"Advancements in experimental and clinical neuroscience of motor and cognitive systems in neurodegenerative diseases".

Type of activity: Summer school (in person with some virtual lectures); 1 half day and 3 full days at an AMU venue
Health domain (s) of reference: Domain 15
CIVIS partner universities involved (at least 3): (SUR, NKUA, UB, ULB, UAM, SU,UT)

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Estimated number of participants who will be benefit from this activity (please specify if they will be academics and/or administrative staff members and/or students and/or PhD candidates. The proposed summer School is oriented to PhD students.

20 students and 5 teachers (in addition to the local teachers and 20 students from AMU).

In case of students please specify the workload in ECTS credits[3] in view of the possible recognition of the activity by the home institution **2 ECTS**

Short description of the initiative (max 200 word)

This CIVIS proposal of a summer school "*Advancements in experimental and clinical neurosciences of motor and cognitive systems in neurodegenerative diseases*" has the objective of promoting international training on the doctoral-level in Europe and to ultimately stimulate projects on the doctoral and post-doctoral level. Specifically, it has the objective to contribute to the training of highly-skilled doctoral candidates and stimulating entrepreneurship creativity and innovation within the CIVIS network. To this aim, international experts from 8 CIVIS partner universities (AMU, SUR, NKUA, UB, ULB, UAM, SU, UT, UG) gather to organize a summer school (in person with some virtual lectures) in Marseille, one of the oldest settlements in Europe, that proposes a teaching program on various aspects of neurodegenerative diseases, including findings from cutting-edge research. The program focuses on clinical, neuroimaging, computational, fundamental, innovative therapeutic approaches and ethical aspects of diagnosis in Alzheimer's disease and Parkinsonian syndromes. Lectures, practical workshops, and career development/funding sessions will allow the students to acquire specific as well as transferable skills. A structured social program such as posters presentation, informal discussions in small groups and a summary of the highlights/take-home messages is also planned in order to enhance cohesion between students and teachers from all CIVIS partners.

PROGRAM - some present and some online
Program may be subject to last minute changes)

Monday: Clinical aspects of neurodegeneration

13h50 Welcome address (A Eusebio/M Didic AMU)

14h00 Clinical approach to patients with neurodegenerative disorders (G. Fabbrini, SUR)
How to detect key clinical aspects that can guide clinicians for diagnosing and classifying neurodegenerative movement disorders. The presence of different clinical symptoms and signs may suggest different disease courses and long-term outcomes in patients with movement disorders.

14h30 Detection of Alzheimer's disease (AD) using neuropsychological tasks (M Didic, AMU)
On the clinical level, Alzheimer's disease (AD) is revealed by cognitive dysfunction. Adequate neuropsychological tasks are therefore critical for the assessment of patients. Which memory-task is most likely to contribute to the early detection of AD remains a matter of debate. We will here present a system-oriented approach that contributes to characterize different phenotypes of AD.

15h Break

15h30 Phenotypical profiles in Parkinson´s disease (Cristina Nombela , UAM)
The essential characteristic of Parkinson´s disease is tremor, particularly in upper limbs. However, one third of patient with Parkinson´s don´t show tremor at all. This is just one out of the less known characteristics of the disorder that may adopt varied phenotypes. Such phenotypes present specific clinical and brain functional features, drug efficacy and prognosis.

16h30 Movement studies in neurodegenerative disorders (M. Bologna, SUR)
Movement studies allow the quantification of various motor abnormalities in patients with neurodegenerative diseases, including those traditionally classified as movement disorders or dementia. In this context, movement studies provide insight into the pathophysiological mechanisms of various pathological conditions but may also be of interest in the clinical setting, e.g., for the differential diagnosis and monitoring of the disease progression in patients.

17h00 Sensory system and movement disorders (A. Conte, SUR)
Sensory abnormalities are commonly present in movement disorders. They can be clinically manifest or represent subclinical sensory system alterations identified with specific psychophysiological/neurophysiological tests. Current evidence on the pathophysiological mechanisms and implications of sensory system abnormalities in movement disorders will be discussed. Understanding the role of sensory abnormalities and sensorimotor integration in movement disorders may introduce new therapeutic scenarios based on non-invasive neuromodulatory strategies.

17h30 End

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Tuesday: Biomarkers in neurodegenerative diseases

8h30-11h30 Multimodal biomarkers in AD

8h30 Modelling the AD-induced neuroinflammation in mice (O Garaschuk, UT)
In humans and mice amyloidosis is accompanied by the activation of brain's immune system, causing profound neuronal, astrocytic and microglial hyperactivity. The lecture will summarize the current knowledge about the interplay between neurons/astrocytes/microglia under disease conditions and will describe the techniques for functional monitoring of these cell populations in vivo, in the living mammalian brain.

9h00 Amyloids in the brain, Amyloid imaging in AD (Eric Guedj- AMU)
Amyloid plaques play a central role in the physiopathology of Alzheimer's Disease (AD). Recently developed ligands for amyloid using PET allow in-vivo detection of plaques. However, the relationship of cognitive function and amyloid remains debated, as well as the impact of amyloid on re-organization of cerebral connectivity.

9h30 Structure and interactions of amyloid-β peptide aggregates unraveled by novel infrared spectroscopy approaches (Andreas Barth, SU)
The most common neurodegenerative disease is Alzheimer's disease, in which the amyloid-ß (Aß) peptide aggregates to amyloid fibers that accumulate in plaques in the human brain. Key aspects of the disease are still unclear and our work sheds light on two of them: (i) the structure of Aβ oligomers in aqueous solution and (ii) interactions of Aβ with other peptides. Here, we exploit the particular advantages of isotope-edited infrared (IR) spectroscopy. In order to generate structural models for Aβ oligomers, we use ^{13}C–labeling of specific amide groups in the backbone to identify intra– and intermolecular contacts similar to solid state nuclear magnetic resonance. To study Aß's interaction with other peptides, we use uniform ^{13}C–labeling of one of the interaction partners to identify both peptides in nanoscale images of the IR absorption. Our results indicate that an anti-amyloid peptide dissolves Aβ fibers.

10h00 APO4, the strongest genetic risk factor for AD (H Nielsen, SU)

10h30 Break

11h00 Functional imaging in AD (S. Goldman and X. De Tiège – ULB)
Neuroimaging has gained a central role in the pathophysiological investigation of the clinical consequences of neurodegenerative processes because it offers two major advantages. First, it provides structural, functional and metabolic information on the brain in topographical way. It provides access to the regional distribution of morphological, functional and metabolic changes that accompany neurodegenerative processes throughout the human brain. The distribution of the changes are easily correlated to the mental, cognitive, sensory and motor disturbances that may be present in various neurodegenerative disorders. Secondly, neuroimaging methods have a variety of practical advantages; they are non-invasive with minimal discomfort for the subjects and patients, they are widely accessible, reproducible and easily subjected to statistical analysis.

11h30 EEG biomarkers of vigilance dysfunctions in Alzheimer's and Parkinson's diseases (C. Babiloni SUR)

Cognitive deficits and neuropsychiatric symptoms occur in patients with Alzheimers', Parkinson's, and Lewy Bodies diseases. Recent studies have found that dysfunctions in the general regulation of cortical excitability and vigilance in wakefulness may be associated with those symptoms. The talk will show recent EEG findings in patients with Alzheimers', Parkinson's, and Lewy Body diseases to frame a better understanding of the neurophysiological models underpinning their dysfunctions in relation to an impairment in the neurophysiological oscillatory mechanisms controlling vigilance in wakefulness. Those findings may ground a neurophysiological model explaining different pathways and neuromodulatory systems underpinning over-excitation of cerebral cortex and abnormal functional connectivity networks at the basis of cognitive and neuropsychiatric symptoms in Alzheimers', Parkinson's, and Lewy Body diseases.

12h-12h30 Computational/bioinformatic aspects of neurodegeneration
- Complexity in neurodegenerative diseases (Viktor Jirsa-AMU)
  Computational approaches based on mathematical models can improve the understanding of neurodegenerative diseases by addressing complexity. In terms of connectivity, the brain is restless even at rest and rs FC continually fluctuates in a way, which is far from being random but displays non-trivial spatiotemporal structure. The relevance of taking brain dynamics into account as well as modelling neurodegenerative diseases using the "Virtual Brain" will be discussed.

12h30-13h00
- Bioinformatics approach to identify gene signatures, pathways and therapeutic targets in neurodegenerative diseases (Maria Mernea - UB)
  Early detection of neurodegenerative diseases could improve the outcome of current therapies and would open the possibility to develop novel therapies. The identification of robust biomarkers of disease onset and new drug targets is an important research direction. This involves the analysis of genetic factors like mutations of protein-coding genes, single nucleotide polymorphisms (SNPs) associated with the disease or changes in gene expression profiles, as well as the analysis of altered molecular pathways and functional networks. Currently, a wealth of gene sequencing and expression data is stored in publically available databases. The analysis of such data relevant for neurodegenerative diseases using bioinformatics tools should help identify novel biomarkers and drug targets.

13h00 Lunch Break

14h00 Practical workshop
- Therapeutic targets in Alzheimer's disease – a bioinformatics approach (Maria Mernea - UB).
  The workshop will focus on using the relevant databases and bioinformatics tools in order to identify and characterize protein targets in Alzheimer's disease.

15h30 Multimodal (Neurophysiological, structural and metabolic imaging) biomarkers of parkinsonian syndromes
- Neurophysiological biomarkers of PD (A Eusebio AMU)
  Which are the neurophysiological biomarkers of PD, how are they recorded, what are their significance and how are they useful for therapeutic applications?
- TMS studies of motor cortex in Parkinson's disease (A. Berardelli SUR)
  In humans, the primary motor cortex (M1) plays a crucial role in voluntary movement control. M1 receives basal ganglia and cerebellar output, and its activity is regulated by multiple inhibitory and excitatory intracortical (i.e., local) circuits. In Parkinson's disease (PD), paired-pulse transcranial magnetic stimulation (TMS) studies have demonstrated the

impairment of specific intracortical M1 circuits, and these abnormalities are involved in the pathophysiology of motor dysfunction. The talk will clarify how specific TMS protocols can assess the interaction between one intracortical circuit and another, thus revealing the connectivity between different local M1 circuits as a significant correlate of movement disorders in PD patients.

- Structural imaging (S Grimaldi AMU)
  How ultra-high field MRI may provide useful biomarkers for the early diagnosis of parkinsonian disorders
- Molecular imaging (E Guedj AMU)
  How PET and SPECT imaging may help for the diagnosis of parkinsonian syndromes and what are the most promising candidates for future biomarkers?

17h30 End

Wednesday: Fundamental aspects of neurodegenerative diseases

9h00 Microglia in Neurodegenerative Diseases: Putative Role and Candidate Biomarkers. (C. Limatola SUR)
In the central nervous system (CNS), glial cells, such as microglia and astrocytes, are normally associated with support roles including contributions to energy metabolism, synaptic plasticity, and ion homeostasis. In addition, microglia and astrocytes act as the resident immune cells in the brain. The talk will show that that glial function may be impacted by multiple aspects including aging and local CNS changes caused by neurodegeneration. Furthermore, it will be shown that glia can also alter the pathology associated with many neurodegenerative diseases while microbiome can impact glial function as well with potential effects on the progression of those diseases. Finally, the talk will provide an overview about candidate biomarkers of microglia dysfunction in preclinical research.

9h30 Amyloid Precursor protein, calcium and synaptic signalling (S Efthimiopoulos, NKUA)
Amyloid precursor Protein (APP) is expressed at the synapse where it interacts with presynaptic and/or postsynaptic proteins. Furthermore, there is evidence that it affects the function of presynaptic and/or postsynaptic proteins, such as calcium channels and neurotransmitter receptors, and subsequently neuronal activity. Through these interactions and effects, APP promotes calcium-mediated synaptic neuroprotective signaling by regulating. An abnormal increase in the synaptic concentration of calcium due to increased levels of Aβ, free radicals, increased glutamatergic activity may disrupt the interactions of APP with synaptic proteins, compromised synaptic function and lead to synapse loss

10h00 In vivo and in cellulo models of AD: a focus on matrix metalloproteinases (MMPs) (S Rivera-AMU)
In Alzheimer's disease, some of the proteolytic pathways that operate at the crossroads of three major pathogenic processes tightly interconnected: neuroinflammation, amyloidogenesis and synaptic dysfunctions. Hence, some matrix metalloproteinases (MMPs) have appeared as new actors in Alzheimer's pathogenesis because they promote neuroinflammation and amyloidogenesis, and alter synaptic transmission as well. Consequently, MMPs may become potential new therapeutic targets.

10h30 Cellular models of Tauopathies: Biosensor cells for aggregation, primary cultures of neurons, IPSC derived neurons (Karelle Leroy and Jean-Pierre Brion, ULB)
Non-neuronal and neuronal cell models are used to study tau phosphorylation and aggregation in different experimental conditions; all these models have respective advantages and limitations. Primary neuronal cultures allows human WT or mutant tau expression in cells with a neuronal phenotype and allow easy treatment with molecules targeting tau pathology. Human IPS-cells derived neurons are differentiated from human donor cells that can be carriers of some genetic risk factors for tauopathies such as the ApoE4 allele in Alzheimer's disease. Biosensors cells are now available to monitor and quantify the seeding activities of tau samples by analyzing FRET signal.

11h00 Break

11h30 In vivo models of Tauopathies: mutant VS WT tau expressing mice, models of tau propagation (Karelle Leroy and Jean-Pierre Brion, ULB)
Several rodent models have been generated to try to reproduce faithfully the development of tau pathology as in human tauopathies. Mice models overexpressing mutant tau (identified in familial forms of tauopathies) develop a tau pathology in a cell-autonomous manner. The human pattern of tau isoforms expression and a physiological level of their expression can be obtained in tau knock-in models. In tau seeding based models, tau pathology is induced after intracerebral injection of human pathological tau, and propagates using a prion-like mechanism. Combined amyloid and tau models are

interesting to analyse the interaction between tau and amyloid pathologies.

12h30 Lunch Break

13h30 Student poster presentations

16h Molecular/cellular aspects of Parkinsonian syndromes
- Molecular aspects (P Kahle, UT)
  α-Synuclein is the major building block of Lewy bodies, the neuropathological hallmarks in the brain of PD patients. On the other hand tau is one of the main components aggregating in atypical parkinsonism such as progressive supranuclear palsy and corticobasal degeneration. This course will focus on the mechanisms of protein aggregation and transmission.
- Cellular aspects (L Stefanis, NKUA)
  This course will focus on the cellular mechanisms of neurodegeneration in parkinsonian syndromes from protein aggregation to cellular dysfunction and ultimately cellular death

17h30 End

Thursday: Therapeutic approaches in neurodegenerative diseases

9h00 DBS strategies for treating motor and cognitive/behavioural symptoms in Parkinson´s disease (Cristina Nombela – UAM; A Eusebio AMU)
Classical DBS strategies are oriented towards ameliorating motor symptoms by varying the stimulation targets and the parameters. Nevertheless, recent experiences have shown how the knowledge generated in treating other disorders (with cognitive and/or behavioural impairments) may apply to Parkinson´s and, so, spreading the opportunities to treat both motor and cognitive symptoms using stimulation techniques.

10h00 Lesional neurosurgical approaches for treating movement disorders. (T Witjas, AMU)
Gamma-knife and high-intensity Focused Ultrasound are growing techniques in the field of movement disorders and have put back lesional treatments back on the map. This talk will discuss the benefits and caveats of such techniques

10h30 Break

11h00 Practical workshop
The students will be divided in smaller groups and have the opportunity to observe in a clinical setting how DBS works in Parkinson's disease.

- DBS (T Witjas/A Eusebio, AMU)

12h30 Lunch Break Career development/funding (T Chaminade AMU)
A comprehensive overview of European grant opportunities adapted to the neuroscientific community as well as job opportunities in academia and more.

14h Age effects on neural networks underlying emotional memory are predicted by machine learning paradigms " (Elena Solesio, UAM)
In this session we will show how to assess the relationship between physical and cognitive disability in AD and the neural substrates. Importantly, innovative interventions, combining both transcranial direct current stimulation (tDCS) and physical exercise have shown physical and cognitive improvement and transfer of results to daily life. Finally, brain activity recordings before and after combined interventions allow us to examine neuroplasticity resulting from training. In this line, machine learning tools are ideal to examine if brain activity can predict physical and cognitive improvements after training.

14h30 Effects of transcranial direct current stimulation on behaviour and motor function in PD (F Fluchère, AMU)
How do tDCS impact decision making strategies and motor impairments in PD and related neurodegenerative disorders?

15h00 Preclinical studies focusing on immunotherapy and silencing strategies (Karelle Leroy and Jean-Pierre Brion, ULB)
Preclinical studies are currently performed in mice models to try to interfere with the formation of tau pathology. These preclinical treatments are focused directly on tau or on pathways targeting tau post-translational changes such as phosphorylation. This includes targeting tau and tau kinases eg

by reducing their expression with si-RNAs or ASOs treatments and also by immunotherapy with anti-tau antibodies.
Recent developments in therapeutic approach that have raised phase 2 and 3 of clinical assays in human patients include immunotherapy, active and passive, against Aß in AD and again tau in AD and in other tauopathies such as PSP. Anti-sense therapy targeting tau is now evaluated in phase 2 trials. Some of these approachs have been validated in terms of target engagement by imaging studies and biomarkers analysis (CSF, blood).

15h30 Application of Advanced Technologies and Artificial Intelligence in Parkinson's Disease (A Suppa, SUR)
The objective evaluation of specific signs and symptoms in Parkinson's disease achieved by using wearable sensors and machine learning analysis is rapidly developing. The focus of the presentation will be an updated discussion of available technologies and machine learning approaches applied to sensor-based data collected in patients with Parkinson's disease manifesting specific disorders including freezing of gait. Perspectives in the field will be discussed.

16h Highlights of the Summer School:
The students divided into 4 groups present the highlights of each day with take-home messages.

17h Concluding remarks and End of the Summer School

17h 30 End of Summer School