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CNN and Riemannian geometry for Alzheimer's Disease progression classification

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Abstract

Alzheimer's Disease (AD) is one of the main neurodegenerative diseases. In France, in 2018, the disease tackled over 1 million individuals, and the amount is predicted to reach 1.8 million by 2050 [1]. This disease is difficult to diagnose and few treatments exist, mainly allowing to deal with symptoms at an early stage of the dementia. To face those difficulties, several publicly available databases have been created, which have facilitated the development of algorithms trained to diagnose AD as early as possible [2]. While significant improvements in accuracy have been achieved, several challenges remain, especially regarding the longitudinal characterization of AD. For that purpose, we developed a workflow to characterize the lifespan trajectory of both individual subjects and populations. The proposed approach estimates continuous curves of the populations in a Riemmanian mathematical space from six time points. These curves are deformed, both temporarily and spatially, to reach individual trajectories, leading to an individualization of AD's evolution. From Alzheimer's Disease Neuroimaging Initiative [3] (ADNI), we extracted 5033 observations, from 883 individuals, and selected the 59 individuals presenting at least 7 time points and a range of at least 3 years between their 6th time point and an ulterior one, allowing a prediction at plus 3 years based on the 6 first time points. We reached 88.1% accuracy for the prediction of the diagnosis evolution after 3 years. These results illustrate the potential of the proposed approach for AD diagnosis.

Keywords: Computer-aided diagnosis, Mixed-Effect Model, Alzheimer's Disease, Alzheimer's Progression, Longitudinal trajectories

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Comparison of Metabolomic Information between Dried Blood Spot and Serum

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ABSTRACT

DBS (Dried Blood Spot) are used for the screening of neonatal diseases and monitoring adults suffering from certain diseases in clinical context. DBS is a self-sampling device which is less invasive and requires less sample than a blood test. They can be sent by mail to the hospital allowing everyone to get access easily to biological analysis even in remote area or for elderly patients with mobility problems. Their use in new contexts has been widespread: carrying out anti-doping tests, the research of biomarkers of galactosemia or detection of cancer. In this work, we propose to compare quantitative data and exploratory metabolomic data between DSB and serum. For quantitative data, we quantified 6 short-chain fatty acids (SCFA), 20 bile acids, 20 tryptophan intermediates and 8 organic acids from TCA cycle. Two trends emerge : the first one is that the majority of the serum information is found in DBS. The second one is that DBS brings complementary information not found in serum. Indeed, an overlay of the metabolic cards of serum and DBS highlights a wider metabolic coverage for DBS. These results make it possible to envisage the use of DBS in both quantitative and exploratory metabolomic analyses. However, building up a cohort can last several months or years, so it will be necessary to clearly define the impact of storage conditions (temperature, hygrometry and light exposure) as well as its lasting.

Team 3 : Genomics and pathophysiology of neurodevelopmental disorders and motor neuron diseases **Léa BEDJA--IACONA**

PI : Patrick VOURC'H

FUNCTIONNAL ANALYSIS OF GENETIC VARIANTS IN AMYOTROPHIC LATERAL SCLEROSIS BY STUDYING EARLY MARKERS OF NEURODEGENERATION

Amyotrophic Lateral Sclerosis (ALS), also known as Charcot disease, is a neurodegenerative disease that causes the death of motor neurons resulting in the death of the patient 3 years after symptoms onset. 20% of cases of ALS are due to pathogenic genetic variants. Over 30 genes have been linked to the development of the disease to date, and the gene *SOD1* coding for the enzyme Superoxide Dismutase 1 is one of them. Over 200 different *SOD1* gene variants have been identified in the disease. Patients with a pathogenic variant in *SOD1* can be treated with Tofersen, an anti-SOD1 antisense strategy.

Several variants identified in ALS patients are considered potentially pathogenic or of unknown significance, these patients cannot receive Tofersen. A part of my project aims to study these particular variants in more detail, by performing *in vitro* studies to identify whether or not they are pathogenic. We are currently studying the function of 20 of these variants.

The different variants are created by site-directed mutagenesis on a plasmid expressing the human wild-type SOD1 protein. The plasmids are used for various *in vitro* functional analyses such as the propensity to form protein aggregates, one of the main hallmark of ALS. Some of the variants of interest will be studied *in vivo*, in collaboration with a team from Montpellier (INM).

The results obtained by theses studies could be exported to the to the clinic. In addition, the *in vitro* and *in vivo* models developed could be used for therapeutic studies under development.

Titre : How does memory age in ASD?

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is characterized by restricted interests and stereotyped behaviors, alterations in social adaptation and communication, but also in non-linguistic cognition and brain functioning. The few studies to date that have explored cognitive ageing in ASD reported contradictory results. Different hypotheses suggest that cognitive ageing could either be accelerated, equivalent or slowed compared to neurotypical ageing. Furthermore, there are no studies considering the mechanisms underlying this evolution. The aim of our study is to characterize the evolution of cognitive profiles in ASD during ageing and to study associated brain mechanisms. Sixty adults with ASD and sixty control adults divided into three age groups (18-40; 40-60; 60-80 years-old) will participate in this study. Several questionnaires and cognitive tests will make it possible to investigate the evolution of processing speed, executive functions and memory. An electrophysiological (EEG) task examining the effect of load on working memory will allow us to explore the underlying brain activity and to characterize the evolution of cognitive capacities in ASD. Moreover, we will explore the hypothesis, proposed for typical ageing, that brain reorganization mechanisms can have compensatory effects (Davis et al., 2007). We will be able to determine if adults with autism present a pattern of brain activity that could also be compensatory, or on the contrary no longer sufficient, especially in the oldest autistic individuals. We will present the methodology used and the first behavioral results in 20 neurotypical adults per age group.

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Tagging and imaging early life traumatic memories in mice

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Early-life stress (ELS) is the most important predictor of psychiatric diseases, such as anxiety disorders, depression and suicide. ELS occurs during childhood and adolescence, a critical period when experiences exert a considerable influence on an individual's development. However, it is unclear how the cellular substrate of traumatic memories associated with ELS evolves through life and can participate in its behavioral outcome. To approach that question, we are developing two mouse models based on social defeat (SD), consisting of chronic bouts of aggression of an experimental mouse by an aggressive mouse. The first one (infantile SD) is based on indirect exposure of pups to the SD of their lactating mother and is applied early in development (P3 and P14), capitalizing on the literature showing that witnessing SD can mimic the behavioral effects of direct exposure. The second (juvenile SD) is based on direct exposure of juvenile mice to SD and is applied later in development (P25). Our first characterization shows that juvenile SD induces a robust social aversion that persists in adulthood. These models will be combined with specific tools to allow lifelong tracking of neuronal populations recruited during ELS and reactivated through life. Using Fos2A-iCreER (FosTRAP2) mice combined with Cre-dependent expression of a fluorescent reporter (tdTomato), calcium indicator (GCAMP6f) and inhibitory opsin (Halorhodopsin), we intend to map brain-wide neuronal ensembles recruited during ELS, follow their activity through life with calcium imaging (fiber photometry), and manipulate their activity by optogenetics to study their contribution to the long-lasting phenotype induced by ELS.

Psychiatric and neurodegenerative pathologies concern approximately 38% of the European population. These pathologies have in common their supposed cerebral substrate but also the importance of predicting their clinical evolution. Several studies have shown the importance of neuroimaging in the understanding of these pathologies and their use is growing in the clinical field. This exploration in neuroimaging can be done anatomically with the T1 sequence of Magnetic Resonance Imaging (MRI), functionally (fMRI) or metabolically with 18-FluoroDesoxyGlucose Positron Emission Tomography (FDG-PET). However, the diagnosis of these pathologies is complex and requires a range of clinical evidence that calls on the experience of the clinician and the radiologist. In parallel, deep learning models are becoming more and more accurate in terms of diagnostic classification and prediction of clinical evolution at the population level. Their use in the clinic remains weak due to their potential poor prediction at the individual level, their lack of resilience to new diagnostic classifications and their restricted classifications to few pathologies simultaneously. The objective of this thesis is to develop an accurate deep learning algorithm, giving probabilistic results, allowing the use of several modalities (e.g. MRI, PET-FDG) and the prediction of several neuropsychiatric pathologies. For this purpose, we plan to use international databases of neurodegenerative and psychiatric pathologies giving access to thousands of examinations such as the "Alzheimer's Disease Neuroimaging Initiative" (ADNI) database for Alzheimer's disease. To solve the question posed, the work will first focus on the selection of a preprocessing method such as cortical surface extraction and then on the production of a convolutional or graph unsupervised deep learning algorithm. Finally, two methods will be explored: the study of the latent space of the trained variational autoencoder model to make the desired classes emerge or the transfer of the trained neural layers to another classification network.

Neural representation of cardiac signals: an electrophysiological characterization study

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Heartbeat Evoked Potential (HEP) is a marker of cardiac signal integration at the cerebral level. HEPs are modulated by experimental conditions such as attention to heartbeats and emotional arousal. However, the HEP is critically under-characterized, with no specific ERP components, and large heterogeneity in the time windows during which effects of interest occur (from 250 to 600ms post R-peak). Moreover, studies describe heartbeat-induced theta rhythm phase resetting (100-250ms post R-peak, measured by Inter Trial Phase Consistency, ITPC) and theta cross-area phase synchronization, suggesting that cardiac signal integration may be associated with multiple components with different functional significance. We hypothesize theta phase resetting to index early primary cardiac signal integration, triggering phase synchronization in a theta network that allows integration of the cardiac signal with other cognitive processes. Then, a late component indexed by the HEP may be associated with elaborative processes. We hypothesize that experimental conditions modulate connectivity patterns and HEP, but not phase resetting. We further expect that behavioral performance will correlate with HEP and connectivity patterns. To further characterize electrophysiological processes associated with cardiac signal integration, HEP, ITPC and theta connectivity will be computed using EEG for 20 participants. The indicators will first be characterized in a rest condition. Then, various task conditions (emotion identification & tact) will be used in order to evaluate task-specific patterns of activity. Finally, reproducibility will be assessed using independent datasets. Experimental condition effects will be assessed on the different indicators using (mass-univariate) t-tests and correlations with behavioral performance will be computed when relevant.

Updating our memories is essential for stamping new events in familiar contexts. The hippocampus is crucial for encoding and updating memories. Ensembles of hippocampal neurons are recruited during encoding to form a stable representation of the initial memory. However, it is unclear how these ensembles adapt to repeated exposures to the environmental context associated to the initial memory. In this longitudinal study, we use calcium imaging in freely behaving mice to determine the reactivation rates of cell ensembles and the stability of their spatial activity across time, by exposing repeatedly at different time interval mice to a familiar context and recording activity of neuronal ensembles in the region CA1 of the hippocampus. To this end, mice were allowed to explore the same environment 4 times per day (0, 1, 4 and 9h) at different time intervals: 1, 2, 7, 14, 21 days. Our preliminary results indicate that repeated visits induce changes in cell ensembles at multiple time scales. The reactivation rates of the neurons recruited decreased with each daily visit. New visits resulted in changes in neuronal activity and stability of spatial representation. These preliminary results suggest that the timestamping of new events involves a progressive reorganization of previously recruited engrams, which might support cognitive flexibility.

Title: Variability of pre-readers profiles in children with speech and/or language disorder.

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Children with speech and/or language disorders (SLD) are at increasing risk of reading impairment (RI). The literature suggests that multiple measures of speech, language and cognitive abilities in kindergarten could help to identify children at risk of RI in general population sample. But risk factors have been less studied in children with SLD. We assessed forty-five kindergarteners with SLD and sixty-one with typical language development (TD), on several known predictors of reading acquisition such as speech and language skills, letter knowledge, phonological awareness, rapid automatized naming, working memory, graphomotor skills and nonverbal abilities. We also collected information about environmental backgrounds (socioeconomic status, home literacy exposure) and familial risk of RI in a first degree relative. The results revealed lower performance in children with SLD on all cognitive skills, although performances varied widely between individuals. Cluster analysis showed the existence of three distinct pre-reader profiles. The first cluster performed well on all reading-related skills and mainly comprised TD children. Most children with SLD (n = 43) were classified in the other two clusters characterized by low reading-related skills. These two groups differed in the severity of their language and cognitive skills difficulties. Both had disadvantageous genetic and environmental backgrounds compared to the first cluster. This study confirmed that assessment of reading-related factors places children with SLD at high risk of RI and broad academic failure. However, results reveal considerable inter-individual variability both in language and reading-related skills.

Tibialis anterior muscle transient response analysis due to fibular nerve electrostimulation using ultrafast US imaging

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder that primarily affects motor neurons in the brain and spinal cord. These motor neurons are essential for transmitting signals to the muscles, controlling voluntary movements (walking, etc.). ALS is characterized by a gradual and progressive degeneration of these neurons, leading to muscle weakness and atrophy. The diagnostic process for ALS involves ruling out other conditions with similar symptoms through various clinical tests.

We propose new method to characterize muscle contractile properties over time using ultrafast ultrasound imaging to achieve early diagnosis. We combine nerve electrostimulation to closely mimic real muscle contraction and ultrafast imaging to measure muscle displacement.

The imaging system is an Aixplorer from Supersonic Imagine with probe SL 18-5. The electrostimulation generator is DSA47 from Digitimer

Muscle displacement was determined studying phase variation of ultrasound. We use a Singular Value Decomposition (SVD) filter. SVD allows for improving the SNR and, by analyzing different filter elements from the SVD, we isolate 95% of the total signal energy corresponding to the global muscle motion.

The aim is to show the selected biomarkers to characterize muscle movement, enabling comparison over time to find the first appearance of muscle degeneration

First test to characterize muscle displacement are very encouraging. A study involving a larger number of healthy volunteers is planned to investigate the evolution of proposed biomarkers across different categories of individuals (sex, age, etc).

Based on the first results from the healthy volunteers, further tests would be conducted on patients affected by ALS.

Pupil size provides an index of the locus coeruleus norepinephrine (LC-NE) system functioning. LC-NE, through its tonic and phasic activity, mediates arousal and optimises behavioural performance. Adaptive gain theory, which follows a Yerkes-Dodson curve, suggests that the LC-NE system plays an important role in controlling performance. Pupil diameter during a resting paradigm would reflect LC-NE tonic component, while LC-NE phasic component could be indexed by pupil reactivity to a target stimulus. The aim of our study is to characterize the link between tonic and phasic LC-NE activity indexed by pupil diameter by comparing rest and reactivity paradigms in the same subjects.

Pupil diameter was recorded with the Tobii pro-fusion eye tracker (250Hz) in thirty adults during a 3-min resting block and a face observation paradigm. Moreover, in order to test the integrity of the autonomic nervous system loop controlling pupil diameter, we also recorded pupil light reflex. We found no relationship between parameters recorded at rest (pupil median diameter and hippus parameters) and amplitude of the pupil light reflex.

Our preliminary results do not show any differences between the parameters recorded at rest (median, amplitude, frequency) and those recorded during the reactivity paradigm (median and median amplitude of the plateau). However, an expected correlation was found between the resting median and the pre-reactivity one.

Overall, the pupil did not allow us to characterise the link between tonic and phasic LC-NE activity. However, it would be interesting to test a reactivity paradigm that would allow greater activation of the LC-NE system.

Event-Related Potentials to Simple, Complex and Social Tactile Stimulations

Mohammad Riaz, Ilias Benkafouf, Kate Loidolt, Marianne Latinus & Claire Wardak.

Research in tactile electrophysiology mostly relies on electrical or robots-delivered stimulations which prevent the investigation of the neurophysiological response to social aspect of touch despite its crucial role through lifetime.

This study aimed to compare event-related potentials (ERPs) generated by different tactile stimulations of the radial nerve. Two distinct protocols were tested on the same 24 adults, each testing a different type of stimulation of the hairy forearm: tapping and stroking.

In the tapping protocol, participants received brief mechanical stimulations delivered automatically by a tactor ("simple condition"), or by an experimenter using the index ("social condition") or a soft Velcro-like object around the finger ("complex condition"). In the stroking protocol, participants received gentle strokes (CT-optimal) delivered by the experimenter's index ("social condition") or the same object as in the tapping study ("object condition"). We performed both a somatosensory ERPs and a spatial-temporal analysis.

Results revealed that in the tapping protocol, all stimuli elicited comparable responses with distinctive P50, N80, N130 and P200 components. In the stroking protocol, an ultra-late potential occurring around 2 seconds after stimulation onset was sensitive to the nature of the stimulation: it peaked earlier for the social condition than the object condition.

Overall, these findings suggest that brief tactile stimulations reliably evoked similar ERPs, regardless of the condition. Continuous stimulation evoked an ultra-late potential sensitive to the type of stimulation. This study highlights the feasibility of measuring ERPs evoked by direct skin-to-skin contacts, allowing to ensure ecological validity and to study affective/social touch processing.

Central nervous system (CNS) barrier impairment has been reported in amyotrophic lateral sclerosis (ALS), highlighting its potential significance in the disease. In this context, we aim to shed light on its involvement in the disease, by determining albumin quotient (QAlb) at the time of diagnosis of ALS in a large cohort of patients. Patients from the university hospital of Tours(n= 307) were included in this monocentric, retrospective study. In total, 92 patients (30%) had elevated QAlb levels. This percentage was higher in males (43%) than in females (15%). Interestingly, QAlb was not associated with age of onset, age at sampling or diagnostic delay. However, we found an association with ALS functional rating scale-revised (ALSFRS-r) at diagnosis but this was significant only in males. The QAlb levels were not linked to the presence of a pathogenic mutation. Finally, we performed a multivariate survival analysis and found that QAlb was significantly associated with survival in male patients (HR = 2.3, 95% CI = 1.2–4.3,p= 0.009). A longitudinal evaluation of markers of barrier impairment, in combination with inflammatory biomarkers, could give insight into the involvement of CNS barrier impairment in the pathogenesis of the disease. The gender difference might guide the development of new drugs and help personalise the treatment of ALS.

Autism Spectrum Disorder is an early onset neurodevelopmental disorder characterized by wide heterogeneity. This wide clinical heterogeneity is characterized notably by a range of particularities, possibly affecting all sensory modalities, as well as high variability in language abilities from one child to another. At the pathophysiological level, different processing steps (from sensory to cognitive processing) are affected, for either simple stimuli or complex stimuli such as language. The main objective of the current PhD project is to identify individual neurophysiological and language profiles of children with and without autism. In this study, the different steps involved in processing of sensory information are studied with electroencephalography in three sensory modalities (audition, vision, and tact) with stimuli of varying complexity. Following a similar approach, structural aspects of language, simple and complex, are assessed with phonological and morphosyntactic tasks, in production (repetition) and in reception (comprehension), adapted to very young autistic children, even those who are minimally or non- verbal using eye-tracking. Combined analysis of neurophysiological and linguistic measures, associated with behavioral measures of autistic symptoms should make it possible to determine individual bioclinical profiles. The aim of this study is to provide better understanding of ASD heterogeneity, by proposing a new individualized approach, which describes individual profiles of children with autism. The over-arching aim is to offer these children individualized care, centered on their own strengths and difficulties.

Early-life adversity is a leading risk factor for developing mental disorders such as depression, anxiety or psychosis in adulthood. Anatomical, cellular and molecular alterations were described under multiple stress paradigms, acute and chronic alike and in various species. However, because of the heterogeneity of both stressors and individuals' respective susceptibility to stress, current knowledge only partially explains the clinical outcomes and mainly fail to describe an accurate temporality of stress processing, especially in young developing individuals.
To allow lifelong tracking of neuronal populations recruited during early-life stress we used a juvenile social defeat model (SDj) in male and female FosTRAP2 mice, in which neuronal activation results, in the presence of 4OH-tamoxifen, in the irreversible expression of the fluorescent reporter tdTomato in neurons activated during this tamoxifen-defined temporal window. This design aims at assessing brain-wide neuronal ensembles activated during the experience of SDj and re-activated during the re-exposure to a social context in adulthood.
Animals were exposed to social defeat from P23 to P30 and then isolated until sacrifice at P105. To assess the dynamics and persistence of SDj-induced social aversion, 4 interaction tests were performed at different timepoints. TdTomato was allowed to be expressed on the last day of aggression and the re-activation of tagged neurons was assessed by c-fos IHC after the last interaction. Our results highlight that SDj induces a strong social aversion, that is maintained through adulthood, with neurons recruited in key regions in juvenile period maintaining their activity life-long in the PVT, and emerging elsewhere in various brain structures we are now exploring.
To better understand the mechanisms involved in the persistence of the behavioural effects of jSD, we are now exploring how the formation of perineuronal nets (PNN), a form of extracellular matrix that stabilizes neuronal networks during critical periods of plasticity, can regulate the activity of stress-responsive neurons. We are focusing on the perifornical nucleus of the anterior hypothalamus, a region that shows a significant recall-induced cellular activation and also displays a very high PNN density.

Pupil dilation reflects the social and motion content of faces

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Interacting with others is a basic human need. Facial processing plays a crucial role in our social communication and interactions. Indeed, faces convey a great deal of information, such as a person's identity or internal emotional state, through the shape and motion of facial features (eyes, nose and mouth). Human faces are therefore salient social stimuli in our environment, attracting our attention and inducing physiological engagement (indexed by pupil diameter variations measured using eye tracking). However, the relative influence of human realism, its social content and the amount of motion on pupil dilation has never been elucidated. Thirty adults (13 females, 19-28 years old) were recorded with a 250Hz portable eye-tracker system. We analyzed the event-related pupil dilation in response to stimuli distributed along a gradient of social salience (non-social to social, going from objects to avatars to real faces) and dynamism (static to micro to macro-motion). Pupil dilation was higher in response to social (faces and avatars) compared to non-social stimuli (objects), with surprisingly a higher response for avatars. Pupil dilation was also higher in response to macro-motion compared to static. After quantifying the amount of motion of each stimulus, we found that the higher the quantity of motion, the higher the pupil dilated, especially for avatars and objects, but only in an additive way. Overall, human realism and its social content, as well as the amount of motion, contributed additionally to physiological mobilization.

Keywords: Eye-tracking, Pupillometry, Human, Avatar, Object, Biological motion

Characteristics of the language profiles of autistic children with and without intellectual development disorders

Little is currently known about language profiles in autistic children. This is due in part to the heterogeneity of linguistic and intellectual abilities in this neurodevelopmental disorder. The language skills of autistic children can vary greatly across language domains (e.g., pragmatics, lexicon, syntax, and phonology). Similarly, there is a broad spectrum of intellectual abilities in autism, with a significant percentage of individuals suffering from Developmental Intellectual Disorder (DID). Moreover, the nature of language difficulties in autism remains poorly understood, particularly whether they are directly attributable to the symptomatology of autism (communication and interactional deficits, and restricted interests and behaviors). The objective of this thesis is to identify language profiles in autistic children with and without DID and to explore the impact of autistic symptomatology on these profiles. To this end, language tools adapted to the autistic population and covering several linguistic domains will be administered to 50 autistic children (half of them with DID) and to 25 neurotypical children aged 6 to 12 years. In addition, two groups of children of the same age (n=25 per group) will be recruited for comparative purposes to explore the effects of autism on the profiles: children with Developmental Language Disorder (a neurodevelopmental disorder primarily affecting language) and children with DID (without autism). Statistical cluster analyses crossing language and non-language measures will identify language/non-language profiles in each group of children, which will then be compared to each other. The clinical and research implications of such a project are major. From a clinical perspective, the identification of language/non-language profiles will allow for the refinement of the categorization proposed by the International Classification of Diseases (WHO, 2018) and for precise targeting of children's needs in terms of speech and language therapy. From a research perspective, this project will make a fundamental contribution to the issues pertaining to the relationship between language and non-language cognition and the nature of language difficulties across disorders.

Key words: Developmental intellectual disorder; Autism; Developmental language disorder; Language

Role of the mGlu4 glutamate receptor and interest of targeting this receptor in depressive and autism like syndrome:

Ph.d supervisors : Catherine BELZUNG & Julie LE MERRER

Depression and autism spectrum disorders are two distinct psychiatric conditions but share several clinical features, notably social withdrawal and altered reward processes. Among many structures, the nucleus accumbens (NAc) emerges as a key brain structure in regulating social motivation under physiological and pathological conditions. The NAc comprises two main neuronal populations: striatal projection neurons expressing dopamine D1 and D2 receptors (SPNs D1 and D2). SPNs play contrasting roles in modulating social behavior. It has been shown that an excess of SPN-D2 activity in the NAc leads to deficits in social interaction and may represent one of the neurobiological substrates of social behavioral deficits observed in autism and depression. To correct such imbalance, the metabotropic glutamate receptor type 4 (mGluR4) represents a promising pharmacological target. Its presynaptic expression, enriched in SPN-D2, and its negative coupling to adenylyl cyclase make it an ideal lever to inhibit SPN-D2 activity. The development of positive allosteric modulators (PAMs) that facilitate mGluR4 activation by glutamate thus offers an innovative pathway to treat these pathologies. The objectives of my PhD project will be to test the effects of mGluR4 PAM treatment in mouse models of depression (social defeat) and Rett syndrome (*Mecp2* heterozygous mice), the later showing autistic-like symptoms. Additionally, we will develop a antibody fragment or nanobody® as a new therapeutic tool to regulate mGluR4 activity.

Characterization of the role of *PURA* in the neurodevelopmental phenotype associated with 5q31 duplications.

Purine rich element binding protein A (PURα) encoded by the *PURA* gene is an important transcriptional regulator that binds DNA and RNA and has a key role in neuronal development and differentiation. Haploinsufficiency of this gene has been reported to cause a severe neurodevelopmental syndrome with a wide range of symptoms including neurodevelopmental delay and intellectual disability. Only one large duplication involving this gene has been described in the literature by Rosenfeld et al. (2011), but the consequences of PURA overexpression on neurocognitive development have never been studied. To understand the impact of these duplications on neuronal development, *in vitro* functional studies will be performed in patients' cells or in cellular models. The first part of this project will focus on human SH-SY5Y neuroblastoma cell line, which can be differentiated into neuron-like cells. *PURA* will be overexpressed in this cell line and in primary cultures of mouse hippocampal neurons in order to mimic gene dosage effect. In addition, induced pluripotent stem cells (iPSCs) carrying the *PURA* duplication will be generated either from individuals with 5q31 duplications or by using CRISPR-Cas9 technology on a reference iPSC line available in the laboratory. These iPSCs will be differentiated into cortical neurons and different parameters of neurogenesis and synaptogenesis will be studied using confocal microscopy. Finally, these *in vitro* experiments will allow us to understand the neuropathological mechanisms associated with 5q31 duplications and to determine whether the duplication of *PURA* alters the neurodevelopmental trajectory.

Intracerebral delivery of therapeutic molecules using the Sonococktail approach: Application to amyotrophic lateral sclerosis

Karen Ea

Neurological and psychiatric diseases affect one in three people, making them a major public health issue. Although drug treatments exist, the blood-brain barrier (BBB) restricts the passage of therapeutic molecules between the systemic circulation and the brain. A promising new method enables these molecules to be delivered locally using gas microbubbles (MBs) in combination with ultrasound (US) in a way that is targeted, effective, safe and non-invasive. The activation of MBs by US (*i.e.* sonoporation) transiently permeates the BBB, increasing the extravasation of therapeutic molecules into the brain, thereby increasing their bioavailability and thus the therapeutic index. There are two limitations to the use of MBs: their rapid clearance and their polydispersity in size. MBs of different sizes will not respond in the same way to ultrasound parameters, so the vast majority will not be sensitive to US, which will reduce the therapeutic effect. To address this issue, we propose to replace MBs with monodisperse and sonosensitive nanodroplets (ND). After validating the efficacy of Sonococktail (ND1 and ND2) on an *in vitro* BBB model (*i.e.* sonoporation, cell viability, therapeutic effect), we want to apply this method to a neurodegenerative disease, amyotrophic lateral sclerosis (ALS), by delivering two molecules, riluzole (used clinically) and anacardic acid (AA, a molecule with therapeutic potential). We will apply this method *in vivo* to a mouse model of ALS by analysing the biodistribution of riluzole and AA using mass spectrometry and then validating the therapeutic effect using behavioural tests.

Keywords: Drug delivery; Sonoporation; Nanodroplets; Gas microbubbles; Amyotrophic lateral sclerosis

Vocal emotion processing in autistic children

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Although the diagnosis of Autism Spectrum Disorders (ASD) requires the joint presence of social communication disorders and repetitive, restricted behaviors, few studies have truly integrated the socio-emotional and perceptual domains. Thus, it remains to be established whether the difficulties of people with ASD are linked to specific emotional deficits, to sensory particularities that would be even more marked for social stimuli, or to both. Using the vocal smile as a model, this thesis aims to explore each major stage of the Perception-Representation-Action loop (Sensory Processing - Perceptual Representation - Motor Resonance) in the same ASD children. At the perceptual level, the neural correlates of the encoding of auditory regularity to emotional stimuli will be studied in electrophysiology (EEG), while trains of repeated emotional or neutral voices will be presented to participants. At the level of perceptual representations, the project will provide a comprehensive characterization of auditory representations of the smiling voice in ASD, using psychophysical paradigms (inverse correlation). Finally, at the level of motor resonance, the project will investigate the mechanisms by which vocal smiles elicit automatic facial muscle and autonomic nervous system responses, and how these may be affected by ASD. These reactions will be studied through the collection of physiological data (facial electromyography, pupillometry) as participants listen to and judge smiling and non-smiling vocal expressions. The experiments carried out shed light on each stage of the perception-action loop. The results will help define precise targets for cognitive-behavioral therapies and educational interventions tailored to each patient subgroup.

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