a complex solution circulating around the brain and spinal cord. Behavior has long been known to be influenced by the content and flow of the CSF, but the underlying mechanisms are completely unknown. CSF-contacting neurons by their location at the interface with the CSF are in ideal position to sense CSF cues and to relay information to the nervous system. By combining electrophysiology, optogenetics, bioluminescence monitoring with calcium imaging in vivo, we demonstrate that neurons contacting the CSF in the spinal cord detect local bending and in turn feed back GABAergic inhibition to multiple interneurons driving locomotion in the ventral spinal cord. Behaviour analysis of animals deprived of this mechano-sensory pathway reveals its contribution in modulating frequency and duration of locomotion. Altogether our approach developed in a transparent animal model shed light on a novel pathway enabling sensory motor integration between the CSF and motor circuits in the spinal cord.

References

* Böhm UL, Prendergast A, Djenoune L, Nunes Figueiredo S, Gomez J, Stokes C, Kaiser S, Suster M, Kawakami K, Charpentier M, Concordet JP, Rio JP, Del Bene F, Wyart C. **Nat Commun.** 7:10866 (2016).

* Fidelin K, Djenoune L, Stokes C, Prendergast A, Gomez J, Baradel A, Del Bene F, Wyart C. **Curr Biol.** 25:3035-47 (2015).
* Djenoune L, Khabou H, Joubert F, Quan FB, Nunes Figueiredo S, Bodineau L, Del Bene F, Burcklé C, Tostivint H, Wyart C. **Front Neuroanat.** 8:26 (2014).
* Hubbard J, Böhm U, Stokes C, Wyart C, in revision.
* Wyart C, Del Bene F, Warp E, Scott EK, Trauner D, Baier H, Isacoff EY. **Nature**, 461, 407 (2009).

IS 009

Neural circuits underlying positive and negative valence

Kay TYE

MIT Cambridge - USA

The Tye Lab is interested in understanding how neural circuits important for driving positive and negative motivational valence (seeking pleasure or avoiding punishment) are anatomically, genetically and functionally arranged. We study the neural mechanisms that underlie a wide range of behaviors ranging from learned to innate, including social, feeding, reward-seeking and anxiety-related behaviors. How are these circuits interconnected with one another, and how are competing mechanisms orchestrated on a neural population level? We employ optogenetic, electrophysiological, electrochemical, pharmacological and imaging approaches to probe these circuits during behavior.

IS 010

Dynamic coding of fear and safety signals in the dorsal prefrontal cortex

Frédéric GAMBINO

Institut Interdisciplinaire de Neurosciences, Centre National de la Recherche Scientifique CNRS UMR5297, Université de Bordeaux, Bordeaux, France

Discrimination of threat versus safety environments is of crucial importance for accurate behaviors as many anxiety disorders, such as post-traumatic stress disorder (PTSD), might be related to fear overgeneralization to harmless environment. While threat learning has been extensively studied using classical fear conditioning, the synaptic mechanisms by which brain encodes safety signals remain largely ignored. Interestingly, the medial prefrontal cortex (mPFC)-basolateral amygdala (BLA) system has emerged as a potent candidate for top-down modulation of both fear learning and extinction. Here, by combining optogenetic, whole-cell recordings and two-photon calcium imaging during discriminative fear conditioning tasks, we revealed a new bottom-up synaptic mechanism that might participate in the formation of discriminative memory traces within the dorsal PFC (dPFC) before the activation of the mPFC to BLA circuit.

IS 011

Prefrontal-periaqueductal gray circuit controls context fear discrimination

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Reducing behavioural uncertainty and appropriately selecting defensive or exploratory behaviours is critical for survival and is strongly influenced by the surrounding environment. Contextual discrimination is a fundamental process for the selection of appropriate defensive behaviour, which is thought to rely on the medial prefrontal cortex (mPFC). Interestingly mPFC circuits for context fear discrimination have not been extensively investigated. In a novel fear conditioning paradigm we systematically altered contextual elements that were present during conditioning to produce periods of fear discrimination during testing. To identify the neuronal circuits supporting contextual fear discrimination we performed single unit recordings coupled with optogenetic manipulations in the mPFC of behaving mice. Re-exposure to the conditioned context produced high levels of freezing, however sequential removal of contextual elements led to context fear discrimination. During fear discrimination we observed elevated activity of dmPFC pyramidal neurons. Consistent with these electrophysiological findings, light-induced activation of dmPFC pyramidal neurons projecting to the ventrolateral periaqueductal gray reduced freezing during contextual fear generalization. In contrast, light-induced inhibition of this same pathway elevated freezing to the discriminated context. Together, these findings suggest that the prefrontal-periaqueductal gray is part of a circuit controlling contextual fear discrimination.

IS 012

Emotions, network dynamics, and brain states

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Emotions do not only serve to assign a particular value to objects or events forming the content of consciousness, but can directly regulate perception, attention, or memory, thus shaping the content of consciousness and action. The talk will describe brain mechanisms by which positive

or negative emotional episodes can influence mental states and cognitive functions in a sustained manner, over prolonged period of time following the emotion eliciting events. Using functional neuroimaging in healthy people and psychiatric patients, our work demonstrates dynamic and lasting changes in both activity and connectivity of brain networks following transient emotion episodes. These effects are strongly modulated by individual affective traits or personality factors. Our findings have implications for better understanding and assessing changes in brain function associated with mood and anxiety disorders.

IS 013

Brain-machine interfaces as a tool for probing motor and cognitive processes

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Brain-machine interfaces (BMI) decode neural activity into commands used to control external devices (i.e. neuroprosthetics) for restoring or substitute lost motor capabilities [1]. Since neuroprosthetic devices are expected to operate in real-life situations, research in BMI is required to develop methods able to process neural activity in a single-trial basis in less-controlled scenarios than typical protocols used in laboratory conditions. In consequence, these methods provide a powerful tool to evaluate neural processes mediating motor and cognitive capabilities in realistic situations (e.g, [3]).

Here we discuss how BMI methods can be applied to investigate the neural patterns elicited in two exemplar cases: (i) movement intention and (ii) cognitive monitoring). In the first case we present single-trial analysis of movement-related patterns using both intra-cranial electrodes and scalp electroencephalography. In all cases, neural patterns preceding self-paced movement execution can be identified [2]. Furthermore, we show how BMI systems in combination with peripheral neuromuscular stimulation can be used to support motor rehabilitation after stroke.

In the second case we illustrate how EEG correlated of cognitive monitoring can be observed and decoded in different situations [4]. In particular, we cortical responses evoked by error perception while interacting with external devices are particularly stable across different feedback modalities and situations –ranging from simple visual stimuli to interactions with real robots. Furthermore, we show how these monitoring signals can be used to control a neuroprosthetic device [5].

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IS 014

Neural circuits for goal-directed sensorimotor transformation

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A key function of the brain is to interpret incoming sensory information in the context of learned associations in order to guide adaptive behavior. However, the precise neuronal circuits and causal mechanisms underlying goal-directed sensorimotor transformations remain to be clearly defined for the mammalian brain. Technological advances in mouse genetics to define cell-types, in optogenetics to control neuronal activity, and in electrophysiological and imaging techniques to precisely measure neuronal activity now begin to make it possible to obtain a detailed mechanistic understanding of the neuronal circuits driving learned goal-directed sensorimotor transformations. Here, I will discuss my laboratory's efforts to characterize a simple behavior in which thirsty head-restrained mice learn to lick a water reward spout in response to a 1 ms deflection of the C2 whisker. Although we are very far from a complete understanding, we find evidence for cell-type specific contributions of different neurons in both neocortex and striatum, which are likely to participate causally in both learning and execution of this reward-motivated sensorimotor task.

IS 015

Mechanisms for synaptic plasticity in the mouse somatosensory cortex

Anthony HOLTMAAT

Université de Genève - CH

In the somatosensory cortex synapses appear and disappear on a daily basis. The rate of synapse turnover depends on sensory input, and the stability of synapses is likely to be associated with long term potentiation (LTP) and depression (LTD)-like processes. We have focused on different forms of sensory-evoked LTP in cortical pyramidal cells. Using whole cell recordings in vivo, we found that LTP can readily be evoked using spiking-dependent paradigms but also using sensory stimuli that do not evoke spikes. Spiking-independent LTP relies on dendritic NMDA-conductances that are in part dependent on the activity of paralemniscal synaptic pathways. The data suggest that the repeated coincident activity of a paralemniscal feedback circuitry may increase L2/3 neurons' sensitivity to future sensory stimuli. Indeed,

preliminary data suggest that LTP-evoking sensory stimuli do cause long-term changes in sensory-evoked calcium dynamics in L2/3 cells. Further characterization of the synaptic circuits underlying feedback-driven plasticity in brain slices suggests that direct and repeated co-activation of paralemniscal and lemniscal synaptic inputs on L2/3 pyramidal cells is sufficient to evoke LTP in the absence of somatic spikes.

IS 016

Sensory integration in the mouse forepaw system

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Primary motor cortex (M1) neurons are involved in the control of voluntary movement, but also respond to sensory stimulation. The heterogeneity of functional response properties and the relationship between sensory input and motor output in M1 is not well understood. Here I will present a study of mouse forelimb M1 during a sensory-triggered reaching task. Mice were trained to reach and press a sensor following brief tactile stimulation of the same forepaw. Extracellular recordings in layer 5 showed that M1 neurons fire preferentially during either early (sensory) or late (motor) phases of the task. Additional independent properties covaried with this categorization including the response to a preparatory sound cue and the recovery dynamics from brief, local M1 optogenetic inhibition. The amplitude of reaching correlated to the firing rate of M1 neurons and was altered by pharmacological and phasic optogenetic inhibition of M1. Together our data suggest that functionally distinct subsets of M1 neurons are key for sensorimotor transformation.

IS 017

Deep-brain dynamics during social behaviors

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Social behaviors such as mating and fighting are important for an animal's chances at reproduction or survival. Neuronal circuits within the amygdala and hypothalamus have been demonstrated, by this lab and others, to control such social behaviors. Cell-type specific optogenetic perturbations identified GABAergic neuronal populations in the medial amygdala that promoted aggression[1], and estrogen receptor-expressing neurons in the ventromedial hypothalamus that were necessary and sufficient for eliciting mating and fighting[2].

However, mating and fighting are also thought of as instinctive behaviors: actions that are performed without any prior experience. Now using microendoscopic deep-brain imaging we analyzed ventromedial hypothalamic population activity in freely behaving male mice, during social interactions with male and female conspecifics. We discovered that population activity largely represented intruder sex identity, encoded by mostly non-overlapping, male- and female-specific neuronal ensembles. Surprisingly, these well-separated representations were not present in socially naïve mice, where the representations were largely overlapping. When these mice gained social experience the male- and female-specific ensembles stabilized. This suggests that stable, non-overlapping neuronal assemblies representing conspecific sex identity emerge in an experience-dependent manner. These findings provide new insights into understanding deep-brain neuronal dynamics that underlie social behaviors.

References:
1 Hong, W *et al*. Antagonistic Control of Social versus Repetitive Self-Grooming Behaviors by Separable Amygdala Neuronal Subsets. *Cell* **158**, 1348-1361.
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IS 018

Deconstructing fear

Andreas LUTHI

FMI Basel - CH

Classical fear conditioning is one of the most powerful models for studying the neuronal substrates of associative learning and for investigating how plasticity in defined neuronal circuits causes behavioral changes. My talk will focus on the organization and function of the neuronal circuitry of fear. I will discuss recent data demonstrating that functionally, anatomically and genetically defined types of amygdala neurons are precisely connected within the local circuitry and within larger-scale neuronal networks, and contribute to specific aspects of fear learning and extinction.

IS 019

Dissecting the role of the habenula-projecting globus pallidus in reinforcement learning

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The habenula-projecting globus pallidus (GPh), a phylogenetically conserved non-motor output of the basal ganglia, has recently emerged as a key controller of the brain's reward system. It

excites the lateral habenula (LHb) that, in turn, drives inhibition onto dopamine neurons when an outcome is worse than expected, and is thus thought to provide the "prediction error" signal essential for learning to avoid unrewarding actions. However, whether the GPh contributes to such a learning process has never been examined, and consequently how it influences behaviour remains unclear. Here we show that the GPh plays a more fundamental behavioural role than currently believed, as it is critical for reinforcing behaviours that lead to reward as well as discouraging those that do not. We found in a classical conditioning task that individual mouse GPh neurons were inhibited or excited, respectively, when an outcome was better or worse than expected. Mimicking these prediction error signals with optogenetic inhibition or excitation was sufficient to drive positive reinforcement or punishment in a probabilistic switching task. Moreover, cell-type-specific synaptic manipulations revealed that the inhibitory and excitatory inputs to the GPh are necessary for mice to appropriately respond to positive and negative feedback, respectively. Our results provide the first direct evidence that the GPh conveys both positive and negative evaluation signals to update the expected value of actions during reinforcement learning.

IS 020

Adaptive rule learning in the primate brain

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We develop a paradigm that allows learning of different rules on a daily basis, and using a feature-based representation we describe dynamics of single neurons recorded in the primate cortex and striatum. We find that neurons in the cingulate-cortex and the Putamen gradually represent the correct category as monkeys learn the rules, whereas the Caudate represent the choice itself. We identify two "types" of learning using a geometrical representation in the feature-space: rotation towards the category, and increase in magnitude. Dynamics of these properties (angle and magnitude) closely match the animals' behavior yet differ between the cortex and the striatum. The framework can be applied by neurons (and experimenters), and can be interpreted in terms of thesegeometric properties: Angular change reflects a search for the new policy; whereas magnitude change reflects changing SNR (or 'confidence').

IS 021

The complex contributions of a simple circuit: the role of hippocampal inputs to the prefrontal cortex

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It is now commonplace to use optogenetic terminal inhibition to probe the functional role of specific projections in behavior. Yet the consequences of such inhibition on neural activity *in vivo* are often inferred rather than directly measured. To test the role of hippocampal inputs to the prefrontal cortex in anxiety-related behavior and spatial working memory, we expressed eArch3.0 in hippocampal neurons and illuminated their terminals in the medial prefrontal cortex (mPFC) during behavior. Simultaneous neural recordings were obtained from the ventral and dorsal hippocampus and the mPFC. Inhibiting vHPC-mPFC inputs impaired task-related neural coding in both tasks, despite minimal effects on firing rates. The effects on neural dynamics were task dependent. Specifically, terminal inhibition impaired gamma-frequency synchrony during the spatial working memory task, and theta-frequency synchrony during the anxiety task. These results demonstrate task-specific contributions of a single circuit element to circuit dynamics.

IS 022

Understanding the role of amygdala-prefrontal projections through optogenetic perturbation

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Animals display fear-associated behavioral responses in the presence of potentially threatening environments or cues. Fear learning invovles the formation of persistent memories linking specific sensory cues with threat, thereby using past experience to avoid such threats. Once a cue is no longer predictive of threat, extinction learning allows the suppression of excessive fear responses. While fear memories can be adaptive, persistent fear memories and failure of extintion have been associated with fear and anxiety disorders[1]. The basolateral amygdala (BLA) and the medial prefrontal cortex (mPFC) are thought to play a key role in coordinating the acquisition and extinction of learned fear associations[2] through strong reciprocal monosynaptic excitatory connections linking these two regions[3]. Whereas mPFC input to BLA was shown to play a major role in fear acquisition and extinction, the reciprocal pathway has received less attention. I will describe experiments aimed at delineating the role of BLA-mPFC synaptic transmission in acquisition and extinction of fear memories. We devised an optogenetic stimulation protocol that triggers long-term synaptic depression in BLA axonal terminals onto mPFC cells. In behaving mice, synaptic depression of BLA inputs to the mPFC impaired the consolidation of cued, but not contextual associations. Induction of synaptic depression in this pathway during extinction training led to suppression of neuronal responses to fear-associated cues in mPFC units, and facilitated extinction learning. Our findings demonstrate the pivotal

role of the monosynaptic BLA input to the mPFC in the formation and maintenance of cued fear memories.

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SELECTED TALKS - ST

ST1

Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep

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Clock-driven circadian rhythms adapt behaviours to the physiological demands of a 24 hour activity cycle; however, it is unclear how the central clock mediates these effects. As previously shown, we found that mice ingest significantly more water prior to sleep (PS; ZT 21.5-23.5) compared to baseline (ZT19.5-21.5). We found that this behaviour is not driven by physiological stimuli for thirst such as increased body temperature, serum osmolality or hematocrit. Restricting water access during the PS period resulted in a significant increase in serum osmolality and hematocrit, indicating that this anticipatory thirst is physiologically relevant. In vitro recordings of thirst neurons in the Organum Vasculosum Lamina Terminalis (OVLT) showed increased activity during the PS period compared to baseline, suggesting these neurons may mediate anticipatory thirst at this time. Injection of fluorescent beads into mouse OVLT retrogradely labelled vasopressin (VP) cells in the Suprachiasmatic Nucleus (SCN), but not in other brain regions containing VP neurons. Visually identified VP SCN neurons in vitro showed a significant increase in activity during the PS period compared to baseline. In vitro electrical stimulation of the SCN caused detectable VP release in the OVLT by sniffer cells prepared by transfecting HEK293 cells with the human V1a VP receptor (V1aR) and GCaMP6m. Moreover, stimulation of the SCN excited OVLT thirst neurons via V1aRs. The role of this SCN-OVLT pathway was further explored using transgenic mice expressing accelerated channelrhodopsin (ChETA) or archaerhodopsin-3 (ArchT) in VP neurons. Application of blue light (473 nm) to the

OVLT during the baseline period caused local VP release as detected by sniffer cells, and excited thirst neurons via V1aRs. In contrast, yellow light (589 nm) applied to the OVLT inhibited VP/V1aR dependent firing during the PS period. To investigate whether these effects contribute to anticipatory thirst, we examined the effects of light delivered to the OVLT via fiberoptic cannula in vivo. Yellow light application during the PS period suppressed anticipatory water intake, whereas blue light application during the baseline period promptly stimulated water intake. Collectively, these findings indicate that anticipatory water intake is mediated by VP release from the axon terminals of SCN clock neurons that project to the OVLT. This work was supported by the Canadian Institutes of Health Research.

ST2

Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation

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Rapid eye movement sleep (REMS) has been linked with spatial and emotional memory consolidation. However, establishing direct causality between neural activity during REMS and memory consolidation has proven difficult because of the transient nature of REMS and significant caveats associated with REMS deprivation techniques. In mice, we optogenetically silenced medial septum g-aminobutyric acid–releasing (MSGABA) neurons, allowing for temporally precise attenuation of the memory-associated theta rhythm during REMS without disturbing sleeping behavior. REMS-specific optogenetic silencing of MSGABA neurons selectively during a REMS critical window after learning erased subsequent novel object place recognition and impaired fear-conditioned contextual memory. Silencing MSGABA neurons for similar durations outside REMS episodes had no effect on memory. These results demonstrate that MSGABA neuronal activity specifically during REMS is required for normal memory consolidation.

ST3

Dimorphic brain region regulation of microglia morphology by adenosine A_{2A} receptors: uncoupling anxiety and cognition

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Microglia morphology, which is highly dynamic (cellular processes constantly retract and extend), is critical for brain functioning and undergoes profound remodelling in neuropsychiatric diseases.

Rats exposed prenatally to synthetic glucocorticoids (GC), such as dexamethasone (DEX), which become anxious and have cognitive deficits at adulthood, exhibit gender-specific changes in microglia morphology in the medial prefrontal cortex (mPFC), a brain region implicated in anxiety. We also observed that the chronic treatment with a selective antagonist of adenosine A_{2A} receptors ($A_{2A}R$), regulators of microglia and also involved in the pathophysiology of anxiety, normalizes microglia morphology in males, but not in females, whereas it was able to ameliorate cognitive deficits in both genders.

The main goal of the present study was to clarify if this functional uncoupling between anxiety and cognition in females treated with the $A_{2A}R$ antagonist could be explained by a dual, brain-region specific effect of $A_{2A}R$ in the control of microglia morphology. We analyzed microglia morphology in the dorsal hippocampus (dHIP) and assessed the functional coupling between mPFC and dHIP by *in vivo* electrophysiology.

We report that prenatal exposure to DEX triggers long-lasting changes in the dHip, namely a hyper-ramification of microglial cell processes, and a lack of neuronal synchronization between mPFC and dHip. Chronic $A_{2A}R$ blockade restored microglia morphology and reverted mPFC-dHIP desynchronization, in line with a cognitive enhancement. These results contrast with observations in the mPFC, where prenatal GC induced microglia de-ramification, not reverted by blocking $A_{2A}R$, which did not ameliorate anxiety.

Microglia are highly plastic cells, acquiring diverse phenotypes in response to different stimuli, but it was recently described distinct microglia transcriptional identities between brain regions. Our data points towards a region-specific and $A_{2A}R$-dependent regulation of microglia morphology, potentially influencing different components of mood disorders, namely anxiety and cognition.

ST4

Fast 3D imaging of spine, dendritic, and neuronal assemblies in behaving animals

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Understanding neural computation requires methods such as three-dimensional (3D) random-access point scanning that can simultaneously read out neural activity on both the somatic and dendritic scales. This method can increase measurement speed and signal-to-noise ratio (SNR) by several orders of magnitude, but suffers from one main disadvantage: fluorescence information is lost during brain movement. In this work we present a novel technology, 3D DRIFT acousto-optical scanning, which can extend each scanning point to small 3D lines or surface or volume elements, preserving fluorescence information for motion correction. Our method effectively eliminates *in vivo* motion artifacts, allowing fast 3D measurement of over 150 dendritic spines with 3D lines, over 100 somata with squares and cubes, or multiple spiny dendritic segments with surface and volume elements in behaving animals. Finally, a four-fold improvement in total excitation efficiency resulted in about 500 µm × 500 µm × 650 µm, scanning volume with GECIs.

POSTERS

INDEX

ABSTRACTS

P1

Neural and synaptic coding of fear memory traces in the dorsal prefrontal cortex of behaving mice

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Dynamics of neocortical function underlie the remarkable learning skills of mammals. This cortical plasticity is supposed to rely on subtle changes in the spatial pattern of neuronal activity that likely depend on wiring diagram rearrangement as a result of changing environmental demands. Our knowledge of this plasticity mostly comes from studies upon gross sensory manipulation (e.g. whisker trimming). Whether this model holds to be true for higher cortical areas upon associative learning is not known. Here, we first show that fear learning, a widely used form of predictive learning, is strongly affected by optogenetic inactivation of the dorsal prefrontal cortex (dPFC). Then, by combining in vivo two-photon

large-scale neuronal calcium imaging and whole-cell recordings in behaving mice, we observe that layer II dPFC pyramidal neurons are activated upon sound presentation. This low and frequency-independent activation may act as an alert system with rapid habituation upon sound re-presentation. Interestingly, when the same sound is associated in time to an aversive stimulus (e.g. a foot-shock), the subsequent activation of dPFC neuronal network synchronizes upon sound presentation with increased spiking reliability across sessions and days suggesting that behaviorally-relevant pattern of activity has been stabilized following fear learning. Altogether our data show that the dPFC plays key role in the formation and expression of fear memory traces. In addition we hypothesize that the dPFC acts as a top-down warning system allowing the animal to detect biologically important events such as downstream fear association by learning about signals of their occurrence.

P2

In vivo dynamics of AMPA receptors during experience-dependent cortical plasticity

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Long-term synaptic potentiation (LTP) is thought to be essential for experience-dependent cortical plasticity and memory formation most likely through the regulation of postsynaptic AMPA receptors (AMPAR)[1,2]. Indeed, pioneer experiments *in vitro* have indicated that the number of AMPARs at a given synapse is not fixed. Instead, it might be dynamically regulated during LTP-like processes by a three-step mechanism, involving (1) exo and endocytosis of AMPARs at extrasynaptic sites; (2) lateral diffusion within the membrane plane and (3) accumulation of AMPARs in synaptic nanodomains[3,4]. Despite the information gathered from cellular models over the last decades, the mechanism underlying LTP *in vivo* remains largely unknown. We recently described that rhythmic sensory stimulation in anesthetized mice might potentiate cortical synapses *in vivo* with the support of NMDARs-dependent dendritic plateau potentials[5]. Interestingly, recent imaging evidences reported an accumulation of the GluA1 subunit of AMPARs during similar sensory stimulation[6], suggesting that lateral mobility of AMPARs might be a key process during *in vivo* LTP as well. Here, we took advantage of *in vivo* whole-cell recordings in the somatosensory cortex of anesthetized mice with our AMPAR cross-linking protocol to further address this question. Our preliminary data suggests that blocking AMPAR lateral diffusion through the extracellular injection of anti-GluA2 antibody strongly impairs whisker-evoked LTP, indicating a critical role for AMPAR surface mobility during whisker-evoked LTP.

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P3

Role of VGLUT3 in the Amygdala: modulation of amygdalar network and acquired fear

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The amygdalar nuclear complex is a deep temporal area which has a critical role in emotional learning and memory, particularly in aversive memory.

In rodent, Pavlovian conditioning such as fear conditioning paradigm is commonly used to study aversive memories. Sensory information about a discrete stimulus (ie.a sound or a light), and electric choc converge into the baso-lateral nucleus of the amygdala (BLA) where the associative process occurs. Then, the central nucleus is necessary to trigger the conditioned fear responses.

In the amygdala, the baso-lateral nucleus is mainly glutamatergic, whereas the central nucleus is only GABAergic (Spampanato et al. 2011). Glutamate is the major excitatory neurotransmitter in the central nervous system. It is internalized in synaptic vesicles by vesicular glutamate transporters, VGLUTs. Three kinds of VGLUTs were identified: VGLUT1 and VGLUT2 are present in glutamatergic neurons, whereas VGLUT3 is expressed in non-glutamatergic neurons. Indeed, we observed VGLUT3 in a subpopulation of GABA interneurons in the cortex and hippocampus, 5HT neurons of Raphe nuclei and cholinergic neurons of striatum (El Mestikawy et al. 2011). VGLUT3 is also present in the BLA (Herzog et al. 2004) but the nature of BLA neurons and terminals expressing VGLUT3 remains unknown.

The aim of my work is to identify the neuronal population expressing VGLUT3 in the amygdala as well as its role in processing aversive memories.

The anatomical characterisation revealed VGLUT3 mRNA presence in BLA GABAergic interneurons. In addition, VGLUT3 protein is also present in cholinergic and serotoninergic terminals in the BLA, identifying two populations of projecting neurons expressing VGLUT3.

In order to decipher the functional role of VGLUT3 in these sub-populations we used viral and genetic approaches to ablate VGLUT3 either in GABAergic, serotoninergic or cholinergic terminals. Our results demonstrate that mice lacking VGLUT3 constitutively show contextual generalization and rapid extinction, whereas inactivation of VGLUT3 in GABAergic interneurons or serotoninergic neurons does not affect aversive memories. However, specific inactivation of VGLUT3 in BLA impairs aversive memories, shedding light on a specific role of VGLUT3 in modulating fear responses through its presence in BLA interneurons.

These new data will be discuss in the context of post-traumatic stress disorder (PTSD) and would open a new direction for the development of therapeutic treatment.

P4

Deciphering an oxytocinergic neuronal network restraining pain

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Oxytocin, a neuropeptide that plays an important role in sociability, is produced in the brain exclusively in the hypothalamic paraventricular (PVN), supraoptic (SON) and intermediate accessory nuclei. OT neurons can be classified in magnocellular OT (magnOT) and parvocellular OT (parvOT) neurons and are distinct in size and shape, subnuclear location, amount of OT production, and involvement in distinct circuitries and functions.

MagnOT neurons of these nuclei release OT into the blood from the posterior pituitary and innervate numerous forebrain nuclei. The PVN also harbors a smaller number of parvOT cells that predominantly project to the brainstem and spinal cord, but their function has not been directly assessed. In contrast to magnOT neurons, parvOT project to distinct brainstem nuclei and different regions of the spinal cord (SC). However, until now the actual number of parvOT has not been estimated because it was technically demanding to visualize the whole population of parvOT cells by back-tracing of their connections from multiple sites in the brainstem and spinal cord, and no genetic access to this neuronal type was available. Furthermore, it is unknown whether parvOT neurons are incorporated into the entire OT system and functionally co-interact with magnOT neurons.

Here we identified, by a combination of latest state of the art anatomical and viral approaches, a small (n ~30) subpopulation of parvOT neurons in the PVN, which projects to magnOT neurons in the SON and to WDR neurons in the SC. Functionally, we further demonstrated that this network can inhibit spinal pain processing in a dual manner with distinct time courses. Thus, nociceptive transmission from Aδ- and C-type primary afferents to second-order WDR neurons is efficiently repressed by OT release both in the SC and in the blood. Release in the SC is directly triggered from parvOT-spinal projections and follows a fast mode of action; release in the blood is indirectly triggered from SON magnOT neurons that are activated by parvOT projections and follows a slower time course. The functional role of this subpopulation of

parvOT neurons was further confirmed in a rat model of inflammatory pain in which mechanical and thermal hyperalgesia were significantly alleviated after its activation

P5

Prefrontal-ventral periaqueductal gray pathway regulates fear behaviour

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Accumulating evidence indicates that the dorsal medial prefrontal cortex (dmPFC) is involved in the expression of conditioned fear responses. In particular, it has been shown that inactivation of the prelimbic area decreases fear expression whereas electrical stimulation facilitates conditioned fear responses. Furthermore, recent data indicate that distinct prefrontal disinhibitory circuit containing paravalbumin (PV) interneurons controls fear expression via its projection to the basolateral amygdala (BLA). Interestingly, anatomical evidence indicates that dmPFC output neurons also project to the ventral periaqueductal gray (vlPAG) where they could potentially modulate conditioned fear responses. However, the specific contribution of this dmPFC-vlPAG pathway during fear behavior is still largely unknown. To address this question, we used single unit and local field potential recordings combined with specific tracing and optogenetic manipulations of the dmPFC-vlPAG pathway in behaving mice submitted to auditory fear conditioning. Single unit recordings indicate that dmPFC-vlPAG projecting principal neurons (PNs) increase their activity during freezing behaviour. Moreover, temporally and anatomically specific optogenetic manipulation of dmPFC-vlPAG projecting PNs indicated that their activation is necessary for the expression of auditory-conditioned fear responses. Furthermore, anatomical trans-synaptic tracing approaches suggested that dmPFC-vlPAG projecting PNs are controlled by somatostatin and paravalbumin interneurons population. Together these data indicate that fear behavior can be regulated at the level of dmPFC-vlPAG projecting neurons and could potentially bypass the BLA to control auditory-conditioned freezing responses.

P6

Mechanisms of dendritic integration in the lateral amygdala during fear learning

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The amygdala is necessary for classical fear learning in mice, during which a tone precedes an aversive electrical foot-shock. When the tone is presented again on the next day, mice show a fear response (freezing) indicating that an associative memory has formed. However, if the tones and the foot-shocks were unpaired, associative memory is not formed and the tone does not elicit a fear response on the test day [1]. In this paradigm, we want to understand what cellular mechanisms underlie the association between the tone and the shock. The lateral amygdala neurons respond to both stimuli and develop a stronger response to the tone over the course of auditory fear conditioning, which is necessary for learning to occur [2]. Therefore, the lateral amygdala is a good candidate for encoding the tone-shock association. To study how principal neurons integrate inputs elicited by either stimuli, we use 2-photon microscopy to image the somata and dendrites of principal neurons expressing the genetically encoded calcium indicator GCaMP6s through a GRIN lens in a paradigm where tones and shocks are presented either as paired or unpaired. This way, we wish to understand how the timing of different stimuli can influence dendritic integration and somatic output in the lateral amygdala and ultimately participate to the formation of associative memories. Additional factors are likely to influence dendritic integration of principal neurons. In particular, the activity of local GABAergic interneurons (SOM^+, PV^+) during auditory fear conditioning has been shown to bidirectionally gate the amount of conditioned freezing observed on the test day, a proxy for the strength of associative fear memory [3]. To better understand the role of SOM^+ and PV^+ interneurons during fear conditioning, we want to map their inputs brain-wide using cell type-specific monosynaptic rabies tracing from the basolateral amygdala.

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P7

Prefrontal neuronal assemblies temporally control fear behavior

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Accurate transmission of information in the brain requires precise temporal patterns of activity and synchronous firing of projection neurons to efficiently drive target neuronal regions. The medial prefrontal cortex regulates fear behaviour via projections to the amygdala, a neuronal

structure encoding associative fear memories. However, the prefrontal neuronal mechanisms allowing for the precise temporal control of fear behaviour are largely unknown. Here, we used a combination of single unit and local field potential recordings along with optogenetic manipulations to show that, in the dmPFC, behavioural expression of conditioned fear is causally related to the organization of neurons into functional assemblies. During fear behaviour, the development of 4 Hz oscillations coincides with the activation of neuronal assemblies nested in the ascending phase of the oscillation. The selective optogenetic inhibition of dmPFC neurons during the ascending or descending phases of this oscillation blocks and promotes conditioned fear responses, respectively. These results identify a novel phase-specific coding mechanism, which dynamically regulates the development of dmPFC neuronal assemblies to control the precise timing of fear responses.

P8

Optogenetic stimulation of hippocampal afferents to the PFC regulates contextual fear expression

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Debilitating clinical conditions, such as post-traumatic stress disorder (PTSD) and generalized anxiety disorder can be caused by memories of traumatic events and brain activity in the hippocampus and medial prefrontal cortex (mPFC) is highly correlated during the exposure-based therapy used to treat anxiety disorders. In recent years, optogenetic tools have provided opportunities to study brain circuits in freely behaving animals. Using a projection targeting technique and context and auditory conditioning, this project aimed to identify a pattern of optogenetic modulation of hippocampal afferents in the PFC that leads to a change in fear generalization. In order to test the role of the pathway in the expression of contextual fear, rats were infected in the ventral hippocampus (VH) with either an opsin-containing or control virus and implanted with mono-fibre-optic cannulae above the mPFC. Animals were divided into three groups (laser-opsin, control virus-laser group, and opsin-no-laser) and context conditioned in context (A). To extinguish generalised fear, they were placed into a new context (B) for 25 minutes the following day. On the third day, the animals were tested for fear recall in context A with optical stimulation for the first 300 s. There was no difference in the percentage of freezing among groups during any of context conditioning experiment, including during optical stimulation of the VH to PFC pathway afferents. In order to test the role of the pathway in the expression of cued fear, another group of animals (divided into three groups as in

experiment one) was used. The second experiment consisted of auditory fear conditioning in context A. On the following 5 to 9 days, the animals underwent 25 minutes of context exposures in context B as well as extinction procedures in context C. Once the animals reached a threshold level of freezing during extinction, they passed into the testing phase the following day. They were then tested in context A, with optical stimulation occurring during the first 180 s, followed by a single tone presentation with no optical stimulation. Although there were no differences in freezing among groups during the sessions leading up to the test, during optical stimulation however, the opsin-laser group showed a decreased expression of fear when compared with the control-virus and opsin-no-laser groups. These results suggest a role for hippocampal-PFC afferents in fear expression during fear recall after cued conditioning and therapy but not after context conditioning and therapy. In order to characterize the effects induced in the PFC by the optical stimulation of hippocampal afferents and unfold the circuit mechanism underpinning decreased fear renewal, we characterized the response of PFC neurons by recording single units during optical stimulation in anesthetized animals. We isolated both putative interneurons and pyramidal cells, and showed that single units either responded with a spike within 1ms of the onset of the laser pulse, or 11ms later, right after the offset of the pulse. We also identified a trend on some putative pyramidal cells, which exhibited a decreased firing rate 5ms after the onset of the pulse and spiking 11ms after. These results suggest that our specific stimulation of hippocampal afferents induces specific and precisely timed responses of the downstream network units in the PFC. Future directions for this work include increasing the sample sizes for behaviour experiments 1 and 2 to confirm results and to then perform multi-site recording in freely moving rats during our fear renewal protocol to identify electrophysiological signatures of pathological responding in single neurons and oscillatory activity.

P9

Basal amygdala inputs to the medial prefrontal cortex support fear strengthening

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The basal amygdala (BA) and the medial prefrontal cortex (mPFC) are interconnected brain regions involved in the acquisition and expression of conditioned fear. To examine the neural basis of fear strengthening we recorded spike activity in the BA before and after conditioned fear was strengthened with an additional training session. Strengthened fear response led to a reduction in the population of BA putative principal neurons encoding the conditioned stimulus, whereas stable non-strengthened fear responding did not change the size of the neuronal population encoding the conditioned stimulus in the BA. Moreover, responding to the fear conditioned stimulus was preferentially carried by BA neurons projecting to the mPFC. Selective optogenetic inhibition of the mPFC terminals of BA neurons during the second

conditioning session prevented fear strengthening. Together, our findings suggest that fear strengthening with additional training leads to a refinement of the neuronal population encoding the conditioned stimulus in the BA, and that mPFC inputs from the BA are necessary for fear strengthening.

P10

Centromedial thalamus (CMT) control of cortical state during sleep

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Mammalian midline thalamus consists of five nuclei of ambiguous function whose integrity is obligatory for maintenance of consciousness, cognition and sleep. Each of these functions relies on a tightly regulated UP-DOWN-states of thalamo-cortical networks. Here, we investigated the role of the midline thalamus on control of local and global cortical states during sleep.
We found that CMT spiking activity is modulated across sleep states. CMT local field potentials show a phase-advancement over other midline-thalamic nuclei and cingulate cortex during the UP state of spontaneous NREM slow waves, which is consistent with a CMT-Cingulate monosynaptic pathway. We further found that optogenetic activation of CMT entrains cortical spiking activity in cingulate, parietal and occipital cortex and was accompanied by wakefulness. Interestingly, parietal and occipital entrainment occurred simultaneously, lagging behind responses observed in the cingulate. Using dual activation-silencing stimuli, we showed that spike and LFP transfer to parietal an occipital cortex, as well as wakefulness, is dependent on the dorsal thalamus. In contrast, stimulation of VB did not result in wakefulness.
Collectively these results implicate the CMT as the main driver of local cortical UP-states via monosynaptic input to the cingulate. However, changes in global cortical state and wakefulness, are dependent on a functional relay located in the dorsal thalamus. These results support both a correlative and causal role of midline-thalamus in control of frontal cortical states during sleep.

P11

Aberrant PV+ neurons affect hippocampal network plasticity and cognitive abilities in Alzheimer's disease

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Several recent studies point to changes in the brain's oscillatory activity as an important hallmark of Alzheimer's disease (AD). It has become clear that, both in AD patients and in animal models of AD, a reorganization of hippocampal and cortical networks occurs early in AD pathology. These changes are characterized by a hyper-synchrony of the different networks, disruptions of the oscillatory activity in the theta and gamma frequencies, and an increase in epileptiform activity. These alterations coincide with early memory deficits in AD. At the cellular level, an excitation/inhibition (E/I) imbalance has been suggested to cause disruption of various networks. Inhibitory interneurons are believed to play an important role in this, but it remains unclear whether dysfunctional interneurons are causally involved in producing AD-like network alterations. We recently showed that hippocampal parvalbumin (PV) interneurons show an increased perineuronal net coating in young APP/PS1 mice, suggesting disturbed activity of PV neurons early in AD pathogenesis. Here, we show that pharmacogenetic inactivation of PV interneurons during learning in the Morris water maze leads to the rescue of cognitive impairments in APP/PS1 mice. Furthermore, we show that prolonged pharmacogenetic activation of hippocampal PV neurons results in a persistent memory deficit in wildtype mice, and an over-excitation of the principal hippocampal network. Together, our data show that PV neuron vulnerability could explain several early clinical symptoms of AD, including hippocampal hyperexcitability, E/I imbalance and memory deficits, making these neurons an attractive target for early intervention.

P12

Neuronal circuits and mechanisms of avoidance behaviour

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When facing a threatening stimulus, animals exhibit a broad repertoire of adaptive defensive behavioural responses with the aim of the removal of the fear eliciting stimuli and consequent avoidance or delay of further pain. In mice, fear responses can range from innate reactions such as freezing to complex learned avoidance responses. Whereas the neuronal circuits and mechanisms mediating freezing responses have been deeply investigated, the neuronal substrates for fear avoidance and the possible interaction with other defensive responses are still poorly understood. Recently, the dorsal medial prefrontal cortex (dmPFC) was shown to be required for fear avoidance expression but the neurobiological underpinnings are still unknown. To identify dmPFC neurons selectively involved in fear avoidance we used a combination of single unit recordings, optogenetics and behavioral approaches. Our behavioural results indicate that mice submitted to an auditory discriminative 2-way active avoidance task

discriminate between a shock-paired (CS+) and a neutral (CS-) tone by performing an avoidance response consisting in shuttle between two symmetric compartments separated by a small hurdle. Video-tracking analysis revealed that prior to the execution of a shuttle response, mice significantly decreased their speed after the CS+ onset and this decreased speed persisted during CS+ trials in which animal did not avoided, suggesting a possible competition between freezing-like and the avoidance responses in a trial-by-trial base. Importantly, a subset of dmPFC neurons exhibited changes in activity anticipating avoidance responses suggesting that this area might be involved in the initiation of avoidance responses.

P13

Single action potential evoked disynaptic inhibition in vivo

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Cortical excitatory neuronal activity is thought be controlled by feedback, disynaptic inhibition from local GABA-ergic interneurons. In vitro, it has been shown that trains of action potential can recruit somatostatin expressing interneurons and disynaptic inhibition of neighboring pyramidal neurons in vitro (Silberberg and Markram, 2007; Kapfer et al. 2007). However, in vivo, layer 2/3 pyramidal neurons activity is very sparse firing only single or doublet of action potentials (Barth and Poulet, 2012). To examine which circuit could underlie disynaptic inhibition in layer 2/3 in vivo, we made in vivo multiple two-photon targeted whole cell patch clamp recordings in somatosensory cortex of neighbouring layer 2/3 excitatory neurons and identified interneurons in anaesthetized mouse. We found that a single excitatory action potential is sufficient to recruit neighbouring parvalbumin expressing interneurons that subsequently inhibit the local excitatory network. Thus the net impact of a single excitatory action potential is inhibition. Our findings provide a rapid inhibitory feedback circuit that may underlie the sparse firing of cortical layer 2/3 pyramidal neurons in vivo.

P14: cancelled

P15

Manipulating and interpreting fast oscillatory dynamics using optogenetics

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Fast network oscillations (30 - 200 Hz) are ubiquitous across neuronal circuits and are believed to be functionally involved in the synchronization of spiking activity within and across brain regions. Multiple mechanisms have been proposed for their generation. In the CA1 region of hippocampus, a host of distinct high frequency oscillations of different origin have been described in different layers. These oscillations can reflect activity in upstream regions or local synchronization and their generation and maintenance involves multiple cell types. During offline states, CA3-paced sharp-wave ripple complexes (SPWRs) dominate the fast network activity in CA1. SPWRs are associated with the neuronal activity replay phenomenon, and are hypothesized to be critical for memory consolidation and synaptic plasticity within and across hippocampal circuits. However, to date, the exact mechanism and conditions for the generation of such intrinsic spontaneous oscillations as well as their functional role for encoding and retrieval of information remain virtually unknown. In the effort to understand the network and cellular mechanisms involved in the generation and maintenance of high-frequency oscillatory activity in the CA1, the ability to generate and terminate intrinsic oscillations in a neuronal circuit would be a valuable tool. Here we take advantage of the temporal and spatial resolution of excitatory and inhibitory optogenetic tools and *in vivo* electrophysiological techniques as well as the cell-type specificity allowed by genetic targeting to explore and characterize the distinct modes of local neuronal synchronization and its oscillatory expression in the freely behaving mouse. Using these tools, we are able to generate artificial oscillations at will, as well as to locally terminate intrinsic oscillations and investigate the repercussions of their generation or termination in downstream structures. Together, these manipulations constitute a set of tools that allows the causal investigation of fast oscillations in the context of memory and behavior.

P16

Prefrontal neuronal circuits of passive and active fear behaviours

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Laboratory rodents show a broad range of conditioned defensive behaviours, as a mean of coping with threatful stimuli or situations, including freezing and avoidance behaviour. Several studies emphasized the role of the dorsal medial prefrontal cortex (dmPFC) in encoding the acquisition as well as the expression of freezing behaviour. However the role of this structure in processing avoidance behaviour and the contribution of distinct prefrontal circuits to both freezing and avoidance responses are virtually unknown. To further investigate the role of dmPFC circuits in encoding passive and active fear-coping strategies, we developed in the laboratory a novel behavioural paradigm in which a mouse has the possibility to choose either to passively freeze to an aversive stimulus or to actively avoid it as a function of contextual elements. Using this behavioural paradigm we investigated whether the same circuits mediate freezing and avoidance or if distinct neuronal circuits are involved. To address this question, we used dmPFC single-units and local field potentials recordings in freely moving mice coupled with antidromic stimulations of targeted regions to identify the projection sites of responsive dmPFC neurons during freezing or avoidance behaviours. Our results indicate that freezing and avoidance behaviours are associated with specific neuronal patterns of activity within distinct dmPFC circuits controlling freezing or avoidance responses.

P17

Opiate withdrawal conditioning alters oscillatory states in the nucleus accumbens

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Opiate withdrawal is a key feature of opiate dependence and this negative emotional state is crucial in the addictive process. Several studies support the existence of conditioned withdrawal effects, which can act to influence drug-seeking and drug-taking behaviors.
The nucleus accumbens (NAC) is a key structure underlying addictive processes, and is crucial for both acute withdrawal and reactivation of withdrawal memories following conditioning. Moreover, NAC gamma oscillations are modified during morphine dependence and acute naloxone-precipitated withdrawal. The objective here was to characterize NAC oscillatory state during opiate withdrawal conditioning and conditioned withdrawal.
NAC local field potentials (LFPs) were recorded in morphine-dependent rats which were conditioned to naloxone-precipitated withdrawal (or saline injection) in a specific context. Electrophysiological recordings were performed daily at each conditioning (5 sessions) or test session. Behavioral signs of withdrawal were scored at each step of the protocol. Data processing includes LFP time-frequency analyses (power spectral densities, wavelet transform, Z-score, PCA,) locked on the occurrence of the various behavioral events.

We found that the gamma oscillatory states are deeply modified along with withdrawal conditioning with a highly specific interplay between low (60 Hz, G60) and high (80 Hz, G80) gamma rhythms. Indeed the G60/G80 frequency variations are strongly correlated both with the intensity of the withdrawal score, and the various behavioral signs of withdrawal. These variations tended to increase with the number of conditioning sessions. This suggests that G60/G80 interplay established through the conditioning process could underlie the coding of opiate withdrawal aversive memory.

P18

Neuronal circuitry for conditioned fear in the basolateral amygdala

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Fear and anxiety are emotions experienced by all individuals and can serve as an adaptive process in shaping decisions and behaviors related to survival of an organism. However when fear becomes pathological, it forms the basis of a variety of potentially devastating anxiety disorders. Numerous studies have provided evidence that the function of the amygdala may be dysregulated in emotional disorders such as anxiety and depression. One region of particular interest is the basolateral amygdala (BLA), which integrates information from sensory structures and other higher brain areas including the hippocampus and the medial prefrontal cortex. Using a combination of optogenetic, anatomical and imaging approaches, we identify and dissect the BLA circuitry which is necessary for the acquisition and expression of conditioned fear responses by linking sensory input to motor output.

P19

Prefrontal cortex parvalbumin interneurons are required for extinction of a cocaine memory trace

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Environmental stimuli present during drug consumption become strongly associated with the rewarding effects of drugs and often trigger relapse during periods of abstinence. For successful

addiction treatment it is crucial to reduce the salience of drug-associated stimuli. This may be achieved by prolonged exposure to drug-associated stimuli in absence of drug reinforcement, a process referred to as extinction learning. Accumulating evidence indicates that medial prefrontal cortex (mPFC) activity mediates extinction of conditioned behavior, however the specific neural circuits and cellular subtypes that support this adaptive mechanism remain to be determined. The rodent cortex is mainly comprised of glutamatergic pyramidal cells (~80-90% of total neuronal population), whose activity is tightly controlled by local GABAergic interneurons (~10-20% of total). Parvalbumin-expressing (PV^+) neurons constitute ~66% of GABAergic interneurons present in mPFC and are the source of perisomatic inhibition of pyramidal neurons, thereby creating a local circuit that regulates pyramidal cell firing and perhaps extinction of conditioned responding to drug-associated stimuli. Therefore, we aimed at unraveling the role of PV^+ neurons in extinction of a cocaine memory trace within the mPFC. To this end, we virally delivered either the inhibitory DREADD (Designer Receptors Exclusively Activated by Designer Drugs) hM4Di-mCherry or mCherry alone in dorsal mPFC of *PV::Cre* mice. Mice were trained for cocaine conditioned place preference (CPP) and 3 weeks later underwent extinction training concomitant with chemogenetic inhibition of PV^+ neurons. A post-extinction test revealed that suppression of PV^+ neurons impaired extinction learning compared with control mice. Using a genetic approach to tag activated neurons, we are currently investigating how PV^+ neurons exert control over mPFC pyramidal neurons that were activated during expression of cocaine CPP. So far, our results indicate that inhibition of pyramidal neurons by PV^+ cells is necessary for adequate acquisition of extinction memory, potentially by suppressing the cocaine memory trace that drives conditioned responding to cocaine-associated stimuli.

P20

Gender-specific microglia remodeling in a model of developmental anxiety

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During development the brain is particularly susceptible to the surrounding environment. The exposure to glucocorticoids above physiological levels, either associated with early life stress or

certain therapies during pregnancy or childhood, contributes to the pathogenesis of psychiatric disorders, namely anxiety. Given the immunomodulatory role of glucocorticoids and the immunological fingerprint found in animals prenatally exposed to these hormones, microglial cells are likely implicated in anxiety genesis. Moreover, these cells are equipped with glucocorticoid receptors (1) and respond to these hormones. Adenosine A_{2A} receptors ($A_{2A}R$), as regulators of microglia and being involved in the pathophysiology of anxiety, emerge as a possible molecular link between microglia and these disorders.
We performed a comparative analysis in males and females prenatally exposed to glucocorticoids and evaluated the impact of this manipulation on the adenosinergic system, microglia morphology, corticosterone levels and behaviour. We found that prenatal exposure to glucocorticoids triggers changes in the adenosinergic $A_{2A}R$ system that are gender-specific, long-lasting and paralleled by a profound remodelling of microglial cell processes in the pre-frontal cortex. Microglial cells re-organization responds in a gender-specific manner to the chronic treatment with a selective $A_{2A}R$ antagonist, which was able to partially revert alterations in microglia morphology and anxiety behaviour in males, but not in females.
Considering the importance of microglia in shaping neuronal circuits, alterations in these cells during development may lead to an impairment in brain wiring, with implication in behaviour. Our results demonstrate microglia involvement in the pathophysiology of anxiety, and highlight the need to carefully consider gender in the screening of therapeutic tools.

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P21

Prefrontal-periaqueductal gray circuit controls context fear discrimination

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Reducing behavioural uncertainty and appropriately selecting defensive or exploratory behaviours is critical for survival and is strongly influenced by the surrounding environment. Contextual discrimination is a fundamental process for the selection of appropriate defensive behaviour, which is thought to rely on the medial prefrontal cortex (mPFC). Interestingly mPFC circuits for context fear discrimination have not been extensively investigated. In a novel fear conditioning paradigm we systematically altered contextual elements that were present during conditioning to produce periods of fear discrimination during testing. To identify the neuronal circuits supporting contextual fear discrimination we performed single unit recordings coupled with optogenetic manipulations in the mPFC of behaving mice. Re-exposure to the conditioned context produced high levels of freezing, however sequential removal of contextual elements led to context fear discrimination. During fear discrimination we observed elevated activity of dmPFC pyramidal neurons. Consistent with these electrophysiological findings, light-induced activation of dmPFC pyramidal neurons projecting to the ventrolateral periaqueductal gray reduced freezing during contextual fear generalization. In contrast, light-induced inhibition of this same pathway elevated freezing to the discriminated context. Together, these findings suggest that the prefrontal-periaqueductal gray is part of a circuit controlling contextual fear discrimination.

P22

A cortico-thalamic-hippocampal circuit for remote fear memory attenuation

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The experience of strong traumata can lead to the formation of over-enduring fear memories that risk to degenerate into a pathological state known as post traumatic stress disorder (PTSD). When recalled, previously acquired memories can enter a labile state where new information can be incorporated. This memory update process forms the basis of the most successful treatments for PTSD, where subjects are repeatedly exposed to the trauma-inducing stimulus in a safe environment, resulting in an attenuation of the fearful component of trauma-related memories. Nevertheless, such extinction paradigms are only effective if administered shortly after the traumatic experience and are less and less effective as the fearful memories become remote.

The recall of recently acquired fearful memories is known to be dependent on the hippocampus, whereas remote memory storage relies more on higher cortical areas such as medial prefrontal cortex. Nevertheless, we hypothesize that, hippocampal reactivation is necessary for remote memory update. In particular, we hypothesize that a bisynaptic cortico-thalamic-hippocampal circuit, involving the anterior cingulate cortex, the nucleus reuniens of

the thalamus, and hippocampal area CA1, is critically involved in this process. To test this hypothesis, we will take advantage of a recently developed inducible double transgenic mouse line allowing for the specific tagging of active cell populations combined with viral based tracing and neural activity manipulation technologies. These state-of-the-art tools will allow us to identify the neuronal population recruited at remote memory recall and to analyze their specific morphological, electrophysiological and transcriptional changes upon extinction. Moreover, we will determine the connectivity of this neuronal population using a pseudotyped rabies virus-based retrograde tracing method. Lastly, we will assess the causal role of this cortico-thalamic-hippocampal circuit in the efficient extinction of remote traumatic memories by combining retrogradely spreading viruses with inducible chemogenetic neural activity manipulation tools.

P23

Nucleus accumbens gamma oscillations encode memories of emotional states associated with opiate withdrawal

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Affective memories associated with the negative emotional state experienced during opiate withdrawal are central in maintaining drug-taking and seeking, and in relapse. Nucleus accumbens (NAC) is a key structure for both acute withdrawal and reactivation of withdrawal memories, however NAC neuron coding properties underpinning the expression of these memories remain largely unknown. Here we aimed to decipher the role of NAC neurons in the encoding and retrieval of opiate withdrawal memory

Chronic single neuron and local field potentials recordings were performed in morphine-dependent rats (n=7) and placebo-controls (n=5). Animals were subjected to an unbiased conditioned placed aversion protocol for which one compartment (CS+) was paired with naloxone-precipitated withdrawal, a second compartment with saline injection (CS-) and a third was neutral (no pairing). After conditioning, animals displayed a typical place aversion for CS+ and developed a preference for CS- that can be attributed to safety learning.

We found that distinct NAC neurons code for CS+ or CS- with highly specific gamma oscillatory signatures, 80 Hz (G80) and 60 Hz (G60) gamma rhythms respectively. No specificity was found in the neutral compartment. Moreover the G60/G80 balance strongly correlated with the strength of the conditioning.

We demonstrate here that the aversive and preferred environments are encoded by distinct groups of NAC neurons and underpinned by specific oscillatory dynamics. This suggest that

G60/G80 interplay – established through the conditioning process- serves as a robust and versatile mechanism for a fine coding of the environment emotional weight.

P24

Prefrontal cortex single unit activity during extinction session of conditioned fear

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Extinction has been commonly perceived as a retroactive inhibition phenomenon, were new learning inhibits the behavioral expression of previously learned association. Extinction of conditioned fear relies on exposing the subject repeatedly to the stimuli that has been previously associated with the threatful event, which elicits conditioned fear response. Extinction procedure is associated with a progressive reduction of fear expression.
It has been shown that medial prefrontal cortex (mPFC) is involved in the acquisition of conditioned fear extinction. In addition, activity of dorsal and ventral region of medial prefrontal cortex has been reported to be associated with opposing behavioral outcomes. One line of studies suggests that expression of fear behavior is associated with the dorsal region activity, while ventral region activity is associated with the suppression of fear behavior. Evidence supporting the opposite roles for dorsal and ventral region has also been documented.
In the present study we recorded in dorsal and ventral regions of the mPFC simultaneously, single cell activity during extinction session. Extinction sessions were long enough to induce large reduction of fear expression upon CS (conditioned stimuli) presentation. We were able to observe different neuronal activity, of CS evoked responses, depending on the location of our electrodes along the dorso-ventral axis. With dorsal region being inhibited during high fear states at the beginning of the session, especially visible upon CS presentation and activity of the ventral region being stable across the extinction session. These results suggest that activity of dorsal mPFC correlates with freezing behavior, while ventral mPFC neuronal responses to threatful stimuli seems to be largely not influenced by the progression of the extinction session.

P25

Editing a representation of space in the mouse hippocampus to cancel a cocaine place memory

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The hippocampus provides the brain's memory system with a subset of neurons holding a map-like representation of each environment experienced. Is it possible to selectively edit the hippocampal neuronal representation of a particular place? Using a c-fos-based transgenic approach, we targeted CA1 neurons active in an environment with the light sensitive proton pump ArchT to later photo-silence them during re-exposure to that environment. We found that photo-silencing ArchT-tagged neurons disrupted the corresponding spatial map, and unexpectedly unmasked a population of non-tagged, previously quiet neurons, enabling them to express a new place code. This alternative code was sustained over time, even in the absence of photo-manipulation, thus replacing the initial spatial map. Drugs of abuse, through their association with environmental cues and contexts, produce powerful and long-lasting memories that precipitate relapse. Here we showed that our optogenetic intervention applied in a cocaine-paired environment did revoke an otherwise long-lasting cocaine-place preference. In doing so, we preserved the ability of hippocampal-recoded mice to recognise this environment while breaking its association to the experience of cocaine. Together, our findings demonstrate that a hippocampal spatial map can be recoded thus replacing a cocaine-place engram by a neutral engram and preventing drug-conditioned spatial behaviour.

P26

Neural correlates of fear conditioned analgesia

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The periaqueductal grey matter (PAG) has been identified as a key structure for the expression of several defensive reactions (freezing, fight, flight, autonomic regulation and analgesia). More specifically, freezing - an innate immobilization behavior when facing a threatening stimulus – has been shown to depend on the ventro-lateral column of the PAG (vlPAG). Interestingly, pain

studies have shown that, electrical stimulations of the vlPAG induce a strong analgesia, indicating that this structure can modulate pain signals. Thus, the vlPAG is a region where fear and pain modulatory networks may interact, however, to date, the neuronal circuits mediating this interaction are still largely unknown. To study this interaction we developed a model of fear induced analgesia (FCA) in the Hot-plate test, which consists in the suppression/reduction of pain sensitivity upon re-exposure to an auditory cue previously paired with an aversive mild footshock. Mice (C57/Bl6) underwent FCA coupled to single unit recordings and optogenetic manipulations of the vlPAG. Following fear conditioning, the CS+ (but not the CS-) induces an "analgesia-like" behavior in the Hot-plate test, which was correlated with conditioned fear levels. Optogenetic inhibition of the vlPAG confirms the role of this region in pain modulation, and single unit recordings indicated that a subset of vlPAG neurons were activated by the CS+ during FCA. These data indicate that a subpopulation of vlPAG cells is recruited during fear modulation of pain behavior.

P27

Relevance of the astrocyte-neuron interaction to the action of oxytocin in the central amygdala and its effect on pain processing

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Oxytocin (OT) is a hypothalamic hormone and neuropeptide well known for its numerous roles in social interaction, anxiety and pain modulation, among others. Particularly, magnocellular OT neurons from the paraventricular nucleus (PVN) of the hypothalamus send few long range projections to the central amygdala (CeA). Endogenous OT is known to modulate the local neuronal circuitry of the CeA in order to strongly decrease the fear response and promote analgesia. However, we still do not know how few axons are able to drive strong and long lasting physiological and behavioral effects.
In the course of our present study, we deciphered the action of OT on the calcium dynamics of astrocytes and the relevance of the astrocyte-neuron interaction to the OT neuromodulatory effect in the CeA. Through calcium imaging and patch clamp experiments on acute slices of rat amygdala and using viral manipulations of astrocytes, we characterize the response of astrocytes and neurons upon specific activation of OT-receptor, decipher the intracellular mechanisms involved and identify putative gliotransmitter(s) of the OT message. Finally, thanks to a neuropathic pain model, we test the relevance of those mechanisms on pain threshold and anxiety levels, demonstrating that astrocytes are both key actor of the oxytocinergic

transmission and mandatory to the beneficial – analgesic and anxiolitic – effect of this neuropeptide.
Our results provide for the first time integrated data regarding the interaction between a neuropeptidergic system and glia. This shed light onto the mechanisms underlying the OT action within mammalian brain and paves the way for future and extended understanding of neuropeptidergic systems in general, and oxytocinergic one in particular.

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GENERAL INFORMATION

MEETING VENUE

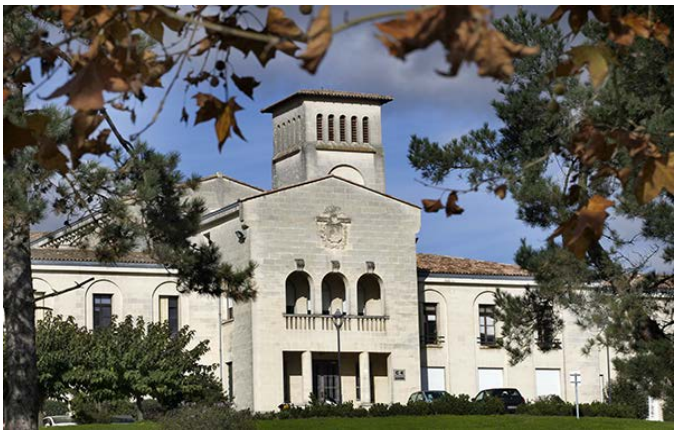
AGORA

Domaine du Haut-Carré
43 rue Pierre de Noailles - TALENCE

GPS: Latitude 44.810012 - Longitude -0.59645

How to get there:
Tram: line B – Forum station (recommended)
Bus: line 20 – Forum station

… and then a short 5 min walk uphill!!! See next page for the map

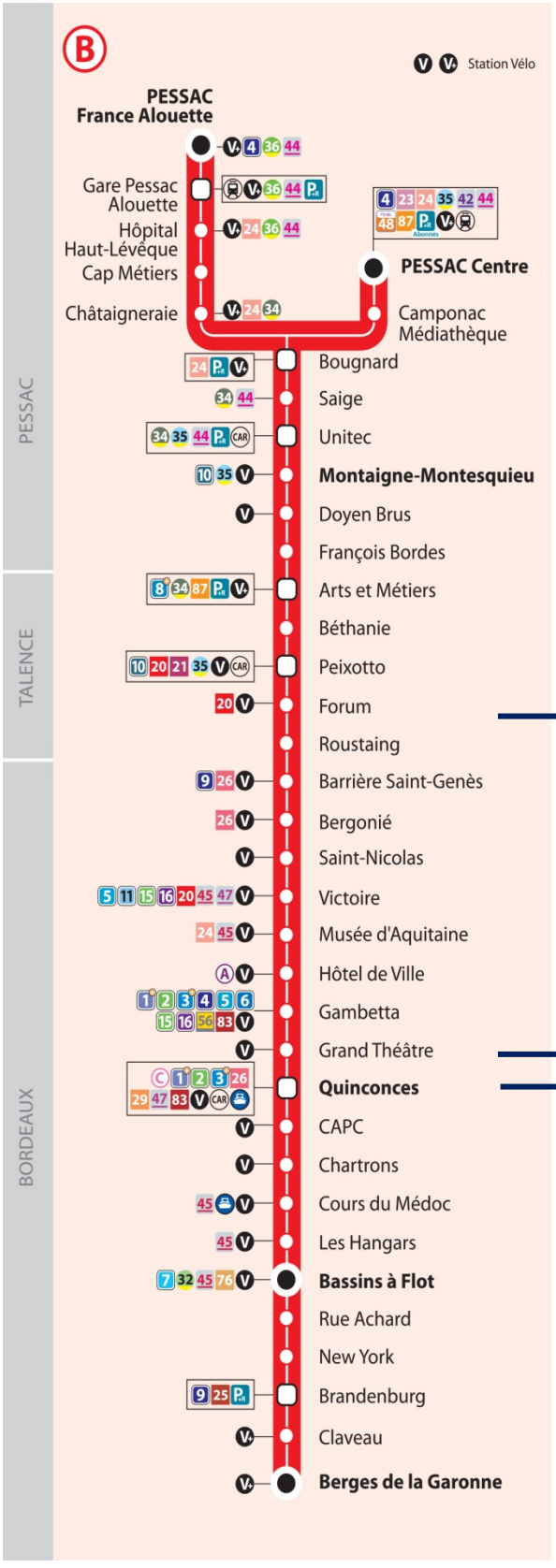


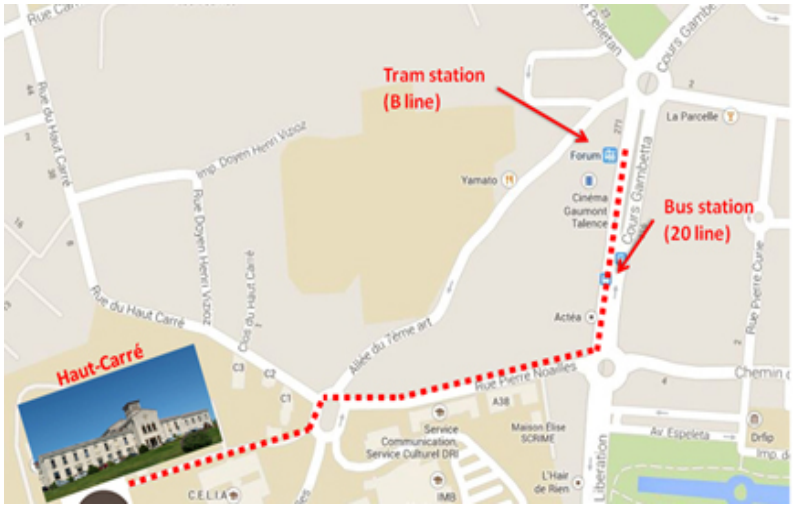
'Plan VIGIPIRATE': Badges and luggages

=> Badges must be worn **at all times**

=> VIGIPIRATE safety instructions strongly recommend to the participants **to avoid to come with their luggages**. Exceptionally, the bags could be left at the "Accueil" after being screened by a member of the conference Organizing Committee.

TBM Transportation Map (Tram, B Line)





Forum station:
AGORA Haut-Carré

Grand Théâtre station
Quinconces station

SOCIAL EVENT: GALA DINNER
Thursday, September 29th

only for participants registered to the gala dinner

Château Luchey-Halde is located in the heart of Bordeaux, in the prestigious Pessac-Léognan appellation, and benefits from an exceptional terroir.

It is constituted of several ridges which contain gravel, pebbles and fine soil deposited by the Garonne River and its tributaries between the end of the Tertiary and the beginning of the Quatenary periods. It is a poor but well-drained soil perfectly adapted to winegrowing in the oceanic climate of Bordeaux.

=> *Transportation by bus: Departure from the Agora to the Château ~18:15/6:15 pm and return ~23:15/11:15 pm with a first stop at the Haut-Carré in Talence, and a second stop Bordeaux downtown 'Allée de Munich' near the Quinconces tram station.*

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Scientific Committee in Bordeaux:

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Cyril HERRY	NeuroCentre Magendie (NCM)
Yann HUMEAU	Interdisciplinary Institute for Neuroscience (IIN