LIST OF PROJECTS (9)

PHD SCHOLARSHIPS FOR INTERNATIONAL STUDENTS

MARCH 2020

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PROJECT D1

Title : Study of the network involving the subthalamic nucleus in various aspects of addiction in the rat

Supervisor : BAUNEZ Christelle (christelle.baunez@univ-amu.fr - +33 (0)4 91 32 40 62)

Laboratory : Timone neuroscience institute (INT, UMR 7289) http://www.int.univ-amu.fr/

Project

STATE OF THE ART : The increasing burden of drug addiction leads to search for new treatment strategies, as no medications are currently efficient to cure addiction, especially in the case of cocaine. In the last few years, Deep Brain Stimulation (DBS) has been used for the treatment of some psychiatric disorders such as obsessive compulsive disorders or treatment-resistant depression with some limited, although promising success (1, 2). Our pioneer work on brain motivational processes has positioned the subthalamic nucleus (STN) as a very interesting target (for review (3)) since its inactivation by lesion or DBS can reduce motivation for cocaine, while increasing motivation for sweet food (4, 5) and also prevent some criteria of addiction such as escalation or loss of control over drug intake (6, 7) or modulate compulsive cocaine seeking (8). All these results are highlighting how STN manipulation could possibly reduce the addicted behaviour towards the drug. However, more specific manipulations of the STN with optogenetic suggest that its network can play a critical role on motivation (9).

OBJECTIVES : Our objective is thus to clarify the specific role of STN itself and its network in addiction models before a possible translation towards human patients.

METHODS : The project will study the effects of optogenetic manipulations of the hyperdirect pathway (prefrontal cortex-STN) i behavioural tests modelling various criteria of addiction in the rat such as motivation, loss of control over drug intake (escalation m and compulsive drug seeking (resistance to a punishment associated with drug seeking).

EXPECTED RESULTS : If the hyperdirect pathway contributes to the effects mediated by STN inactivation on addiction models, t stimulation should induce opposite effects to those observed after STN inactivation. It should thus increase motivation for cocaine, reducing that for sweet food, facilitate escalation of cocaine intake and maybe reduce compulsive cocaine seeking.

FEASABILTY : The team has the expertise of the models of drug addiction in rats, has the equipment to perform all the behavioural testing and optogenetic manipulations.

EXPECTED CANDIDATE PROFILE : experience with rodent laboratory work, possibly familiar with intravenous self-administration procedures and cerebral surgery. Interest for behaviour and brain networks. MatLab and/or Python programming would be a plus.

NAMES AND DATES OF THE CURRENTLY SUPERVISED PHD STUDENTS :

- Cassandre Vielle

NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Alix TIRAN-CAPPELLO (2014-2018)
- Elodie GIORLA (2013-2017)
- Emmanuel BREYSSE (2011-2015)

PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- A. Tiran-Cappello
- Pelloux Y*, Degoulet M*, Tiran-Cappello A, Cohen C, Lardeux S, George O, Koob GF, Ahmed SH and Baunez C(2018) "Subthalamic nucleus inactivation prevents and reverses escalated cocaine use" **Mol Psychiatry, 23** : 2266–2276
- -Tiran-Cappello A, Pelloux Y, Degoulet M, Brocard C, Baunez C. Subthalamic optogenetic manipulations: a glimpse at deep brain stimulation mechanisms. In revision for eLife, bioRxiv: doi:https://doi.org/10.1101/450767
- - Degoulet M, Tiran-Cappello A, Baunez C*, Pelloux Y* Low frequency oscillatory activity of the subthalamic nucleus is a predictive biomarker of compulsive-like cocaine seeking, bioRxiv doi:https://doi.org/10.1101/451203

- E. Giorla
- Pelloux Y, Meffre J, Giorla E, Baunez C (2014) The subthalamic nucleus keeps you high on emotion: behavioral consequences of its inactivation. Frontiers Behav Neurosci8:414 ; doi: 10.3389/fnbeh.2014.00414
- Montanari C, Giorla E, Pelloux Y, Baunez C (2020) "Subthalamic nucleus mediates the modulation on cocaine self-administration induced by ultrasonic vocalizations playback in rats" Addiction Biol 25(1):e12710; DOI:10.1111/adb.12710, bioRxiv: doi:https://doi.org/10.1101/450437
- Pelloux Y, Giorla E, Montanari C, Baunez C (2019) Social modulation of drug use and drug addiction. Neuropharmacology.159:107545;doi: 10.1016/j.neuropharm.2019.02.027
- Giorla E, Nordmann S, Pelloux Y, Roux P, Rosellini S, Davranche K, Huguet P, Carrieri P*, Baunez C*(2018) Presence and familiarity of a peer as key factors to modulate drug intake: translational evidence from rats to cocaine users. bioRxiv, 10.1101/286518
- E. Giorla
- Pelloux Y, Meffre J, Giorla E, Baunez C (2014) The subthalamic nucleus keeps you high on emotion: behavioral consequences of its inactivation. Frontiers Behav Neurosci8:414 ; doi: 10.3389/fnbeh.2014.00414

- E. Breysse
- Nougaret S, Meffre J, Duclos Y, Breysse E, Pelloux Y. (2013) First evidence of a hyperdirect prefrontal pathway in the primate: precise organization for new insights on subthalamic nucleus functions. Front Comput Neurosci. 7:135. doi: 10.3389/fncom.2013.00135.
- Breysse E, Pelloux Y, Baunez C. (2015) The Good and Bad Differentially Encoded within the Subthalamic Nucleus in Rats. eNeuro. 2(5). pii: ENEURO.0014-15.2015. doi: 10.1523/ENEURO.0014-15.2015.
- Wade CL, Kallupi M, Hernandez DO, Breysse E, de Guglielmo G, Crawford E, Koob GF, Schweitzer P, Baunez C, George O. (2017) High-Frequency Stimulation of the Subthalamic Nucleus Blocks Compulsive-Like Re-Escalation of Heroin Taking in Rats. Neuropsychopharmacology. 42(9):1850-1859. doi: 10.1038/npp.2016.270.

PROJECT D2

Title : Fine-tuning of synapse plasticity: role of micro-RNAs

Supervisor : BECLIN Christophe (christophe.beclin@univ-amu.fr - +33 (0)4 91 26 97 70)

Laboratory : Developmental Biology Institute of Marseille (IBDM, UMR 7288)

http://www.ibdm.univ-mrs.fr/fr/

Project

STATE OF THE ART : Synaptic communication between neurons is the basis of cognitive processes like learning and memory. Moreover, downstream neurons respond to an information transmitted by the upstream neuron by changing their gene expression. As synapses are often centimeters away from the cell-nucleus, local mRNA translation is a mechanism to assure the timely protein production. Micro-RNAs, small regulatory molecules that negatively control mRNA translation and stability, are often found at synapses and have been proposed to play a role in this adaptive protein expression regulation. However, experimental tools to study in detail such synaptic mRNA/micro-RNA regulation in normal in vivo conditions are still limited. In this project we will use new and original molecular tools, in particular unique transgenic mouse lines, to study micro-RNA expression and function at the brain synapse directly in the living animal. These tools allow the trapping of synaptic micro-RNAs in specific brain regions and under defined experimental conditions. This information will be used to establish a map of synaptic micro-RNAs and to functionally study the link between inhibitory action of micro-RNAs at the synapse and the activity of neurons in response to environmental stimuli.

The olfactory bulb is the first relay in the brain in which olfactory stimulation is processed. It is also one of the two regions of the mouse brain where neurogenesis continues throughout the entire lifespan, providing a permanent and accessible model to study both neurogenesis and sensory functions. In the past the Cremer group used this system to identify and characterize a variety of factors and signalling cascades that regulate neurogenesis. These functions include specification (Tiveron et al., 2017; J. Neuroscience), migration (Hack et al., Nature Neuroscience, 2002), differentiation (Boutin et al., PNAS 2009), synapse formation (Burk et al., 2012, J. Neuroscience) and functional integration (Platel et al., elife, 2019). A key aspect of our work concerned the role of micro-RNA regulation in the adult neurogenesis process (de Chevigny et al., Nature Neuroscience 2012; Beclin et al., Sci. Reports 2016; Follert et al. Frontiers in Molecular Neuroscience 2014). Micro-RNAs are very short (22nt) and regulate gene expression through sequence homology by inhibiting translation and subsequently increasing mRNA degradation. Each micro-RNA is predicted to regulate many target mRNAs and a specific target can be controlled by several micro-RNAs. Micro-RNA regulation is proposed to fine tune gene expression. However, due to their specific structure and their mode of action there are technical limitations for establishing the role and identifying the targets of individual micro-RNA.

EXPERIMENTAL APPROACH : The successful candidate will use unique in vivo methods to investigate the expression and function of micro-RNAs in the brain. In particulate she/he will use a new method to isolate active micro-RNAs either from synapses and/or from cytoplasmic compartment under stimulation or inhibition. This method is based on a CRE-inducible mouse line expressing a small peptide that is able to capture local micro-RNAs from specific cellular compartments. Synaptic micro-RNAs will be compared to cytoplasmic micro-RNAs to define the synaptic "miR-nome ". Adaptation of this miR-nome to neuronal stimulation or inhibition will be analysed. Finally, the signification of this molecular adaptation will be evaluated by functional analyses based on our inhouse in vivo mouse brain electroporation technics (Boutin et al. 2008) and state-of-the-art imaging. Altogether, these studies will provide new and fundamental insight into the control of synaptic function and plasticity.

NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Philippe Follert (2009-2012)

PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- miR-200 family controls late steps of postnatal forebrain neurogenesis via Zeb2 inhibition.
- Beclin C, Follert P, Stappers E, Barral S, Coré N, de Chevigny A, Magnone V, Lebrigand K, Bissels U, Huylebroeck D, Bosio A, Barbry P, Seuntjens E, Cremer H.Sci Rep. 2016 Oct 21;6:35729.
- MicroRNAs in brain development and function: a matter of flexibility and stability.
- Follert P, Cremer H, Beclin C.Front Mol Neurosci. 2014 Feb 7;7:5.
  miR-7a regulation of Pax6 controls spatial origin of forebrain dopaminergic neurons.
  de Chevigny A, Coré N, Follert P, Gaudin M, Barbry P, Beclin C, Cremer H.Nat Neurosci. 2012 Jun 24;15(8):1120-6.
  Dynamic expression of the pro-dopaminergic transcription factors Pax6 and Dlx2 during postnatal olfactory bulb neurogenesis.
  de Chevigny A, Core N, Follert P, Wild S, Bosio A, Yoshikawa K, Cremer H, Beclin C.Front Cell Neurosci. 2012 Feb 27;6:6.

PROJECT D3

Title : Role of motoneuron-astrocyte crosstalk in spasticity after spinal cord injury

Supervisor : BROCARD Frédéric (frederic.brocard@univ-amu.fr) - +33 (0)4 91 32 40 29)

Laboratory : Timone neuroscience institute (INT, UMR 7289) http://www.int.univ-amu.fr/?lang=en

Project

STATE OF THE ART : Spasticity is a common motor impairment after spinal cord injury (SCI). One of the main clinical manifestation is a chronic hypertonia associated with hyper-reflexia. Current treatments are limited mostly to supportive measures and there is no satisfactory cure. Thus, there is a critical need for a better understanding of cell interaction mechanisms to develop appropriately targeted repair strategies. Successive works from our group demonstrated that spasticity results from a excitatory/inhibitory imbalance of motoneurons (MN) in part due to an increase of the persistent Na+ current (Brocard et al. Nat. Med. 2016), concomitant with a disinhibition (Boulenguez et al. Nat. Med. 2010) both driven by calpain-I proteolytic activity (Plantier et al. Elife, 2019). However, the upstream initiators of this calpain-mediated excitatory/inhibitory imbalance are still not unknown. Although most of the proposed mechanisms focused on neuronal elements, it is now well appreciated that astrocytes actively modulate neuronal circuit excitability after CNS injury (Nimmerjahn and Bergles, 2015). Astrocytes are thus considered as active partners in neural information processing: (1) Reactive astrocytes interact with neighbouring neurons by releasing neuroactive substances such as glutamate and ATP (Koizumi et al. 2005). ATP release dynamically inhibits glutamatergic synaptic transmission (Witts and Miles, 2017) but display opposite effects in injured CNS (Coull et al. 2005). (2) Astrocytes also modulate neuronal excitability by taking up extrasynaptic glutamate (Gluo) and potassium (K+o) mainly via the glutamate transporter GLT-1 and the K+ channel Kir4.1, respectively (Sofroniew and Vinters, 2010). Although it has been shown that these two astrocytic proteins focally decrease after SCI in the surrounding sites of the lesion (Olsen et al. 2010), it is totally unknown if this decrease also occurs in the motor pool of MN and whether astrocytic glutamate and ATP release vary after SCI.

OBJECTIVES : The aim of this PhD project will consist in determining to what extent the spinal astrocytes modulate the MN firing properties and contribute to the development of spasticity in SCI mice. Aim 1 (cellular level, spinal slice): Determine the astrocyteMN crosstalk mechanisms responsible of MN hyperexcitability (impaired K+/glutamate homeostasis and increased gliotransmitters release). Aim 2 (microcircuit level, whole-mount spinal cord): Image and modulate the reactive astrocytic activity and gliotransmitters spillover surrounding the MN pool from SCI mice. Aim 3 (systems level, in vivo): Recording hindlimb muscles activity after targeting astrocytes with gene therapy to alleviate spasticity.

METHODS : Multi-scaled approaches based on two−photon calcium imaging (astrocytic activity), electrophysiology (patch-clamp of motoneurons/astrocytes, extracellular ventral root recordings, EMGs), single-cell RT-PCR (astrocyte), opto-genetics (ChR2-H134R, eArchT3.0) and AAVs injection from transgenic mice lines (ALDH1L1-eGFP, floxed Gcamp6f, ALDH1L1-CreERT2, Chat-Cre) will be used.

EXPECTED RESULTS : We hypothesize that synergistic action of (1) astrocytic impaired K+ and glutamate clearance with (2) increased release of glutamate/ATP by reactive astrocytes contribute to the excitatory/inhibitory imbalance of extensor MNs following SCI.

FEASABILITY : All the experimental approaches are already established in the Brocard group. The team has a qualified technical staff for genotyping and AAVs injections/surgery. All mutant mice and AAVs are already available or will be present at the start of the project. Ethical approvals are in place. The team has also ongoing grants and an excellent track record to secure funding.

EXPECTED CANDIDATE PROFILE : We are looking for a motivated, curious and well-organized candidate with interest in neuronastrocytes crosstalk and spinal physiology. Previous experience in two-photon calcium imaging, electrophysiology, and/or use of viral vectors will be considered as a plus.

NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Tazerart Sabrina (2006-2010)
- Bouhadfane Mouloud (2011-2014)
- Plantier Vanessa (2012-2015)
- Irénée Sanchez-Brualla (2015-2018)

PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Tazerart Sabrina doi: 10.1152/jn.00316.2007 doi: 10.1523/JNEUROSCI.1437-08.2008. doi: 10.1523/JNEUROSCI.6310-09.2010 doi: 10.1177/1073858409346339. doi: 10.1016/j.neuron.2013.01.026. doi: 10.1523/JNEUROSCI.1483-13.2013.

- Bouhadfane Mouloud doi: 10.1016/j.neuron.2013.01.026. doi: 10.1523/JNEUROSCI.1483-13.2013.
  doi: 10.7554/eLife.06195. doi:
  10.1038/nm.4061. Epub 2016 Mar 14.

- Plantier Vanessa doi: 10.1038/nm.4061.
  doi: 10.1051/medsci/20173306020.
  doi: 10.7554/eLife.51404.

- Irénée Sanchez-Brualla doi: 10.1089/neu.2017.5152. doi: 10.1016/j.neuroscience.2017.08.033. doi: 10.7554/eLife.51404.

PROJECT D4

Title : Eye-Hand coordination in discrete versus continuous actions

Supervisor : DANION Frédéric (frederic.danion@univ-amu.fr - +33 (0)4 91 32 40 20)

Laboratory : Timone neuroscience institute (INT, UMR 7289)

http://www.int.univ-amu.fr/?lang=en

Project

STATE OF THE ART : Eye and hand movements are key in many of our everyday activities. Moreover a large portion of our brain is dedicated to the control of these two effectors. As a result understanding how eye and hand actions are controlled and coordinated is important both from a theoretical and a societal perspective. In the literature an important distinction is made between discrete and continuous movements. Not only they rely on partly distinct neural substrates but they also rely on substantially different control processes. The goal of this proposal will be to investigate to what extent eye-hand coordination may differ under discrete and continuous actions. To achieve this goal we propose two lines of research. In the first line of research, we propose to investigate movements that fall in the interval between continuous and discrete actions. Our method will consist in asking participants to track a visual target that moves along a smooth path, but depending on the conditions, the target will be displayed either continuously or at fixed time intervals. By manipulating the rate at which the target is displayed we aim at bridging the gap between discrete and continuous actions. This task will be performed either with the eye, the hand (by means of a joystick), or both effectors simultaneously. Such protocol will allow characterizing the performance of each effector in isolation, and therefore assessing more effectively the effect of eye-hand coordination. In the second line of research, we plan to investigate how dependent are the adaptation of discrete and continuous actions. To achieve this goal we plan on using a visual perturbation, called visuomotor rotation, in which participants are provided biased visual feedback about their hand movements, such that the mapping between the joystick motion and the cursor motion is rotated by 90°.

OBJECTIVES : Here the objective will be to determine whether visuomotor adaptation under continuous hand tracking transfers to the context in which hand reaching movements are initiated from a fixed position toward stationary targets. Conversely we also plan to examine whether the adaptation of discrete hand movements performed in different directions transfers to continuous hand tracking. If major transfer of adaptation is observed between these two tasks, these results will challenge the view that discrete and continuous actions are governed by largely independent processes.

FEASABILITY AND METHODS : Regarding the feasibility of the project, we already have all the required equipment and our expertise with eye-hand coordination and visuomotor-adaptation has been validated by 6 recent publications, all issued from a single PhD project.

EXPECTED RESULTS : If major transfer of adaptation is observed between these two tasks, these results will challenge the view that discrete and continuous actions are governed by largely independent processes

EXPECTED CANDIDATE PROFILE : The new PhD student will be involved in all aspects of the research, including experimental design, data collection and analysis. Given the nature of the project, a solid interest in behavioral and computational neurosciences will be appreciated. Experience with Matlab coding and data collection will also be valued.

NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- James Mathew (sept 2018)
- Mederic Descoins (july 2007)

PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Mederic Descoins

- M. Descoins, F. Danion, Bootsma R (2006). Predictive control of grip force when moving an object with an elastic load applied on the arm. Experimental Brain Research 172 : 331-342
- F. Danion, M. Descoins, RJ Bootsma (2007). Aging affects the predictive control of grip force during object manipulation. Experimental Brain Research 180 :123-137
- F. Danion, M. Descoins, RJ Bootsma (2009). When the fingers need to act faster than the arm: Coordination between grip force and load force during oscillation of a handheld object. Experimental Brain Research 193 : 85-94.

James Mathew

- J. Mathew, A. Eusebio, F. Danion (2017). Limited contribution of primary motor cortex in eye-hand coordination: a TMS study. Journal of Neuroscience 37(40) : 9730-9740. doi :10.1523/JNEUROSCI.0564-17.21017
- J. Mathew, P.M Bernier, F.R. Danion (2018). Asymmetrical relationship between prediction and control during visuomotor adaptation. eNeuro 0280-18.2018. doi.org/10.1523/ENEURO.0280-18.2018
- N. Gouirand, J. Mathew, E. Brenner, F.R. Danion (2019). Eye movements do not play an important role in the adaptation of hand tracking to a visuomotor rotation. Journal of Neurophysiology 121(5) 1967-1976 doi: 10.1152/jn.00814.2018.
- J. Mathew, F.R. Sarlegna, P.M. Bernier, F.R. Danion (2019). Handedness matters for motor control but not for prediction. eNeuro 0136-19.2019. doi:10.1523/ENEURO.0136-19.2019
- J. Mathew, R. Flanagan, F.R. Danion (2019). Gaze behavior during visuomotor tracking with complex hand-cursor dynamics. Journal of Vision vol. 19, 24. doi:https://doi.org/10.1167/19.14.24
- J. Mathew, A. De Rugy, F.R. Danion (2020). How optimal is bimanual tracking? The key role of hand coordination in space. Journal of Neurophysiology 123(2) 511-521 doi: https://doi.org/10.1152/jn.00119.2019

PROJECT D5

Title : Zinc-induced protein aggregation in neurodegenerative disease: TPD-43 and Amyotrophic Lateral Sclerosis (ALS)

Supervisor : DEVRED François (francois.devred@univ-amu.fr - +33 (0)4 91 83 55 96)

Laboratory : Institute of NeuroPhysiopathology (INP, UMR 7051)

http://www.inp.univ-amu.fr/

Project

STATE OF THE ART : Most neurodegenerative diseases are characterized by the presence of aggregation-prone proteins associated with the pathology. For instance, amyloid- β and tau are found aggregated in Alzheimer's disease, α-synuclein in Parkinson disease, TDP-43, FUS and SOD1 in ALS. Remarkably, these proteins, which differ so much in their structures and functions, share common features. For instance, most of them are known to bind zinc ions. While zinc might not be the causative agent of these diseases, it was shown to bind to these proteins and favor their aggregation. Until recently, TDP-43 was not recognized as a zinc-binding one. It does not contain any known zinc-binding motifs. Still, recently together with our colleagues from Moscow State University we have demonstrated that TDP-43 is able to binds zinc and showed that this binding significantly decreases stability and induces its irreversible aggregation (Garnier et al. 2017).

OBJECTIVES : (1) Identify TDP-43 zinc-binding site and resolve its 3D structure; (2) Determine the role of this site in zincinduced aggregation (in vitro, in cell and in vivo)

METHODS : To achieve these objectives, the application of a large number of methods both in vitro and in vivo is necessary. In the frame of the first objective, a set of TDP-43 mutants and fragments will be generated using standard biochemical approaches (direct mutagenesis, HPLC etc). Then interaction of purified mutants with zinc will be studied using biophysical methods such as Isothermal Titration Calorimetry (ITC), Differential scanning Calorimetry and fluorimetry (DSC and nanoDSF). Finally, the complex of TDP-43 with zinc will be characterized using structural methods, such as NMR. To achieve the second objective the aggregation of TDP-43 mutants and its fragments will be studied in vitro using Turbidimetry and Dynamic Light Scattering (DLS) and in cells using GFP constructs, microscopy, flow-cytometry. At last, TDP- 43 aggregates from brain of ALS animal models will be purified to measure the content of metal ions, in particularly zinc.

EXPECTED RESULTS : We expect to determine the amino acids that chelate zinc ions in TDP-43 and resolve its 3D structure in complex with zinc. By mutating these amino acids, we expect to reduce significantly zinc-induced aggregation of TDP-43. Also, we expect to find zinc in TDP-43 aggregates extracted from the brain of ALS animal models. In case of success, we will be able to propose new pathological pathway of ALS development and new drug targets for ALS therapy.

FEASABILITY : Institute of NeuroPhysiopathology and collaborators have all necessary equipment and infrastructure to accomplish proposed research project. Moreover, similar project on tau zinc-induced aggregation have been successfully performed in the laboratory by another PhD student.

CANDIDATE PROFILE : We are looking for a motivated candidate with good fundamental background and who is willing to acquire complementary expertise in in vitro, in cell and in vivo approaches.

NAMES AND DATES OF THE CURRENTLY SUPERVISED PHD STUDENTS :

- Romain La Rocca (2017-2020)

NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Andrei Roman (2014-2017)
- Roqyia Nouar (2009-2013)

PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Philipp O. Tsvetkov, **Romain La Rocca**, Soazig Malesinski, François Devred. Characterization of Microtubule-associated proteins and tubulin interactions by isothermal titration calorimetry. Microcalorimetry of Biological Molecules: Methods and Protocols, Methods in Molecular Biology, (chap. 12) vol. 1964, 2019
- **Andrei Roman**, François Devred, **Romain La Rocca,** Cyrille Garnier, Deborah Byrne, Evgeni Yu. Zernii, Vincent Peyrot, Philipp O. Tsvetkov. Zinc-dependent reversible selfassembly of tau. J Mol Biol 2018
- Philipp O. Tsvetkov, **Andrei Roman**, Viktoriia E. Baksheeva, Aliya A. Nazipova, Marina P. Shevelyova, Vasiliy I. Vladimirov, Michelle F. Buyanova, Dmitry V. Zinchenko, Andrey A. Zamyatnin Jr., François Devred, Andrey V. Golovin, Sergei E. Permyakov, Evgeni Yu. Zernii. Functional status of neuronal calcium sensor-1 is modulated by zinc binding. Frontiers in Molecular Neuroscience. 2018
- Philipp O. Tsvetkov, Emeline Tabouret, **Andrei Roman**, Sylvie Romain, Céline Bequet, Olga Ishimbaeva, Stéphane Honoré, Dominique Figarella-Branger, Olivier Chinot, Francois Devred Differential Scanning Calorimetry of plasma in glioblastoma: toward a new prognostic / monitoring tool. Oncotarget. 2018
- Cyrille Garnier, Francois Devred, Deborah Byrne, Rémy Puppo, **Andrei Roman**, Soazig Malesinski, Andrey Golovin, Régine Lebrun, Natalia Ninkina, Philipp O. Tsvetkov, Zinc binding to RNA recognition motif of TDP-43 induces the formation of amyloid-like aggregates. Scientific Reports 2017
- **Roqiya Nouar**, Gilles Breuzard, Sonia Bastonero, Svetlana Gorokhova, Pascale Barbier, François Devred, Hervé Kovacic, Vincent Peyrot. Direct evidence for the interaction of stathmin with the length and the plus-end of microtubules in cells. FASEB J. 2016
- **Andrei Roman**, Francois Devred, Alexander A. Makarov Aslan A. Kubatiev, Vincent Peyrot, Philipp O. Tsvetkov. Sequential binding of calcium ions to B-repeat domain of SdrD from Staphylococcus aureus. Canadian Journal of Microbiology 2016
- **Gilles Breuzard**, Pierre Hubert, **Roqiya Nouar**, Tiffany De Bessa, François Devred, Pascale Barbier, James Sturgis, and Vincent Peyrot. “Molecular Mechanisms of Tau Binding to Microtubule and its Role in Microtubule Dynamics in Live Cells.” J Cell Sci, 2013

- **Roqiya Nouar**, François Devred, Gilles Breuzard, and Vincent Peyrot. " FRET and FRAP imaging: approaches to characterise tau and stathmin interactions with microtubules in cells." Biol Cell. 2013

PROJECT D6

Title : Defining
Neurofeedback parameters to reduce anxiety

Supervisor : KHALFA Stéphanie (stephanie.khalfa@gmail.com - +33 (0)6 89 99 07 12)

Laboratory : Sensory and Cognitive Neuroscience Laboratory (LNSC, UMR 7260)

https://lnsc.fr/

Co supervisor (Marseille) : REY Arnaud (arnaud.rey@univ-amu.fr - +33 (0)6 30 50 56 32)

Laboratory : Cognitive Psychology Laboratory (LPC, UMR 7290) https://lpc.univ-amu.fr/fr

Duration : 50% AMU lab, 50% partner lab

Project

STATE OF THE ART : Electroencephalographic (EEG) Neurofeedback (NF) is a technic that measures a subject's EEG signal. Based on this rest EEG, one or several parameters of interest are presented in visual and/or auditory forms to subjects so that they can learn how to modulate their brain activity (Micoulaud, 2015). NF can be used in several pathologies such as developmental disorders, but it also appeared to be efficient in reducing anxiety (Menella et al., 2017) that seems to be associated to power increase in the frontal high beta band (Marzbani et al., 2017). Few studies have been conducted on anxiety disorders modulation by NF (Moore et al., 2000; Hammond, 2005) despite that up to 33.7 % of the population is affected by anxiety disorders during the life time (Bandelow & Michaelis, 2015). Even if the alpha and theta band training appeared effective treatments for anxiety disorders beyond placebo, NF remains classified as "possibly efficacious". Scientific validation of NF efficacy with anxiety disorders is therefore necessary as well as the establishment of precise protocols.

OBJECTIVES : The objectives of the research project is therefore to identify the EEG signature(s) of the anxiety state and define the parameters (electrods position, frequency bands to regulate, number of sessions) allowing to reduce anxiety with NF at best in anxiety disorders.

METHODS : Anxiety defined by questionnaires (Stai A and B) will be assessed before and after 10 to 15 NF sessions in 4 groups of participants with anxiety disorders according to 4 conditions (alpha or theta band regulation, and frontal or parietal electrod), and a control placebo group. Anxiety disorders will be evaluated according to DSM-V criteria for anxiety disorders and STAI questionnaires (State-Trait Anxiety Inventory (Schweitzer & Paulhan, 1990)). Before and after each NF session, rest EEG from 19 electrods will be recorded (Mitsar system) to assess the EEG evolution. During the NF sessions performed thanks to Though Technology apparatus, EEG values will be measured each 3 minutes.

EXPECTED RESULTS : This research project is expected to first allowing to define one or several rest EEG profiles of the anxiety state. Second, we expect to validate the NF efficiency for anxiety disorders reduction. Third, we expect defining the best NF protocol for anxiety reduction in terms of electrode site, frequency bands and number of sessions to be chosen. We therefore will be able to define the most efficient neuronal plasticity to reduce anxiety (frontal or parietal mechanisms and low of middle frequency bands).

EXPECTED CANDIDATE PROFILE : For this research project, the candidate is expected to have solid knowledge in neuroscience and if possible in electrophysiology.

KHALFA / NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- El-Khoury Myriam (2008-2011)
- Reynaud Emmanuelle (2009-2012)

- Boukkezzi Sarah (2013-2017)
- Rousseau Pierre-François (2013-2018)

KHALFA / PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- **Boukezzi S**, Baunez C, **Rousseau P-F**, Warrot D, Silva C, Guyon V, Zendjidjian X, Nicolas F, Guedj E, Nazarian B, Trousselard M, Chaminade T, Khalfa S. Posttraumatic Stress Disorder is associated with altered reward mechanisms during the anticipation and the outcome of monetary incentive cues. Neuroimage: Clinical. 2019; 25: 102073.
- **Rousseau PF**, Malbos E, Verger A, Nicolas F, Lançon C, Khalfa S, Guedj E. Increase of precuneus metabolism correlates with reduction of PTSD symptoms after EMDR therapy in military veterans: an 18F-FDG PET study during virtual reality exposure to war. European Journal of Nuclear Medicine and Molecular Imaging. 2019; 46(9): 1817-1821.
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REY / NAMES AND DATES OF THE CURRENTLY SUPERVISED PHD STUDENTS :

- Laure Tosatto (co-direction)
- Guillem Bonafos (co-direction)

REY / NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Muriele Brand
- Ibrahima Giroux
- Kévin Le Goff
- Sylvain Madec

- Laure Minier
- Raphaëlle Malassis
- Alain Parra

REY / PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- **Parra**, A., & Rey, A. (2019). The interoception and imagination loop in hypnotic phenomena. Consciousness & Cognition. Doi: 10.1016/j.concog.2019.102765
- Rey, A., **Le Goff**, K, Abadie, M., & Courrieu, P. (2019). The primacy order effect in complexe decision making. Psychological Research. Doi:10.1007/s00426- 019-01178-
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- **Le Goff**, K., Rey, A., Haggard, P., Oullier, O., & Berberian, B. (2018). Agency modulates interactions with automation technologies. Ergonomics
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- **Madec**, S., **Le Goff**, K ., Anton, J.-L., Longcamp, M., Velay, J.-L., Nazarian, B., Roth, M., Courrieu, P., Grainger, J., & Rey, A. (2016). Brain correlates of phonological recoding of visual symbols. NeuroImage. doi: 10.1016/j.neuroimage.2016.02.010
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- **Giroux**, I., & Rey, A. (2009). Lexical and sub-lexical units in speech perception. Cognitive Science, 33, 260- 272.
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PROJECT D7

Title : Layer-specific dynamics of primate parieto-motor cortical networks

Supervisor(s) : KILAVIK Bjorg Elisabeth (bjorg.kilavik@univ-amu.fr - +33 (0)4 91 32 40 40)

Laboratory : Timone neuroscience institute (INT, UMR 7289)

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Project

STATE OF THE ART : The cerebral cortex is organized into multiple layers. The superficial layers of motor cortex receive the majority of bottom-up sensory inputs from parietal cortex and the thalamus, and mainly project to local and distant cortical regions. Deep layers receive inputs of cortical origins and mainly project to sub-cortical regions including the striatum, thalamus and spinal cord. Beyond these anatomical insights, we have very sparse knowledge about the functional properties of neurons in different motor cortical layers of non-human primates (NHP). Furthermore, the laminar-specific bottom-up and top-down connectivity including motor cortex is less well understood compared to sensory areas in the NHP. Whether general coding principles and a "canonical cortical microcircuit" extend from sensory to frontal areas is therefore still debated.

OBJECTIVES AND METHODS : The student will train macaques in visuomotor arm reaching behavior, and perform electrophysiological recordings with multi-electrode laminar arrays from motor and parietal cortical areas. She/he will also be involved in data analysis (matlab/python). Neuronal spiking activity and local field potentials (LFPs) will be analyzed to study the dynamics of local interactions across cortical layers and inter-areal communication. These network dynamics will be compared across brain states and different levels of predictability. While this project will mainly focus on the macaque model, via institute collaborations we can have access to parieto-motor data from lissencephalic marmoset monkeys, enabling laminar analysis of areas buried in sulci in macaques.

EXPECTED RESULTS : We will quantify the information in neuronal spiking activity and LFPs related to different task aspects (e.g. rules, visual targets, arm movements) at different laminar depths of motor cortex (M1 and PMd) via for instance decoding. This will be linked to large-scale processing involving parietal cortex 7a (visual coding, connected with PMd) and 5d (somatosensory coding, connected with M1). The large-scale information routing will be quantified via for instance phase-amplitude coupling and Granger causality measures. The results will be compared to established functional connectivity patterns in sensory cortices, to determine if a canonical microcircuit can extend to frontal cortices.

FEASABILITY AND ENVIRONMENT : The research program is ongoing, with equipment and ethical committee approval in place. Laminar data from motor areas is already available for analyses, and will be extended with new data from parietomotor recordings. This PhD project is partly related to a recently funded HBP FLAG-ERA project also involving Dr. Brochier (INT) and two labs in Greece and Germany, and the candidate will perform experimental work with a FLAG-ERA funded post-doc. Functional connectivity analyses will be done in collaboration with Dr. Brovelli (INT) and Dr. Battaglia (Inst. of Systems Neuroscience, Marseille). The candidate will join a team with 5 Principal Investigators interested in cognitive motor control, combining behavioral and electrophysiological studies in NHP and in human participants and patients.

CANDIDAT PROFILE : A background in biology, neuroscience, physics or engineering is particularly appropriate. The project will combine experimental work (training and recording from NHPs) and data analysis, providing an excellent opportunity to gain solid training in integrative neurosciences.

NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS

Joachim Confais, 2008-2013

PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Kilavik BE, Roux S, Ponce-Alvarez A, **Confais J**, Grün S, Riehle A (2009) Long-term modifications in motor cortical dynamics induced by intensive practice. J Neurosci 29: 12653-12663
- Kilavik BE, **Confais J**, Ponce-Alvarez A, Diesmann M, Riehle A (2010) Evoked potentials in motor cortical local field potentials reflect task timing and behavioral performance. J Neurophysiol 104: 2338-2351
- Kilavik BE, Ponce-Alvarez A, Trachel R, **Confais J**, Takerkart S, Riehle A (2012) Contextrelated frequency modulations of macaque motor cortical LFP beta oscillations. Cereb Cortex 22: 2148-2159
- **Confais J**, Kilavik BE, Ponce-Alvarez A, Riehle A (2012) On the anticipatory pre-cue activity in motor cortex. J Neurosci 32: 15359-68
- Kilavik BE, **Confais J**, Riehle A (2014) Signs of timing in motor cortex during movement preparation and cue anticipation. Adv Exp Med Biol 829: 121-142
- **Confais J**, Malfait N, Brochier T, Riehle A, Kilavik BE (2019) Is there an intrinsic relationship between LFP beta oscillation amplitude and firing rate of individual neurons in monkey motor cortex? doi: https://doi.org/10.1101/586727 (currently under revision in a peer-review journal)

PROJECT D8

Title : French-Arabic bigraphism: behavioural and neuroimaging studies of the interactions between two languages in the motor system

Supervisor : LONGCAMP Marieke (marieke.longcamp@univ-amu.fr - +33 (0)4 13 55 10 86) **Laboratory** : Cognitive Neurosciences Laboratory (LNC, 7291) https://lnc.univ-amu.fr/

Project

STATE OF THE ART : In some Arabic-speaking countries, learning Arabic and French implies mastering two different graphic systems and being bilingual also means being a 'bi-scripter'. Is there a 'cost' of bigraphy? Studies on the influence of bigraphism on the acquisition of writing are very rare, especially for Arabic. Motor procedures for writing Arabic and French are different because of the opposite writing direction in the two languages. Interference between the two graphic systems can occur in a bi-scripter and sometimes inappropriate motor commands are used (an 'accent' which can materialize in the written trace and/or kinematics).

OBJECTIVES : The project consists in kinematics studies in adults and children at different training levels, in order to precisely characterize the interactions that occur between the two languages in writing single words. We will also assess writing difficulties in bigraphic children in order to find out whether their dysgraphia has the same impact and the same features in both languages. These behavioral studies will be carried out in Marseille and in Lebanon. In parallel, we will conduct studies using fMRI during writing and reading of Arabic and French words in bigraphic adults. We will use state-of-the-art multivariate techniques to test the overlap vs dissimilarity of the two languages within the components of the motor system in the brain.

METHODS : In the behavioural experiments in France and Lebanon, all writing acquisitions will be made on a graphic tablet. The neuroimaging experiments will be carried out in Marseille. We will record writing kinematics within the fMRI scanner using a graphics tablet specially designed for the fMRI environment. We will couple these data with the recordings of brain activity.

EXPECTED RESULTS : Analyzing the interference between two graphic systems will provide important insights into the cognitive processes involved in writing in different systems at both the behavioral and neural levels, and allow to adopt the most appropriate rehabilitation strategies when necessary.

FEASABILITY : Behavioural studies will be conducted in parallel in France and Lebanon in the context of a collaboration that was established during previous funding (PHC 'Cèdre') with St Joseph University in Beirut. Our group routinely runs fMRI studies of writing and has proven expertise in that field. A request for CPP to the CNRS has already been made. The cost of the fMRI studies will be covered by funding already obtained (e-Fran Arabesc project).**APPLICANT'S PROFILE** : A highly motivated student (Psychology; Neuroscience; Engineering) interested in adolescent development. Skills in statistics and experience with brain imaging are desirable.

EXPECTED PROFILE : In addition to a good understanding of the principles of cognitive neuroscience and brain imaging, knowledge on recordings and analyses of movement kinematics will be appreciated. Clinical knowledge on developmental disorders would also be a plus. In addition, it is essential that the student recruited for this project is bilingual and is a French/Arabic biscripter, mastering both graphic systems with equal fluency.

NAMES AND DATES OF THE PREVIOUSLY SUPERVISED PHD STUDENTS

- PALMIS Sarah (AMU, ED62, 2016-2019)
- WAMAIN Yannick (Toulouse, 2008-2011)

PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Palmis S., Velay J.L., Nazarian B., Sein, J., Anton J.L., Habib M., Longcamp M. The handwriting brain of middle-age children. (in revision)
- Palmis S., Velay J.L., Fabiani E., Nazarian B., Anton J.L., Habib M., Kandel S., Longcamp M. (2019) The impact of spelling regularity on handwriting production: A coupled fMRI and kinematics study. Cortex. 113:111-127.
- Palmis S., Fabiani E. & Longcamp M. (2019). Bases cérébrales de l'écriture : orthographe et contrôle moteur de la production. Revue de neuropsychologie.;11(3):168-175. doi:10.1684/nrp.2019.0514
- Palmis S, Danna J, Velay JL, Longcamp M. (2017) Motor control of handwriting in the developing brain: A review. Cogn Neuropsychol. 11:1-18. doi: 10.1080/02643294.2017.1367654.
- Wamain Y, Tallet J, Zanone PG, Longcamp M. (2012) Brain responses to handwritten and printed letters differentially depend on the activation state of the primary motor cortex. Neuroimage. 63(3): 1766-73.
- Wamain Y, Tallet J, Zanone PG, Longcamp M. (2011) "Biological geometry perception": visual discrimination of eccentricity is related to individual motor preferences. PLOS one. 6(1):e15995

PROJECT D9

Title : Neural mechanisms supporting brain asymmetry for speech and music

Supervisor : MORILLON Benjamin (bnmorillon@gmail.com) **Laboratory**

: Institute of System Neurosciences (INS, UM_S1106) http://ins-amu.fr/

Project

STATE OF THE ART A major debate in cognitive neuroscience concerns whether brain asymmetry for speech and music emerges from differential sensitivity to acoustical cues or from domain-specific neural networks. This debate is closely related to the question of the origins of hemispheric specialization. Despite years of debate and empirical work, these issues have remained unresolved, and indeed have generated intense disagreement in the literature. We believe this situation is due to the insufficiently specific computational specification of prior models, and to a lack of clear grounding in neurophysiology.

OBJECTIVES ANX EXPECTED RESULTS : This PhD project will tackle these questions by taking advantage of the spectrotemporal modulation framework, a rigorous approach that has received much support from single-neuron recordings and human imaging. According to this framework, auditory cortical neurons are best characterized functionally in terms of their responses to spectral and temporal power fluctuations (Singh and Theunissen 2003, Chi et al. 2005, Flinker et al. 2019).

EXPECTED RESULTS : In a set of inter-related studies involving human participants, the PhD candidate will follow-up on our recent work (Albouy et al., 2020) to investigate the respective sensitivity of the left and right hemispheres to low-level acoustical cues and its modulation by attention and prior knowledge. The respective neural dynamics underlying auditory processing in left and right hemispheres will be characterized, and their selective role in the processing of speech and music will be highlighted. This will be done by 1- taking advantage of the spectrotemporal modulation framework, 2- capitalizing on a recently created corpus of sung speech stimuli in which melodic and verbal content is crossed and balanced, and 3- recording neural responses with intracranial and scalp recordings of human brain activity (with intracranial electroencephalography, sEEG and magnetoencephalography, MEG).

FEASABILITY : Feasibility of SEEG and MEG studies is ensured by the excellent infrastructures offered at our System Neurosciences Institute

EXPECTED CANDIDATE PROFILE : The PhD candidate is expected to have programming skills in Python (or Matlab), to have at least good notions of English, to be highly motivated and to be willing to perform collaborative work.

NAMES AND DATES OF THE CURRENTLY SUPERVISED PHD STUDENTS

- Jérémy Giroud (50%)
- Arnaud Zalta (50%)

PUBLICATIONS OF THE PREVIOUSLY SUPERVISED PHD STUDENTS :

- Zalta A, Petkoski S, Morillon B, Natural rhythms of periodic temporal attention, Nature Communications, 11:1051
- Giroud J, Trébuchon A, Schön D, Marquis P, Liégeois-Chauvel C, Poeppel D, Morillon B,


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