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Cendra AGULHON's team

Team: Glia-Glia & Glia-Neuron Interaction group

Fields of research: Neurophysiology/systems neuroscience

Internship project:

Investigating the role of astrocytic signaling in the physiopathology of neurodegenerative diseases

Supervisor: Cendra AGULHON

Neurodegenerative diseases are leading contributors to cognitive illness, imposing emotional burdens on families as well as individuals. Based on recent literature, we hypothesize that a common abnormal activation of astrocytic signaling may trigger transmitters and inflammatory mediators release from astrocytes. Both of these effects could consequently alter neuronal activity and contribute to neuronal cell death, and thus to the pathogenesis of neurodegenerative and cognitive disorders. We propose to directly test this hypothesis using chemogenetics, biochemistry, immunohistochemistry and electrophysiology.

Period: Anytime from January 2016 to June 2016

Maria Cecilia ANGULO's team

Team: Physiology of NG2 cells

Fields of research: Neurophysiology/systems neuroscience

Internship project:

Role of GABAergic synaptic connectivity of oligodendrocyte progenitors in the somatosensory cortex

Supervisor: Maria Cecilia ANGULO

Myelination is a fundamental process required to speed up neuronal transmission by insulating axons from current leakage. Major developmental brain disorders induce irreversible myelination defects. One possibility to overcome myelination impairment is to stimulate the production of mature oligodendrocytes from endogenous oligodendrocyte precursor cells (OPCs). To reach this aim, however, it is necessary to understand the cellular and molecular signals that control OPC proliferation and differentiation during postnatal development.

Recent advances have revealed functional synaptic connections between neurons and OPCs which role remains elusive. Synaptic neurotransmitter release onto OPCs constitutes a suited mechanism to control the fate of these cells. We recently demonstrated that GABAergic synaptic activity in cortical OPCs is higher at the onset of oligodendrogenesis and disappears after (Balia et al., 2015, Orduz et al., 2015). This correlation between transient synaptic innervation and oligodendrogenesis suggests that GABAergic inputs influence OPC differentiation and thus myelination.

The candidate will participate in a program that aims at unraveling whether GABAergic connectivity of OPCs has an impact on OPC proliferation, differentiation and/or myelination during postnatal development of the somatosensory cortex. He/She will evaluate the regulation of activity-dependent oligodendrogenesis during myelin repair by using an optogenetic approach in freely moving mice. Optogenetics, combination of optics and genetics, allows for a simple and rapid control of targeted cells with light by activating the photosensitive proteins channelrhodopsin-2. He/she will use different transgenic mice targeting the activity of interneurons with an optogenetic approach. We expect to demonstrate that cortical oligodendrogenesis depends on the activity of interneurons. The demonstration that OPC GABAergic synaptic activity regulates oligodendrogenesis may have profound consequences for the design of innovative therapies promoting myelination and oligodendrocyte regeneration in myelin disorders. Indeed, if the involvement of synaptic inputs onto OPCs influences the generation of myelinating oligodendrocytes, strategies aiming at modulating the synaptic activity of OPCs could be envisaged.

Recent publications:

1. Wake H*, Ortiz FC*, Woo DH, Lee P, Angulo MC, Fields D (2015) "Non-synaptic junctions on myelinating glia promote preferential myelination of electrically-active axons". Nat Commun 6:7844
*Co-first authors

2. Orduz D*, Maldonado PP*, Balia M, Vélez-Fort M, de Sars V, Yanagawa Y, Emiliani V, Angulo MC (2015) Interneurons and oligodendrocyte progenitors form a structured synaptic network in the developing neocortex. eLife 4:e06953
*Co-first authors

3. Sahel, A*, Ortiz, FC*, Kerninon, C, Maldonado PP, Angulo MC#, Nait Oumesmar B# (2015) Alteration of synaptic connectivity of oligodendrocyte precursor cells following demyelination. Front Cell Neurosci 9:77. doi: 10.3389/fncel.2015.00077
*Co-first authors; #Co-senior authors

4. Balia M*, Vélez-Fort M*, Passlick S, Schäfer C, Audinat E, Steinhäuser C, Seifert G, Angulo MC (2015) Postnatal down-regulation of the GABAA receptor γ2 subunit in neocortical NG2 cells accompanies synaptic-to-extrasynaptic switch in GABAergic transmission mode. Cereb Cortex, 25(4):1114-23
*Co-first authors

Period: Anytime from January 2016 to June 2016

Etienne AUDINAT's team

Team: Neuron-Glia Interactions

Fields of research: Neurophysiology/systems neuroscience

Internship project:

Microglial control of synapse maturation during cortical development

Supervisors: Etienne AUDINAT & Sofia BAPTISTA

Recent evidence indicates that microglial cells, the resident macrophages of the brain, have important functions during the normal development of synaptic networks. Our team has recently shown that reciprocal interactions between microglia and neurons are necessary for the proper maturation of thalamo-cortical synapses during the first postnatal week in the mouse somatosensory "barrel" cortex. On the one hand, the neuronal cytokine fractalkine regulates the recruitment of microglia at maturating thalamo-cortical synapses. On the other hand, this recruitment of microglia controls the maturation of thalamo-cortical synapses by modulating the functional expression of glutamate receptors (Hoshiko et al., 2012; Arnoux et al., 2013; 2014; Arnoux, Audinat 2015). We are currently testing whether BDNF and TNFalpha contribute to the effects of microglia on the maturation of thalamo-cortical synapses.

We combine electrophysiological and optical recordings in acute thalamo-cortical slices of transgenic mice together with in vivo manipulation (sensory deprivation, microglia depletion, microglia immune activation) immunohistochemistry, and molecular biology to identify the signaling pathways through which microglial cells influence the maturation of cortical synapses.

During this internship, the student will be trained in electrophysiology (in vitro patch-clamp recordings) and will study development of cortical synapse in transgenic mice in which BDNF or TNFalpha has been selectively disrupted in microglia (CX3CR1-CreER x floxed BDNF/TNFalpha). The student must therefore be motivated to learn electrophysiology and to study synapse physiology. This project is part of a collaborating program involving several other labs in the Paris area but also in Bordeaux and in Japan.

References:

Arnoux I, Audinat E (2015) Fractalkine signaling and microglia functions in the developing brain. *Neural Plasticity, special issue "Glial Plasticity", doi 10.1155/2015/689404*

Arnoux I, Hoshiko M, Sanz Diez A, Audinat E (2014) Paradoxical effects of minocycline in the developing mouse somatosensory cortex. *Glia* 62(3): 399-410

Arnoux I, Hoshiko M, Avignone E, Mandavy L, Yamamoto M, Audinat E (2013) Adaptive phenotype of microglial cells during the normal postnatal of the somatosensory "barrel" cortex. *Glia* 61(10): 1582-94

Hoshiko M, Arnoux I, Avignone E, Yamamoto N, Audinat E (2012) Deficiency of the microglial receptor CX3CR1 impairs postnatal functional development of thalamo-cortical synapses in the barrel cortex. *The Journal of Neuroscience* 32:15106-15111

Period: Anytime from January 2016 to June 2016

Laure BALLY-CUIF's team

Team: Zebrafish Neurogenetics

Fields of research: Neurogenetics/neurodevelopment

Internship project:

Molecular control of adult neural stem cell quiescence and fate in th zebrafish telencephalon

Supervisor: Laure BALLY-CUIF

The adult brain of teleost fish maintains multiple neural stem cell (NSC) niches, which are engaged in constitutive neurogenesis and can be efficiently recruited for repair upon mechanical injury [1]. In the telencephalon, a broad germinal zone has been identified, encompassing areas homologous to the mammalian NSC niches (SEZ, SGZ) but extending largely beyond these domains to cover the entire telencephalic ventricular zone [2,3]. NSCs of the adult zebrafish telencephalon, like their mammalian counterparts, express glial markers and are strongly quiescent [4]. We are using this model to probe the molecular and cellular mechanisms controlling NSC formation and maintenance, and driving their quiescence/activation cycle. We recently demonstrated that distinct Notch receptors (Notch3 and Notch1, respectively) are sequentially involved in the NSC recruitment process to control NSC activation then division or stemness [5]. From these results, we are currently moving in three complementary directions: (i) the identification of mediators or modulators of Notch3 activity at the single cell and population levels (ii) the impact of NSC heterogeneity on the control of adult NSC pools homeostasis, and (iii) how NSC activation timing and lineage properties drive brain construction. The proposed project will relate to point (i) and aim to test the function, in vivo in the adult zebrafish brain, of potential quiescence factors isolated through profiling quiescent, activated or *notch3*-/- NSCs or through gene candidate approaches. The main techniques used will be in vivo invalidation of gene function using antisense oligonucleotides administered to the adult brain, and cell fate tracing using clonal assays, immunocytochemistry and in situ hybridization on whole-mount preparations.

1. Kizil, C. et al. *Dev Neurobiol* **72**, 429-461 (2012).
2. Adolf, B. et al. *Dev Biol* **295**, 278-293 (2006).
3. Grandel, H. et al. *Dev Biol* **295**, 263-277 (2006).
4. Than-Trong, E. & Bally-Cuif, L. *Glia* **63**, 1406-1428 (2015).
5. Alunni, A. et al. *Development* **140**, 3335-3347 (2013).

Period: Anytime from January 2016 to June 2016

Pierre BILLUART & Thierry BIENVENU's team

Team: Genetics, Pathophysiology and Therapeutics of Mental Spectrum Disorders

Fields of research: Neurogenetics/neurodevelopment

Internship project:

Function of the RhoGTPase regulator Oligophrenin1 in neuronal migration: consequences in human pathology

Supervisors: Yoann SAILLOUR &Pierre BILLUART

Intellectual Disability (ID, also called learning disability, mental retardation, or cognitive deficit) is defined by an overall Intelligence Quotient (IQ) lower than 70 associated with deficit in conceptual, social, and practical adaptive skills with an onset before the age of 18 years. The causes of ID are heterogeneous and include genetic and/or environmental factors that influence the development and function of the Central Nervous System during the pre-, peri-, or post-natal period. Genetic causes, including chromosomal abnormalities, such as in Down syndrome, and monogenic causes, seem to be responsible for 40 to 50% of moderate to severe ID (IQ < 50), whereas environmental factors primarily contribute to mild ID (50 < IQ < 70). ID with a preserved CNS organization (i.e., normal MRI scan) has been found associated to numerous mutated genes; some of them (ie: *OPHN1*, *IL1RAPL1*, *MECP2*...) encode for proteins functionally involved in synapse formation, the regulation of dendritic spine morphology, the regulation of the synaptic cytoskeleton or the synthesis and degradation of specific synapse proteins.

Recently, we investigated the earlier function of the Ophn1 RhoGAP protein in cortical development. Whereas patients with *OPHN1* mutations have no cortical malformations, gene inactivation in a mouse model impairs the migration of pyramidal neurons at embryonic day 18.5. This delay may lead to the asynchronous development of neuronal networks that would impact the cognitive functions in human similarly to the Fragile-X model.

During his internship, the student will explore further this phenotype in *Ophn1*-KO mice models. He /she will assess the question of whether this migration impairment is an arrest or a transient phenomenon by studying later stages of development. Furthermore, it will be interesting to not only decipher the functional role of different Ophn1 protein domains in neuronal migration but also study the functional consequences of mutations found in human patients using complementation assays. Mutant and rescued cells will be generated in either WT or KO ophn1 backgrounds to study the cell and non-cell autonomous effects of ophn1 loss of function on neuronal migration.

This project is mainly based on the *in utero* electroporation method coupled using shRNA and Cre recombinase mediated genetic inactivation. Electroporated brains are analyzed with histological and microscopic techniques.

Period: Anytime from January 2016 to June 2016

Gilles BONVENTO's team

Team: Cell-cell interactions in neurodegenerative diseases

Fields of research: Neurological and psychiatric diseases

Internship project:

How do reactive astrocytes contribute to Alzheimer's disease?

Supervisor: Carole ESCARTIN

Astrocytes play many critical functions in the brain, in support to neurons. They become "reactive" in response to virtually all pathological situations including neurodegenerative diseases such as Alzheimer's disease (AD). Astrocyte reactivity involves well-described morphological changes. However, the functional changes occurring in reactive astrocytes are less understood and they could have significant consequences on neuronal survival (Escartin and Bonvento, *Mol Neurobiol.*, 2008, Ben Haim et al., *Front Cell Neurosci.*, 2015).

We have developed viral vectors that prevent astrocyte reactivity in the rodent brain, by blocking the JAK/STAT3 pathway, an instrumental cascade mediating astrocyte reactivity (Ben Haim et al., *J. Neurosci,* 2015). With these new molecular tools, we will evaluate how reactive astrocytes influence disease outcomes in a mouse model of AD. We will study the contribution of reactive astrocytes to AD at the molecular, histological, functional and behavioral levels. For that, we will use a variety of techniques on post-mortem mouse brain samples (qPCR, western blotting, ELISA, immunofluorescent stainings and confocal microscopy) and we will perform behavioral evaluation of AD mice.

This project is partially financed by a grant from the FRC (http://www.frc.asso.fr/la-frc/Appel-d-offres) and it will be performed in MIRCen, which has the necessary technical platforms and biosafety level 2 laboratories to manipulate viral vectors (http://i2bm.cea.fr/dsv/i2bm/Pages/MIRCen.aspx).

This multidisciplinary project will contribute to delineate the roles of reactive astrocytes in AD and to evaluate their therapeutic potential.

Period: Anytime from January 2016 to June 2016

Jocelyne CABOCHE & Peter VANHOUTTE's team

Team: Neuronal Signaling and Gene Regulation

Fields of research: Neuropharmacology/cell signaling

Internship project:

Neuronal PAS domain protein 4 (NPAS4) and neuroprotection in Huntington's Disease

Supervisor: Jocelyne CABOCHE

HD is an autosomal dominant genetic disorder caused by a CAG repeat expansion in the first exon of *HTT* gene that induces a polyglutamine expansion in the Huntingtin (HTT) protein. Individuals with 35 CAG repeats or more will develop the clinical symptoms. At the physio-pathological level, HD is characterized by a neuronal degeneration and a selective vulnerability of the striatum, a subcortical structure involved in the control of voluntary movements and reward related learning. The neurodegeneration is likely caused by a loss of normal functions of HTT and a toxic gain of function related to the PolyQ expansion. HTT plays a key role in many cellular processes such as brain-derived neurotrophic factor (BDNF) cellular trafficking, developmental neurogenesis and transcriptional regulation (reviewed in Roze et al., 2011; Moumné et al., 2013). Analyses of HD brains at early neuropathological stages and pre-symptomatic HD transgenic mice showed that this transcriptional dysregulation is an early event involving many genes displaying various functions and explaining some of the subsequent cellular dysfunctions observed in HD.

The team recently discovered that Neuronal PAS domain protein 4 (NPAS4), an immediate early gene regulated by neuronal activity and critically involved in neuroplasticity, was deficient in HD mouse models (R6/2 transgenic mice that express the human exon 1 of HTT with an expanded PolyQ region of 150 repeats) and in STHdh cells expressing the expanded form of HTT (STHdh Q111). Restoring NPAS4 expression, *in vitro*, was neuroprotective in HD striatal neurons in culture.

The aim of the proposed project is to further study NPAS4 in HD. For this purpose, we will first investigate, by western-blots, expression levels of NPAS4 in post-mortem tissues (cerebral cortex, caudate putamen) from HD patients when compared to normal ones. Next, we will use viral (AAV) mediated restoration of NPAS4 in striatal neurons *in vitro* and *in vivo*. *In vitro*, we will investigate whether NPAS4 restores normal mitochondrial functions. Primary cultures of striatal neurons will be infected with AAV encoding HTT with either 25 or 103CAG repeat, in the presence or not of AAV encoding NPAS4. Glutamate-induced mitochondrial membrane potential will be studied using imaging approaches (Rhodamine loading and confocal analysis by videomicroscopy). *In vivo*, AAV encoding NPAS4 will be stereotaxically injected in the striatum of R6/2 mice and their wild type littermate. Behavioral studies (rotarod, open field, foot print) will be performed in order to analyze a possible neuroprotective role of NPAS4 in this HD rodent mouse model.

Altogether these data will provide new insights towards a possible neuroprotective role of NPAS4 in HD, and will open new routes to therapeutical approaches in HD patients.

Martin E, Betuing S, Pagès C, Cambon K, Auregan G, Deglon N, Roze E, and ***Caboche J*** (2011) Mitogen- and stress-activated protein kinase 1-induced neuroprotection in Huntington's disease: role on chromatin remodeling at the PGC-1-alpha promoter. *Hum Mol Genet* *20*, 2422–2434.

Moumné L, Betuing S, and ***Caboche J*** (2013) Multiple Aspects of Gene Dysregulation in Huntington's Disease. *Front Neurol* *4*, 127.

Roze E, Saudou F, and ***Caboche J*** (2008a) Pathophysiology of Huntington's disease: from huntingtin functions to potential treatments. *Curr Opin Neurol* *21*, 497–503.

Roze E, Betuing S, Deyts C, Marcon E, Brami-Cherrier K, Pagès C, Humbert S, Mérienne K, and ***Caboche J*** (2008b) Mitogen- and stress-activated protein kinase-1 deficiency is involved in expanded-huntingtin-induced transcriptional dysregulation and striatal death. *FASEB J* *22*, 1083–1093.

Period: Anytime from January 2016 to June 2016

Serge CHARPAK's team

Team: From sensory processing to functional hyperaemia

Fields of research: Neurophysiology/systems neuroscience

Internship project:

Two-photon imaging of resting oxygen during hypoxia

Supervisor: Serge CHARPAK

The economical cost of brain diseases associated with hypoxia is extremely high. To understand the relationship between oxygenation, blood flow and brain disease, and in the long run how therapeutics can be optimised to reduce brain damage, it is important to determine how oxygen is delivered to and consumed by neurons *in vivo*. Recently, a two-photon phosphorescent probe PtP-C343 has been generated and two-photon phosphorescence lifetime microscopy (2PLM) has been used for depth-resolved micron-scale measurements of Po_2 in brain vessels (Lecoq et al. 2011, Nat Med) and tissue (Parpaleix et al. 2013, Nat Med.).

The project will consist, in mapping the drop of resting PO2 in response to acute and focal hypoxia induced by capillary photocoagulation in the olfactory bulb superficial layers.

Period: Anytime from January 2016 to June 2016

Filippo DEL BENE's team

Team: Neuronal Circuit Development

Fields of research: Neurogenetics/neurodevelopment

Internship project:

In vivo imaging of mRNA axonal transport in the zebrafish embryo

Supervisor: Filippo DEL BENE

Motor proteins ensure the transport of cytoskeleton components from the cell body to the growing axon by slow axonal transport, but also perform faster transport to shuttle various cargos along the microtubules to the synaptic terminal, including vesicles, mRNAs, organelles, and signaling molecules. They also ensure axon clearance of proteins and organelles that are taken to the cell body for degradation.

Defects in both transport of material for development or clearance of detritus in the axon can lead to neuronal stress and culminate in cell death. Motor neurons present a specific challenge in this regard because they need to extend very long axons in order to reach their target muscle fibers and establish the neuromuscular junction. As expected, axonal transport deficits have been reported in various neurodegenerative diseases including pathologies affecting motor neurons, like ALS and spinal and bulbar muscle atrophy (SBMA) (Chen *et al, Molec Neurodeg,* 2013).

In the context of ALS, it is still unknown whether the observed axonal transport defects are causative or consequences of other pathophysiological processes like mitochondrial disturbances or protein aggregates.

Using the embryonic zebrafish model, we are probing the transport dynamics of target mRNAs, which are transported to the synapse for local synthesis. By using a technique described in yeast (Larson *et al, Science*, 2011) we are imaging the transport of mRNA molecules using the MS2/PP7 system. For this, multiple repeats of a hairpin sequence (MS2 or PP7) is inserted into the 5' or 3' UTR of a gene of interest. Co-expression of this mRNA with a GFP-tagged coat protein that specifically recognizes and binds to the hairpin loops (MCP or PCP, respectively) allows the direct visualization of the mRNA *in vivo*, and its transport in real time, imaged with timelapse confocal microscopy.

We will be looking at various mRNA targets, described to be transported along the axon, and at mRNAs of genes involved in ALS.

Period: Anytime from January 2016 to June 2016

Alain DESTEXHE's team

Team: Oscillatory and stochastic dynamics in thalamo-cortical networks

Fields of research: Computational neurosciences/neural theory

Internship project:

Characterization of network states from multiunit recordings in humans

Supervisor: Alain DESTEXHE

This project aims at characterizing the dynamical properties of neuronal ensemble activity, as recorded using multiunit recording techniques in humans. "Utah-array" type recordings are available for several days, spanning multiple brain states, spanning the different phases of the wake-sleep cycle, as well as epileptic seizures. These data constitute one of the most accurate high-density "local" recordings available today for human brain activity. They include up to 100 discriminated units, usually separated into excitatory and inhibitory neurons, and about 100 local field potential (LFP) signals, recorded using the same electrodes in a 4x4 mm2 area of cerebral cortex.

The goal of this project is to obtain a fine characterization of the "brain state" using such high-density recordings. We would like to determine which variables could be correlated to various behavioral states, such as level of vigilance, level of consciousness, sleep, dreaming, etc. For example, the neuronal activities during wakefulness and during paradoxical (REM) sleep are extremely similar, but the subject is in a different behavioral state (awake vs. dreaming); can we find correlates to this by using a detailed analysis of neuronal discharges or LFP activity ? Another related question is that patients usually "feel" the seizure several minutes before it occurs, a phenomenon called the "aura". However, there is no obvious correlate of the aura that can be seen from the neuronal activity. This activity is here recorded for the first time with high precision, so there is hope to find such behavioral correlates using appropriate analyses of the data.

Thus, the student will use computer-based analyses (Python or Matlab), and will have access to the multi-electrode data of the laboratory. We will proceed in two steps. First, perform a "safe" characterization of the different brain states, by measuring the level of irregularity and the level of synchrony, and see how such variables evolve in time. This "safe" part of the project should provide a general characterization of the different states. In a second step, we propose to use more sophisticate tools such as mutual information, information transport, or tools from dynamical systems to characterize the collective aspects of neuronal activity. The goal of this second step will be to identify relevant measures that could correlate with behavioral state.

During this work, the student will have the opportunity to work at two different places, first the UNIC (Unit for Neuroscience, Information and Complexity, http://www.unic.cnrs-gif.fr) of Gif sur Yvette, a CNRS research lab consisting of mixed experimental and theoretical teams, and second, the EITN (European Institute for Theoretical Neuroscience, http://www.eitn.org) in Paris, which is solely devoted to theoretical neuroscience, analysis and modeling. These two places provide a very stimulating environment where theoreticians and experimentalists interact in a daily manner.

5 Selected publications:

Muller, L.E., Reynaud, A., Chavane, F. and Destexhe, A. The stimulus-evoked population response in visual cortex of awake monkey is a propagating wave. Nature Communications 5: 3675, 2014.

Estebanez, L., El Boustani, S., Destexhe, A. and Shulz, D. Correlated input reveals coexisting coding schemes in a sensory cortex. Nature Neuroscience 15: 1691-1699, 2012.

Peyrache, A., Dehghani, N., Eskandar, E.N., Madsen, J.R., Anderson, W.S., Donoghue, J.S., Hochberg, L.R., Halgren, E., Cash, S.S., and Destexhe, A. Spatiotemporal dynamics of neocortical excitation and inhibition during human sleep. Proc. Natl. Acad. Sci. USA 109: 1731-1736, 2012.

Marre, O., El Boustani, S., Fregnac, Y. and Destexhe, A. Prediction of spatio-temporal patterns of neural activity from pairwise correlations. Physical Review Letters 102: 138101, 2009.

Destexhe, A. and Contreras, D. Neuronal computations with stochastic network states. Science 314: 85-90, 2006.

Period: Anytime from January 2016 to June 2016

Emmanuel DUPOUX's team

Team: Computational Mechanisms of Cognitive Development

Fields of research: Cognitive neurosciences/neuropsychology

Internship project:

Bio-inspired machine learning and infant language acquisition

Supervisor: Emmanuel DUPOUX

The general aim of this project is to understand how human infants spontaneously learn their first language by applying a 'reverse engineering' approach, i.e., by constructing an artificial language learner that mimics the learning stages of the infant.

The student will apply weakly supervised or unsupervised, bio-inspired machine learning algorithms to large corpora of child-adult verbal interactions in one or several languages and compare the results with behavioral and/or neural recording data (EEGs, ECoG). Possible topics (not exhaustive):
modeling neural processing in the auditory cortex, context effects, inverse articulation modeling
unsupervized discovery of spoken terms, of phonetic, prosodic, semantic or grammatical categories
modeling the effect of external feedback loops (babbling, social, interactions)
testing the universality of learning algorithms across very different languages

The tools use may include:
- signal processing (speech, video, brain imaging features)
- deep neural networks or sparse dictionary methods
- hierarchical non parametric Bayesian models

The student will work in a multidisciplinary team composed of researchers with various backgrounds (neuroscience, psycholinguistics, machine learning, etc) located at the Ecole Normale Supérieure in the quartier latin in Paris, and will have access to high performance computing resources (CPU/GPU cluster), large language databases, and cutting edge expertise in the cognitive (neuro)science of language as well as machine learning algorithms for speech and language applications. Some of the projects will involve a collaboration with other teams in France (INRIA) or abroad (J. Hopkins, MIT, Facebook AI, etc).

Background required: engineering, computer science, applied maths, physics or formal/computational linguistics. Familiarity with cognitive/language science is a plus.

More details about the project in www.syntheticlearner.net

5 Selected publications:

Versteegh, M., Thiollière, R., Schatz, T., Xuan-Nga, C., Anguera, X., Jansen, A. & Dupoux, E. (2015). The Zero Resource Speech Challenge 2015. In INTERSPEECH-2015.

Martin, A., Schatz, T., Versteegh, M., Miyazawa, K., Mazuka, R., Dupoux, E. & Cristia, A. (2015). Mothers speak less clearly to infants: A comprehensive test of the hyperarticulation hypothesis. Psychological Science, 26(3), 341-347.

Fourtassi, A., Schatz, T., Varadarajan, B. & Dupoux, E. (2014). Exploring the Relative Role of Bottom-up and Top-down Information in Phoneme Learning. In Proceedings of the 52nd Annual meeting of the ACL, 2, (pp 1-6) Association for Computational Linguistics.

Martin, A., Peperkamp, S. & Dupoux, E. (2013). Learning Phonemes with a Proto-lexicon. Cognitive Science, 37, 103-124.

Cristia, A., Minagawa-Kawai, Y., Egorova, N., Gervain, J., Filippin, L., Cabrol, D. & Dupoux, E. (2014). Neural correlates of infant dialect discrimination: A fNIRS study. Developmental Science, 17(4), 628-635.

Period: Anytime from January 2016 to June 2016

Carsten JANKE's team

Team: Regulation of Microtubule Dynamics and Function

Fields of research: Neurogenetics/neurodevelopment

Internship project:

Regulation of neuronal microtubule-based transport by polyglutamylation

Supervisor: Maria MAGIERA

Intracellular transport is a basic cellular mechanism. Due to their compartmentalization and size, every eukaryotic cell needs to transport intracellular cargoes to specific sites. The probably most complex intracellular transport system exists in neurons, which due to their long axons and the complex morphology of the dendritic trees require a particularly efficient and well-coordinated transport network.

The neuronal transport uses microtubules as tracks. Cargoes are attached to specific molecular motors, such as kinesins or dynein, and are then transported to their specific destination. But how do the motors know where to go? One part of the answer are the intrinsic properties of the motors - some move plus-end directed, others minus-end directed on microtubules. For a more precise regulation of their intracellular destinations, however, complex regulatory mechanisms are needed. One of them could be the tubulin code, a complex signaling system with the potential to create specific 'road marks' on microtubules, which could guide the transport complexes. Out of various posttranslational modifications of microtubules, polyglutamylation is highly enriched in differentiated neurons, and is a strong candidate for regulation of axonal transport.

Our laboratory has demonstrated that deregulation of polyglutamylation in the brain leads to severe neurodegeneration, however the molecular mechanisms of this degeneration have remained unknown. In this project the student will investigate the impact of polyglutamylation on axonal transport. For this, neuronal cell culture, micro-fabrication, imaging and mouse biology will be combined to develop appropriate techniques to quantify the impact of differential polyglutamylation of microtubule tracks on neuronal traffic. The student will participate in a project in which specific microfluidic devices are used to grow neurons in defined shapes, and quantify the impact of microtubule polyglutamylation on axonal transport. Different reporters for axonal transport will be used in this approach, such as tagged vesicle markers. We will quantify various parameters of axonal transport such as speed of transport, directionality of transport, pauses in the transport, endurance, etc.

The paradigms studied in this project will in the future allow elucidating the potential roles of microtubule posttranslational modifications in complex diseases such as neurodegeneration.

References:

Rogowski K, van Dijk J, Magiera MM, Bosc C, Deloulme J-C, Bosson A, Peris L, Gold ND, Lacroix B, Bosch Grau M, Bec N, Larroque C, Desagher S, Holzer M, Andrieux A, Moutin M-J, Janke C (2010) A family of protein-deglutamylating enzymes associated with neurodegeneration. *Cell* **143:** 564-578
(this publication describes for the first time the link between tubulin polylgutamylation and neurodegeneration in a mouse model)

Janke C (2014) The tubulin code: Molecular components, readout mechanisms, and functions. *J Cell Biol* **206:** 461-472 *(a general review on tubulin posttranslational modifications)*

Period: Anytime from January 2016 to June 2016

Thierry LEVEILLARD's team

Team: Rod-Derived Cone Viability Signaling for the Treatment of Inherited Retinal Degenerations

Fields of research: Neurological and psychiatric diseases

Internship project:

Does brain redox homeostasis involve the glutaredoxin protein RdCVF2L?

Supervisor: Thierry LÉVEILLARD

The nucleoredoxin-like genes *NXNL1* and *NXNL2* are bifunctional, coding by alternative splicing for a thioredoxin and a trophic factor, called Rod-derived Cone Viability Factor (RdCVF)[1]. RdCVF exerts its protective effect on cone photoreceptors by stimulating glucose uptake via its cell surface receptor, BSG1 that forms a complex with the glucose transporter GLUT1[2]. Glucose is metabolized by cones through aerobic glycolysis to provide carbohydrates metabolites that support the daily renewal of cone outer segments packed with opsin molecules, essential for vision. RdCVF is a promising therapeutic for inherited retinal degenerations[3]. *NXNL1* and *NXNL2* are both expressed by photoreceptors however *NXNL2* is also expressed in other neurons in specific brain regions. Importantly, by studying the *Nxnl2-/-* mouse and by using post-mortem human tissues, we have obtained convincing evidences for the epigenetic implication of the *NXNL2* gene in Alzheimer's disease.

The objective here is to test if RdCVF2L has a glutaredoxin activity that could be involved in redox homeostasis. The conservation of the CXXS motif in placental mammalian species, versus CXXC in more distant species is very intriguing[4]. Thioredoxin-fold proteins with the sequence CXXS exists in other proteins and most notably glutaredoxin 5[5]. Under oxidative conditions, heterologous disulfides can be formed non-enzymatically between proteins and the tripeptide glutathione (GSH) the most important thiol buffers in the cell. Reduced GSH is oxidized to GSSG or in protein-CysSG. This reaction, termed S-glutathionylation is a protection of protein thiols under oxidative conditions, since it can be reversed. The protein S-glutathionylation cycle is initiated under conditions of oxidative stress and is reversed when a reducing environment is restored. Deglutathionylation is catalyzed by glutaredoxins (GLRX) through a monothiol reaction that depends only on the N-terminal active site cysteine residue.
In order to test for a possible S-glutathione reductase activity of RdCVF2L, we will compare retinal extracts of the *Nxnl2-/-* mouse to that of the *Nxnl2+/+* mouse by western blotting using anti-glutathione antibody (ab19534, Abcam)[6]. It may be necessary to induce transient oxidative conditions in the retina to be able to capture an excess of non deglutathionylated proteins in the retina of the *Nxnl2-/-* mouse. We will use photo-oxidative exposure from 50 to 2,500 lx. Any positive signal will be challenged by injection of AAV8-RdCVF2L. S-glutathionylated proteins of the *Nxnl2-/-* mouse will be identified by MS/MS analysis after anti-glutathione immunoprecipitation.

1. Leveillard *et al.*, ***Science translational medicine*** 2, 26ps16 (2010).
2. Ait-Ali *et al.*, ***Cell*** 161, 817 (2015).
3. Byrne *et al.*, ***The Journal of clinical investigation*** 125, 105 (2015).
4. Elachouri *et al.*, ***Free radical biology & medicine*** 81C, 22 (2015).
5. Hanschmann *et al.*, ***Antioxidants & redox signaling*** 19, 1539 (2013).
6. Xiong *et al.*, ***Antioxidants & redox signaling*** 15, 233 (2011).

Period: Anytime from January 2016 to June 2016

Sophie NICOLE & Bertrand FONTAINE's team

Team: NeuroGenetics & Physiology

Fields of research: Neurological and psychiatric diseases

Internship project:

Role of Multiple sclerosis genetic susceptibility on blood-brain barrier permeability to immune cells

Supervisor: Mohamed EL BEHI

Background and significance:

Multiple Sclerosis (MS) is an incurable and often disabling immune-mediated neurodegenerative disease of the central nervous system (CNS) characterized by inflammation, demyelination, axonal injury and gliosis [1]. The aetiology and exact pathogenesis of MS are unknown but it is considered to be an autoimmune disorder, likely triggered by environmental exposure in genetically susceptible individuals.

Studies in different experimental models of MS led to the consensus that disease begins with the formation of inflammatory lesions due to a disruption of the Blood Brain Barrier (BBB) and the infiltration of immune cells. The BBB is composed by endothelial cells (EC) that line parenchymal microvessels. ECs in the BBB differ from those found in other organs by the lack of fenestrations and by the presence of specialized tight junctions (TJ). Pericytes that surround ECs, and astrocytes endfeet assemble with ECs and contribute to maintain a tight BBB. Although the BBB is tightly sealed and create an anatomical impermeable wall between blood and CNS, small numbers of lymphocytes constantly patrol within CNS, a process called immune surveillance [2]. The importance of this process has been further demonstrated by the appearance of CNS infections in MS patients treated with therapeutics that inhibit lymphocytes transmigration through the BBB [3]. Nonetheless, the pathological mechanisms leading to increased immune cells trafficking across the BBB in MS remain unclear.

Our research team participated recently to an international genome wide association study (GWAS) involving more than 10,000 MS patients [4,5]. Results obtained identified 110 genes variants that are clearly associated with MS risk. The majority of these genes is involved in immune system function and more specifically in six T helper cells differentiation pathways, which reinforce the autoimmune origin of the disease. Our preliminary data on genetic analysis and clinical observations indicates that MS patients stratified according to their susceptibility genes involved in each of the 6 immune pathways present different form and severity of MS.

Objectives:

Using the existing well-characterized French REFGENSEP cohort (3000 patients and 800 healthy controls) typed for 110 MS associated polymorphisms and clinically annotated (age at onset, MS severity, clinical and historic of treatments), we will determine whether genetic stratification of MS patients in genes controlling specific T helper cells pathways will influence immune cells capability to traffic through the BBB. We will also determine whether different immune cell subsets from genetically stratified patients and healthy controls affect BBB integrity by analysing their individual action on CNS-derived endothelial cells. Data obtained in these in vitro studies will be then tested in vivo in humanized experimental models of CNS inflammation.

Methodology:

- Cell culture
- Flow cytometry (sorting and analysis)
- Immunocytochemistry
- Multiplexed quantitative PCR and ELISA
- Animal models of CNS inflammation

References:

1. Frohman EM, Racke MK, Raine CS: Multiple sclerosis--the plaque and its pathogenesis. N Engl J Med 2006, 354:942-955.
2. Ousman SS, Kubes P: Immune surveillance in the central nervous system. Nat Neurosci 2012, 15:1096-1101.
3. Derfuss T, Kuhle J, Lindberg R, Kappos L: Natalizumab therapy for multiple sclerosis. Semin Neurol 2013, 33:26-36.
4. International Multiple Sclerosis Genetics C, Wellcome Trust Case Control C, Sawcer S, Hellenthal G, Pirinen M, Spencer CC, Patsopoulos NA, Moutsianas L, Dilthey A, Su Z, et al.: Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 2011, 476:214-219.
5. International Multiple Sclerosis Genetics C, Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kemppinen A, Cotsapas C, Shah TS, Spencer C, Booth D, et al.: Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat Genet 2013, 45:1353-1360.

Period: Anytime from January 2016 to June 2016

Alessandra PIERANI's team

Team: Genetics and Development of the cerebral cortex

Fields of research: Neurogenetics/neurodevelopment

Internship project:

Developmental role of Slitrks in migration of cortical neurons

Supervisor: Alessandra PIERANI

Extensive migration serves during development to direct neurons to their final location. Altered migration processes at embryonic stages lead to the construction of pathological neural circuits in adults. The project aims at testing how the Slitrk family of proteins, sofar exclusively studied as organizer of mature synapses, control radial versus tangential migration in the developing cerebral cortex. We have found that Slitrks are expressed at the earliest stage of corticogenesis where they control specific steps during migration. Slitrk variants are associated with obsessive compulsive spectrum disorders, schizophrenia and bipolar disorders suggesting a possible developmental role for these proteins in the aethiology of pathological conditions. The student will use gain- and loss-of function approaches by *in utero* electroporation, mouse genetics, *in vitro* primary cell culture and timelapse microscopy.

Period: Anytime from January 2016 to June 2016

Laure RONDI REIG's team

Team: Cerebellum, navigation and memory
Fields of research: Neurophysiology / systems neuroscience

Internship project:

Development of testing to evaluate the executive functions in mice

Supervisor: Laure RONDI REIG

Research to confirm the diagnosis of Alzheimer disease currently privilege the discovery and the development of new biomarqueurs. However, although related to the evolution of the disease, these biomarqueurs do not evaluate the deterioration of the cognitive functions which reduces the autonomy of the person gradually. They do not evaluate the loss of autonomy nor do they put forward a quantitative measure of the disorders described by the patients or their family. It is thus essential to develop, in parallel of these biomarqueurs, cognitive tests able to objectify the deterioration of the cognitive functions by the disease but also their possible improvement by pharmacological treatments. In the Alzheimer disease, the loss of autonomy is associated with the deterioration of several functions among which: spatio-temporal memory (which make it possible to be located in time and space) and the executive functions (which make it possible to plan, initiate and conclude an action directed towards a goal). To evaluate the spatio-temporal memory, Laure Rondi-Reig and its team developed the mouse and human Starmaze, a navigation test (Rondi-Reig et al., 2006, Fouquet et al, 2011; Igloi et al., 2009; 2010). Recently, using a virtual version of the Starmaze made it possible to differentiate Alzheimer patients from fronto-temporal and normal ageing people (Bellassen et al., 2012). The tasks of navigation have the advantage of being at the same time close to the situations met on a everyday basis, nonverbal and perfectly translational. They thus make it possible to propose a relevant test to evaluate the quality of life of the patients in terms of adaptation to the cognitive requests which they usually meet and to directly compare the results obtained in humans and mice. The principal objective of the project will be to adapt the Starmaze test in order to evaluate specifically various executive functions (planning, behavioral flexibility, inhibition) in conditions of navigation. Our goal will be to quantify at the individual level various executive functions. We will test this with Alzheimer animal models compared with littermates controls. This project first developed in mice will then be adapted for human study.

Period: Anytime from January 2016 to June 2016

François ROUYER's team

Team: Molecular genetics of circadian rhythms

Fields of research: Neurogenetics/neurodevelopment

Internship project:

Identification of neuronal circuits controlled by the circadian clock in Drosophila

Supervisors: François ROUYER & Abhishek CHATTERJEE

Drosophila has about 150 clock neurons that control time-of-day information and orchestrate circadian behavioral rhythms such as sleep-wake cycles. Different periods of diurnal time, e.g., morning and evening, are encoded by distinct neuronal subpopulations. We are interested in (a) deciphering the pathway of information flow from these master clock neurons, (b) and in understanding how the downstream circuit decodes temporal information. To this end we have selected transgenic lines that express Gal4/LexA transgenes in specific populatins of neurons whose anatomical location in the brain suggests possible connections with clock neurons. These transgenes allow the considered neurons to be analyzed anatomically and functionally. The project will focus on neurons that might be downstream targets of the clock neurons that contribute to the evening peak of activity in light:dark cycles. We will use molecular-genetic tools (GRASP) to anatomically verify whether these putative downstream neurons form synapses with different types of evening clock neurons. The behavioral contribution of these neurons will be analyzed by manipulating their activity (thermogenetic hyperexcitation or silencing) in different environmental conditions. We will then ask whether the connection is monosynaptic or not, which neurotransmitter system mediates their communication and whether the connection strength shows circadian-time dependent plasticity. The experiments will involve Drosophila genetics, behavioral analysis (sleep-wake cycles), immunolabeling and microscopy analysis and functional imaging (Ca2+) of the clock neurons.

Period: Anytime from January 2016 to June 2016

Sylvie SCHNEIDER-MAUNOURY's team

Team: Morphogenesis of the vertebrate brain

Fields of research: Neurogenetics/neurodevelopment

Internship project:

Coordination of morphogenesis with axonogenesis in the developing olfactory placode

Supervisor: Marie BREAU

Cranial placodes are patches of ectodermal cells which give rise to essential parts of the peripheral nervous system in the vertebrate head, such as the olfactory sensory neurons, the entire inner ear and cranial ganglia. Placode progenitors are initially dispersed and intermixed within a continuous region surrounding the anterior neural plate, the so-called pan-placodal domain. As development proceeds, placode cells progressively coalesce into compact and discrete placodal structures. The mechanisms driving this coalescence process are still poorly understood, and the relative contribution of localised cell proliferation/apoptosis, cell shape changes, or cell movements is still a matter of debate (Breau and Schneider-Maunoury, 2014, 2015). In neurogenic placodes, cells not only have to shape their sensory organ or ganglion, but also to establish appropriate axonal connections with their target region in the brain. How the emergence of axons (or axonogenesis) occurs in this context and how it is coordinated with placode morphogenesis represents a fascinating, yet unexplored question in the developmental biology of sensory organs and ganglia.

We use the developing olfactory placode in zebrafish as a system to address the mechanisms of placode coalescence and its coordination with sensory axonogenesis. The student will use high resolution live imaging techniques to visualise movements, cell divisions, morphology changes, and intracellular architecture dynamics of sensory neuron progenitors and their forming axons during olfactory placode coalescence. In parallel, the student will analyse the function of molecular candidates such as cytoskeleton components and genes mutated in Kallmann syndrome, a pathology affecting reproduction and olfaction, caused by impaired development of olfactory sensory axons.

References:

Breau MA*, Schneider-Maunoury S. Cranial placodes: Models for exploring the multi-facets of cell adhesion in epithelial rearrangement, collective migration and neuronal movements (2014) Dev Biol 401(1):25-36*corresponding author

Breau MA*, Schneider-Maunoury S. Mechanisms of cranial placode assembly (2014) Int J Dev Biol 58:9-19. *corresponding author

Period: Anytime from January 2016 to June 2016

German SUMBRE's team

Team: Zebrafish neuroethology

Fields of research: Neurophysiology/systems neuroscience

Internship project:

Bi-stability in the zebrafish visual system

Supervisor: German SUMBRE

When perceiving bi-stable visual stimuli, the brain is not able to simultaneously perceive both stimuli, and instead perception switches from one percept to the other in a random manner. The reasons and mechanisms for the switch between percepts still remain a mystery for the neuroscience and the psychology communities.

Using zebrafish larvae, we will first study whether they can perceive bi-stable visual stimuli. We will thenuse two-photon microscopy in combination with zebrafish larvae expressing the genetically encoded calcium indicator GCaMP5 to monitor the activity of large neuronal networks, still with single-cell resolution, in an intact vertebrate while generating eye movements.

More specifically, we will monitor the dynamics of large neuronal networks at the main visual centres of the larva (retina and optic tectum, the latter playing a role in spatial detection, orienting behaviours and attention) while presenting the bi-stable visual stimulus and recording the bi-stable motor behaviour. We will ask what are the changes in the patterns of brain activity that lead to the perceptual switch. Using channelrhodopsin-2 we will further test causality by direct stimulation of the optic tectum while monitoring eye movements.

Knowledge in computer programming (python, matlab or c++) will be very advantageous.

Period: Anytime from January 2016 to June 2016

Laurent VENANCE's team

Team: Dynamic and Pathophysiology of Neuronal Networks

Fields of research: Neurophysiology/systems neuroscience

Internship project:

Input-timing dependent plasticity of cortical and thalamic inputs at striatal synapses: an ex and in vivo study

Supervisor: Laurent VENANCE

We aim at studying the biological substrate of the procedural learning and memory at basal ganglia and its pathophysiology (Parkinson's disease).

Basal ganglia, a subset of subcortical nuclei, are involved in adaptive control of the movement and procedural learning and memory (habit formation). Striatum, the main inputs nucleus of basal ganglia, acts as a coincidence detector of cortical and thalamic glutamatergic inputs: striatum extracts from background noise information judged as pertinent depending on the context. This crucial property is tightly modulated by dopamine, as dramatically illustrated in Parkinson's disease in which there is a massive degeneration of dopaminergic neurons.

Learning and memory are mainly underlain by synaptic plasticity. We are focusing on spike-timing dependent plasticity (STDP), a synaptic Hebbian learning rule, which is currently view as the elementary brick for the building of learning and memory. We have pioneered the field of STDP at the level of basal ganglia (Fino et al., 2005; Fino et al., 2009; Fino et al., 2010; Paillé et al., 2013; Cui et al., 2015; for reviews see: Fino and Venance, 2010; 2011). We have characterized, thank to the ex vivo multi-patch-clamp technique, the various form of STDP and the signaling pathways. We have recently show a new form of LTP underlain the endocannabinoid system (Cui et al., 2015). In addition, we are also focusing on the role of neuromodulatory systems such as acetylcholine, dopamine or endocannabinoids on the cortico-striatal and thalamo-striatal information processing. In this frame, we are studying the impact of the loss of dopamine, i. e. in Parkinson's disease, on cortico-striatal and thalamo-striatal STDP.

The proposed project is to explore a step further STDP: the input-timing dependent plasticity (ITDP). Indeed, if STDP represent the most advanced protocol to study Hebbian synaptic plasticity, it requires the injection of the somatic current, which is not very much physiological. Here, we aimed at investigated ex vivo and in vivo with patch-clamp recordings associated with tetrodes the impact on striatal synaptic weight of quasi-concomitant stimulation of cortex and thalamus. These stimulations will be performed with electrical electrodes or with optogenetics. The in vivo recordings will be performed on freely moving mice. This study will be realized in physiological conditions and in 6-OHDA-lesioned mice, a rodent model of Parkinson's disease. This project should help to better understand how cortical and thalamic activity concurred to striatal synaptic plasticity and the engram of procedural learning.

Techniques: electrophysiology (ex and in vivo patch-clamp), optogenetics, two-photon calcium imaging, multi-channel recordings & behavior, Parkinson's disease rodent model.

Period: Anytime from January 2016 to June 2016