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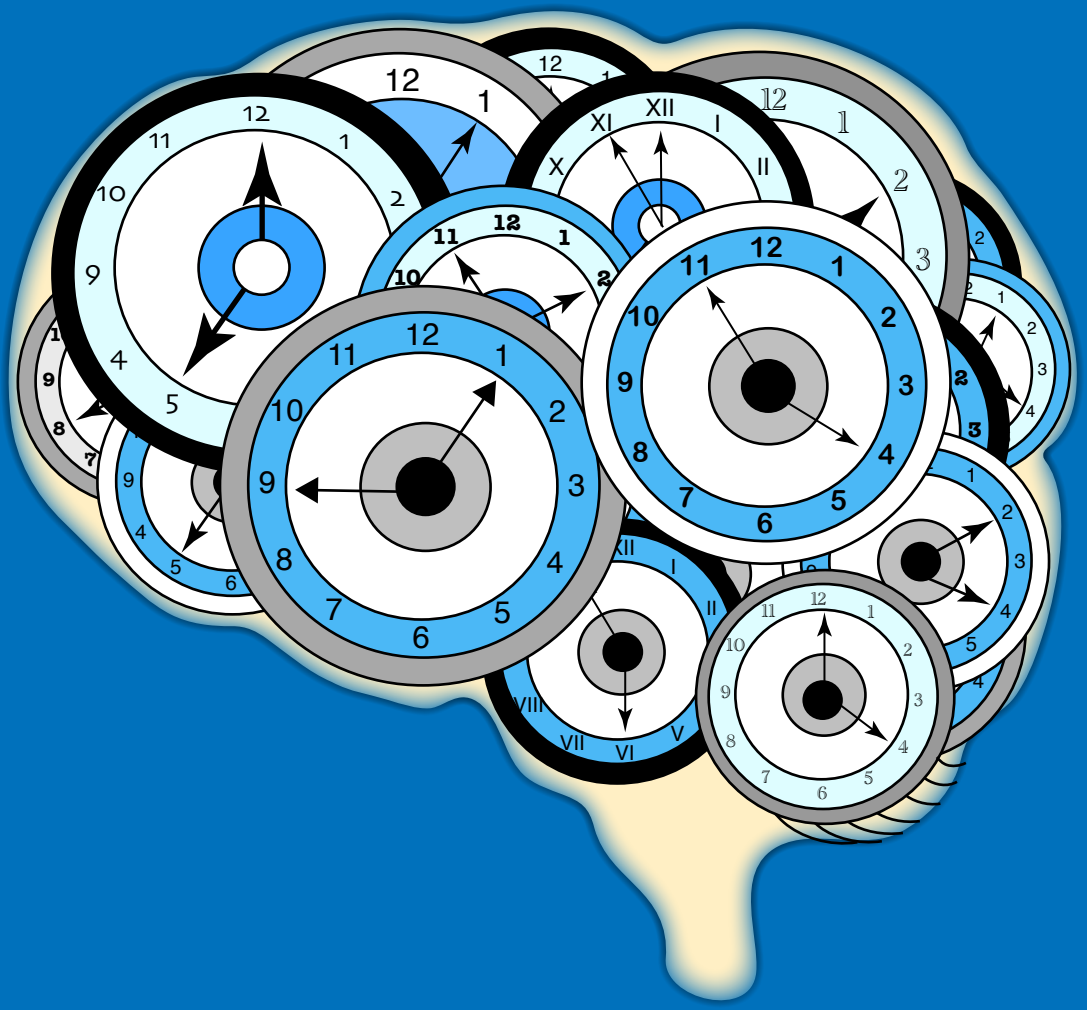
The AGING BRAIN



« INC Day »
October 24th 2024

Institut Necker Enfants-Malades
160 rue de Vaugirard, 75015 Paris
Auditorium 2

EUR Université de Paris — Neuroscience GRADUATE SCHOOL

EUR Université Paris Cité — Psychological Science GRADUATE SCHOOL

Keynote Speaker: David Rubinsztein (University of Cambridge)

FNP Fondation des Neurosciences de Paris

Speakers:

Vincent Prévot (Lille Neuroscience Cognition)
Claudia Cavadas (University of Coimbra)
Nora Abrous (Bordeaux Neurocampus)
Patricia Boya (University of Fribourg)
Frédéric Saudou (GIN, Grenoble)
Davide Pozzi (Humanitas, Milan)
Sandrine Humbert (ICM, Paris)

INC Day 2024 : **The Aging Brain**

24 October 2024, Paris

Venue : ***Institut Necker Enfants Malades, Auditorium 2,***
160 Rue de Vaugirard 156, 75015 Paris

Organizers : Franck Oury, Mehrnaz Jafarian-Tehrani, Thierry Galli

Welcome: 8h45-9h00

- **Session 1: Neuroendocrinology of brain aging (9h00-10h30)**
    - Vincent Prévot, Univ. Lille, Inserm, CHU Lille, France
      Age-related loss of GnRH expression and rhythmic release in cognitive disorders: a role for minipuberty?
    - Claudia Cavadas, Center for Neuroscience and Cell Biology, Univ. Coimbra, Portugal
      Innovative Strategies to Tackle Aging and Age-Related Diseases
    - Short talk
      Amaia Dominguez-Belloso, Institut Pasteur, France
      Brain function regulation by circadian rhythm at the choroid plexus

Pause: 10h30-11h00

- **Session 2: Neurogenesis/Neurosenescence in aging (11h00-12h30)**
    - Sandrine Humbert, Sorbonne Université, ICM, Inserm, CNRS, France
      Huntington disease: from neurodevelopment to neurodegeneration
    - Nora Abrous, Univ. Bordeaux, INSERM, Magendie, U1215, France
      Role of adult-born dentate neurons in successful cognitive aging
    - Short talk
      Barbara Ozkalp-Poincloux, LaPsyDÉ, France
      More creative than we think: when older adults outperform young and middle adults in a creative task involving fixation bias

Lunch : 12h30-14h00

Keynote: 14h00-15h00

David Rubinsztein, University of Cambridge, UK
Autophagy and its roles in neurodegeneration

- **Session 3: Aging brain, autophagy, proteostasis (15h00-16h00)**
    - Patricia Boya, University of Fribourg, Switzerland
      Mitophagy at the crossroads of neuroinflammation during aging and disease
    - Short talk
      Thomas Hinault, Inserm, U1077 NIMH, Caen, France
      Age-related changes of neural synchrony underlying temporal aspects of cognition

Pause: 16h00-16h30

- **Session 4: Neurotransmission in aging and neurodegeneration (16h30-18h00)**

    - Frédéric Saudou, Grenoble Institut Neurosciences, France
      Energy supply for axonal transport in health and pathological aging

    - Davide Pozzi, Humanitas University, Milan, Italy
      Prenatal stress as a risk factor for pathological aging: the role of maternal IL-6

    - Short talk
      Filipa Raposo Pereira, Paris Brain Institute (ICM), France
      Event-related potential signatures of episodic memory decline predicting progression to Alzheimer's disease in asymptomatic at-risk subjects: a longitudinal study

Access map

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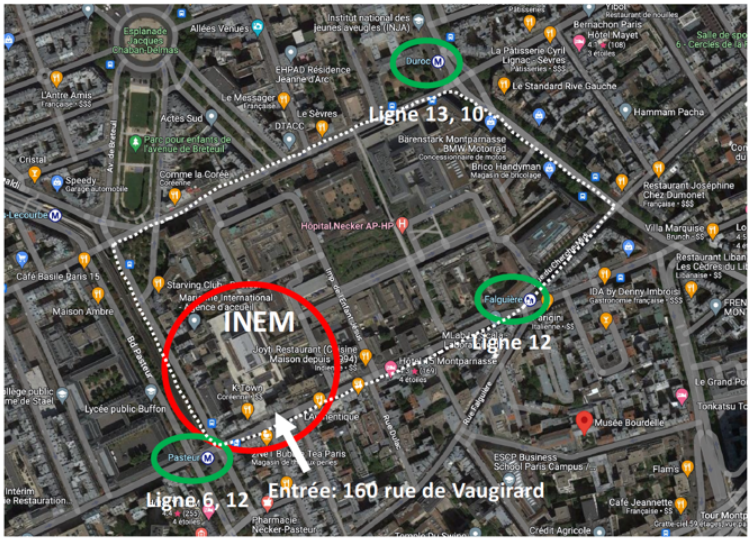
160 rue de Vaugirard 75015 Paris



Métro: Pasteur, Duroc ou Falguière

Suivez le fléchage pour vous rendre à **l'amphi 2 au rez-de-chaussée**

Age-related loss of GnRH expression and rhythmic release in cognitive disorders: a role for minipuberty?

Vincent Prévot
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Pulsatile secretion of gonadotropin-releasing hormone (GnRH) is essential for activating and maintaining the function of the hypothalamic-pituitary-gonadal (HPG) axis, which controls the onset of puberty and fertility. Two provocative recent studies [1,2] suggest that, in addition to controlling reproduction, the neurons in the brain that produce GnRH are also involved in the control of postnatal brain maturation, odor discrimination, and adult cognition. I will discuss the development and establishment of the GnRH system, and especially the importance of its first postnatal activation, a phenomenon known as minipuberty, to its later functions, reproductive and non-reproductive. In addition, I will discuss the beneficial effects of restoring physiological, i.e. pulsatile, GnRH levels on olfactory and cognitive alterations in Down syndrome and preclinical models of Alzheimer's disease, as well as the risks associated with long-term continuous, i.e. non-physiological, GnRH administration in certain disorders [3]. Finally, I'll discuss the intriguing possibility that pulsatile GnRH therapy may hold therapeutic potential for the management of some neurodevelopmental cognitive disorders as well as pathological aging in the elderly.

This work was supported by National Grant no. ANR-17-CE16-0015 (GRAND), ANR-11-LABEX-0009 (DistAlz) and ANR-16-IDEX-0004 (I-SITE ULNE), and European Grant no. 101123221 (ERC-2023-PoC UPGRADE).

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Innovative Strategies to Tackle Aging and Age-Related Diseases

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In this conference I will share our previous and very recent research where we investigated strategies to delay aging & aging-related disease and dysfunctions, inspired in the hypothalamic functions and in the communication between the periphery and the brain.
We showed that caloric restriction induces autophagy in hypothalamic and cortical neurons, and these effects are mediated, in part, by NPY and ghrelin receptors activation [1,2]. In addition, evidence from both hypothalamic neuronal in vitro models and mice overexpressing NPY in the hypothalamus, show that NPY, *per se*, stimulates autophagy in the hypothalamus [1]. Since both autophagy and NPY levels decrease with age, the rescue of hypothalamic NPY levels provides a new putative strategy to delay aging. In fact, using a premature aging mouse model, the reestablishment of NPY levels specifically in the hypothalamus rescued relevant aging markers, including memory dysfunction. Ans using ghrelin administration we could see a rescue of molecular and histopathological aging features and lifespan extension of a short-lived Hutchinson-Gilford Progeria Syndrome mouse model [3].

In another line of research where we are investigating a fatal genetic neurodegenerative disorder Machado-Joseph (MJD) disorder – that caloric restriction, sirtuin 1 overexpression, or NPY were able to mitigate the motor and balance impairments and cerebellar pathology in a mouse model of MJD [4,5,6]. We are now investigating new diet- or circadian-based interventions to tackle this fatal disease.

And more recently, we hypothesized that senescent cells in the skin can spread aging to distant organs, thereby accelerating systemic aging processes, including brain aging [7,8]. We transplanted senescent skin cells (fibroblasts) into the dermis of young mice and assessed various age-associated parameters. The results show that the presence of senescent cells in the dermal layer of young mice increased frailty, and impaired musculoskeletal function. Additionally, there was a significant decline in cognitive function, concomitant with increased expression of senescence-associated markers within the hippocampus brain area. These results support the concept that accumulation of senescent cells in the skin can exert remote effects on other organs including the brain contributing to physical and cognitive decline associated with aging [8].

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Short talk

Brain function regulation by circadian rhythm at the choroid plexus

A. Dominguez-Belloso[1], O. Mirabeau [1,2], T. Matijevic[1], J. Josephides[1,2], R. Pedone[1], A. Deczkowska[1]

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Recent studies have linked circadian disruption to an increased risk of developing dementia, with Alzheimer's disease (AD) being the most prevalent[1-2]. Interestingly, the choroid plexus (CP), an epithelial structure in the brain involved in CSF production and brain maintenance, exhibits strong day/night cycling[3]. However, it remains unclear whether CP's circadian function is essential for brain homeostasis and whether dysregulation contributes to brain aging and disease.

Preliminary bulk RNA-Seq analysis of CPs from wild-type 3-month-old mice revealed 1032 cycling genes grouped into 6 clusters. In contrast, rhythmicity was lost in wild-type 8-month-old mice, while AD mouse model (5XFAD) showed aberrant CP rhythmicity.

Surprisingly, one of the gene clusters peaking at ZT-12 in wild-type 3-month-old mice featured neuronal genes. Single-cell ATAC-Seq identified epithelial cells with open chromatin regions within neuronal genes at ZT-12, including NeuroD2 and Rbfox3 (NeuN). Immunostainings confirmed Sox2, Pax6, NeuroD2, and NeuN-positive cells at the CP, with NeuN levels peaking at ZT18 (Fig. 1). These results suggest an unknown nocturnal cell state at the CP. Future experiments will investigate its origin and contribution to CP and brain physiology in health, aging and AD.

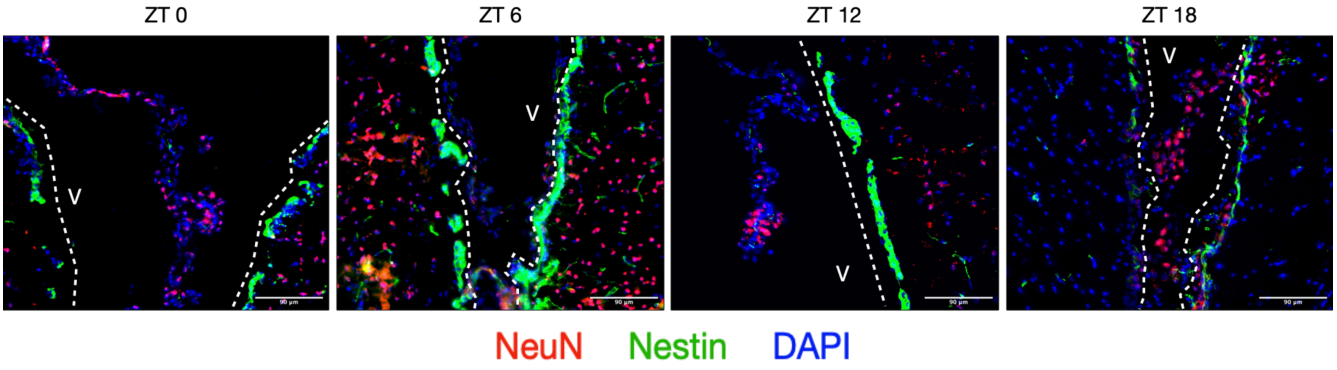

Fig. 1. Cryosections (12 µm) of choroid plexus (located inside of the ventricle) from WT, 3 month-old, male mice stained for NeuN (red), Nestin (green) and DAPI (blue). V = ventricle.

This work was supported by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie actions Grant Agreement no 945298-ParisRegionFP to A. Dominguez-Belloso, and European Research Council starting grant, Alzheimer Association, and Federation pour la Recherche sur le Cerveau grants given to A. D Deczkowska.

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Huntington disease: from neurodevelopment to neurodegeneration

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Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington disease (HD), present their full-blown forms later in life, typically after mid-adulthood. The first three of these diseases are typically sporadic but have rare familial forms that tend to manifest earlier and more severely. Still, even these inherited forms appear in adulthood, and aging is considered the major risk factor for developing these diseases. Most research on these conditions has sought to unravel the causes of the motor and cognitive deterioration as well as pathologies such as the clumps of misfolded proteins that figure in post-mortem samples, even though these are relatively late-stage phenomena. The dominant paradigm is that it takes time for misfolded proteins to overwhelm the cellular degradation machinery and accumulate beyond a certain threshold to cause neurotoxicity, which then leads to neuronal dysfunction, cell death and overt symptoms. Yet proteopathy-related proteins are expressed in the brain before birth.

Among these disorders, HD is dominantly inherited and caused by a dominantly inherited expansion of a CAG tract in *HTT*, which encodes an abnormally long polyglutamine (polyQ) tract in the huntingtin (HTT) protein. Pathogenesis involves both the abnormal activities of mutant HTT (mHTT) and partial loss of the normal functions of wild-type HTT (which is at half-dosage in HD, since it is normally expressed on both alleles). HD is characterized by the dysfunction and death of adult neurons from two brain regions, the cortex and the striatum. Striatal degeneration in HD is due, at least in part, to defective cortical signaling to the striatum. One important feature of the cortico-derived circuits in HD is their early alteration. For instance, cortico-striatal connections are altered decades before overt neurodegeneration as revealed by neuroimaging studies in premanifest HD gene carriers paving the way for the idea that abnormalities during development may contribute to disease onset. In fact, the *HTT* gene is expressed during development and there has been compelling evidence from mouse studies that it is essential for embryogenesis and neurodevelopment.

I will discuss how huntingtin regulates several steps of mouse cortical development. I will show that mutant huntingtin interferes with cortical development in HD mouse models and human mutation carrier fetuses [1]. To mediate its effect during neurogenesis HTT regulates the neurocytoskeleton; these properties are modified in HD [2]. I will then show that defects in the developing cortex contribute to HD early alteration in the cortico-derived circuits and adult abnormal connectivity and behavior [3]. Finally, I will present data supporting the hypothesis that in addition to their developmental component, HD pathological mechanisms also involve accelerated ageing.

This work was supported by Fondation pour la Recherche Médicale (FRM: équipe labellisée DEQ202203014675), ANR (AXYON: ANR-18-CE16-0009-01), AGEMED program from Inserm.

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Role of adult-born dentate neurons in successful cognitive aging

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Aging is accompanied by a decline in memory but these alterations are extremely variable between subjects: some individuals preserve cognitive abilities (Resilient, Res), whereas others show a clear substantial cognitive decline incapacitating in everyday life (Vulnerable, Vul). These inter-individual differences have also been described in rodents especially in tasks measuring spatial memory abilities. We believe that understanding the processes underlying such individual differences is a key step to predict, prevent or slow age-related cognitive disorders.
Spatial memory processes depend upon the hippocampus and more particularly upon the creation of new neurons in the dentate gyrus. Aging is associated with an exhaustion of the pool of new neurons and their delayed maturation. Their role in cognitive aging, in particular in resilience against cognitive decline, and their potential as a valuable tool for rejuvenating memory abilities will be discussed.

This work was supported by Inserm, the Agence Nationale de Recherche (ANR) (project ID AN4-20-MSR2-0011-01), Fondation pour la Recherche Médicale (projects ID ECO201906009074 and FDT202204015090) and 'La Fondation FYSSEN'.

Short talk

More creative than we think: when older adults outperform young and middle adults in a creative task involving fixation bias

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Decades of creativity research have converged to show that the ability to generate original ideas can be blocked by intuitive biases leading to fixation effect[1,2]. Although considerable efforts have been devoted to identifying the developmental trajectory of this fixation bias in children and adolescents[1,2], less is known about how creative thinking changes with age during adulthood. Previous studies examining creativity across the lifespan have provided discrepant results. Indeed, early investigations have suggested that creativity decreases with age[3]. In contrast, more recent researches have evidenced that creative ideation is preserved in older adults when they were not under time pressure[4]. The aim of the present study was to examine how the ability to overcome fixation effect in creative problem solving develops with age. To do so, young, middle and older adults completed a creative task involving fixation effect. Results revealed that older adults provided significantly more creative ideas (quantitatively and qualitatively) than young and middle adults. In addition, analysis of the originality of the responses over the time indicated that older adults generated these creative ideas at the beginning of the generation phase. Taken together these results suggested that older adults might be intuitively more creative than younger participants and provide new fuel for the current debates on the dual-process view of creative idea generation.

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Keynote

Autophagy and its roles in neurodegeneration

David Rubinsztein

So Jung Park[1,2], Sung Min Son[1,2], Antonio Daniel Barbosa[1], Lidia Wrobel[1,2], Eleanna Stamatakou[1,2], Ferdinando Squitieri[3], Gabriel Balmus[4,5] and David C. Rubinsztein[1,2*]

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Intracellular protein aggregation is a feature of many late-onset neurodegenerative diseases, including Parkinson's disease, tauopathies, and polyglutamine expansion diseases (like Huntington's disease (HD)). Many of these mutant proteins, like that causing HD, cause disease via toxic gain-of-function mechanisms. Therefore, the factors regulating their clearance are crucial for understanding disease pathogenesis and for developing rational therapeutic strategies.

We showed that autophagy induction reduces the levels of mutant huntingtin and attenuated its toxicity in cells, and in *Drosophila,* zebrafish and mouse HD models. We have extended the range of intracellular proteinopathy substrates that are cleared by autophagy to other related neuro-degenerative disease targets, like alpha-synuclein in Parkinson's disease and tau in various dementias and Alzheimer's disease.

In this talk, I will discuss how genetic lesions causing neurodegeneration impact autophagy at different stages of the pathway and will describe some of our attempts to identify therapeutic targets. I will focus on describing how the Huntington's disease mutation impacts autophagy both in cell-autonomous [1] and non-cell-autonomous [2] manners. Then I will describe how autophagy is synthetic lethal with defective proteasome and nuclear pore function - phenomena that can be explained by our observation that autophagy-deficient cells shuttle cytoplasmic autophagic substrates to the nucleus for proteasomal degradation. This proteostatic control mechanism appears to be compromised in Huntington's disease, where there is both defective autophagy and altered nuclear pore function, suggesting that some of the pathology in this disease may be due to combined defects in apparently distinct pathways [3].

This work is supported by the UK Dementia Research Institute through UK DRI Ltd, principally funded by the Medical Research Council (DCR and GB), and the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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Mitophagy at the crossroads of neuroinflammation during aging and disease

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Loss of proteostasis and dysregulated mitochondrial function are recognized as core hallmarks of aging, with recent revisions also highlighting impaired macroautophagy and chronic inflammation. Mitophagy, a crucial process in mitochondrial quality control, lies at the nexus of these aging-related phenomena; however, its age-associated perturbations have been largely unexplored. In our recent study, we conducted a comprehensive analysis of mitolysosome levels in mice and discovered that, contrary to the established decline in non-selective macroautophagy, mitophagy either remains stable or increases with age across all examined tissues. This upregulation is mediated by the PINK1-PRKN-dependent pathway. Further investigation revealed a simultaneous increase in mitochondrial DNA (mtDNA) leakage into the cytosol and activation of the CGAS-STING1 inflammation axis, phenomena that were also observed in primary fibroblasts from older human donors. We propose that mitophagy may be selectively upregulated during aging to enhance mitochondrial function and mitigate mtDNA-induced inflammation. Notably, treatment with the mitophagy inducer urolithin A alleviates age-related neurological decline, evidenced by improved synaptic connectivity, cognitive memory, and visual function. In alignment with our hypothesis, urolithin A decreases cytosolic mtDNA levels, reduces CGAS-STING1 activation, and diminishes neuroinflammation. Additionally, using an in vitro model of mitochondrial membrane permeabilization, we confirmed that PINK1-PRKN-mediated mitophagy is vital for resolving cytosolic mtDNA-triggered inflammation. These findings suggest a novel integrative approach to addressing aging and enhancing healthspan through the induction of mitophagy

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Short talk

Age-related changes of neural synchrony underlying temporal aspects of cognition

Thomas Hinault[1]

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While behavioral studies have been conducted to specify age-related changes of time perception and the temporal structuration of memory content[1,2], the neural bases underlying these changes remain unknown. Cognitive functioning depends on temporally specific and synchronized communications across brain regions, as can be measured by electroencephalography (EEG) and magnetoencephalography (MEG). These brain rhythms are impaired with advancing age and in presence of neurodegenerative disease[3]. Such disorganization of the brain's rhythmic communications underlies behavioral changes, and can be predictive of individual longitudinal trajectories. The team is currently investigating the heterogeneity of cognitive trajectories across aging individuals, by specifying age-related changes in the neural mechanisms underlying temporal processing using simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI). Individual levels of fronto-parietal theta-gamma synchrony are expected to be associated with the activity of the striatum and the functional connectivity of the fronto-striatal network. These fronto-parietal theta-gamma coupling have been found to be involved in the maintenance of durations in working memory and showed a greater variability as a function of decreased striatal activity in older adults[4]. By applying multiscale modelling to investigate network dynamics association with temporal processing, new insights can be obtained on both the evolution of the neural bases of temporal processing with advancing age and the heterogeneity of aging trajectories across individuals.

This work was supported by Fondation de France and the Normandy Region

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Energy supply for axonal transport in health and pathological aging

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Univ. Grenoble Alpes (UGA), and Grenoble University Hospital CHUGA

Abstract
Huntington's disease (HD), a late onset neurological disease characterized by accelerated aging and death of neurons, is caused by the abnormal polyglutamine expansion in the N-ter part of huntingtin (HTT), a large protein of 350kDa. Over the past years, we proposed that HTT associates to vesicles and acts a scaffold for the molecular motors and through this function, regulates the efficiency and directionality of vesicular transport in neurons. HTT controls the microtubule-based fast axonal transport (FAT) of neurotrophic factors such as BDNF. Importantly, polyQ expansion in HTT alters this function, leading to a decrease in neurotrophic support and death of striatal neurons.

By developing microfluidic approaches allowing to study healthy and defective corticostriatal networks in vitro that are compatible with high-resolution videomicroscopy and the use of biosensors, we found that HTT scaffolds the whole glycolytic machinery on vesicles to supply constant energy, independently of mitochondria, for the transport of vesicles over long distances in axons. We also found that HTT by activating specific signaling complexes ensures that certain types of vesicles such as signaling endosomes find their way to the nucleus by having an on-board navigational system. Importantly, we found that HTT could orchestrate different energy supply pathways depending on the type of vesicles and the level of cellular stress. We will discuss how these machineries are activated in physiological situations and how they are altered in disease.

Prenatal stress as a risk factor for pathological aging: the role of maternal IL-6

Davide Pozzi

D. Pozzi[1], B. Silva[2], G. Desiato[3], Camarena Delgado Maria[2], E. Fraviga[3], R. Grassi[3], F. Mirabella[4], S. Bariselli[1], A. Contestabile[5], M. Matteoli[1]

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Age-related brain diseases, including Alzheimer's disease (AD), are the most common cause of dementia, with over 10 million new cases each year worldwide [1]. Despite extensive efforts to uncover the underlying causes, early factors predisposing individuals to these diseases remain poorly understood. A growing body of evidence supports the fetal origin theory of human disease [2], which suggests that stressful events during prenatal stages may predispose the fetus to a wide range of disorders later in life, including conditions with late-onset, such as AD[3]. In particular, maternal immune activation (MIA) resulting from either prenatal infections or maternal stress gives rise to the production of immune molecules that may influence the neurodevelopmental trajectory of the fetus with long-lasting consequences in adulthood[4]. Despite these evidences the underlying molecular or cellular mechanisms are still poorly understood. Here we provide a new putative molecular framework for this phenomenon highlighting a key role of maternal pro-inflammatory IL-6. Our preliminary data indicate that, in a mouse model of AD (the APP/PS1 line), prenatal stress was associated to increased amyloid load and brain-wide neuronal activity in male but not female mice. In line with its intermediary role between inflammation and stress[5], IL-6 levels were found to be increased at the fetal level following maternal stress. Supporting the link between prenatal IL-6 elevation and the risk of AD, embryos prenatally exposed to IL-6 displayed an altered transcriptional profile involved in neurodegeneration, including APP, SNCA, APOE, and VPS35. Furthermore, mice prenatally exposed to IL-6 exhibited increased excitatory synaptic connections, a major hallmark of AD [6], as a result of the activation of the transcription factor STAT3 [7]. These data strongly support the hypothesis that early stressful conditions occurring at prenatal stages increase the risk of neurodegenerative disorders later in life via detrimental effects of immune mediators, such as IL-6.

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Short talk

Event-related potential signatures of episodic memory decline predicting progression to Alzheimer's disease in asymptomatic at-risk subjects: a longitudinal study.

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At every 3.2sec a new case of Alzheimer's disease (AD) appears, and ±¾ of these are never diagnosed [1-2]. The finding of preclinical markers of progression to AD could be key to mitigate this problem. Hence, we aimed to identify event-related potentials (ERPs) of episodic memory (EM) that can serve as signatures of AD-progression in elderly asymptomatic at-risk individuals. From the INSIGHTpreAD cohort we matched 15 progressors to AD (considered before diagnosis) in age, sex, education and level of β-amyloid burden (Aβ+) and neurodegeneration, to 15 controls (Aβ-) and 15 stable (Aβ+) participants. Behavioural and ERP data (EGI 256-electrodes; sampling rate: 250 Hz) were collected during an Old/New word recognition task over 6 yearly sessions. Group differences in behaviour (reaction-time, accuracy, Old/New discrimination sensitivity [dprime] and response bias [criterion]) and in EM-related ERPs (i.e. P3 [0.250-0.340ms], FN400[0.412-0.572ms], P600 [0.620-0.772ms], monitoring [0.872-1.040ms]) were assessed with linear-mixed effect models. Behaviourally, the progressors showed significantly lower accuracy and dprime and higher reaction-time than the other groups. Electrophysiologically, they showed a distinct P600 mean-amplitude over the left Parietal-Occipital region. Overall, the mean-amplitude was higher for Old vs. New words in the left hemisphere and posterior parietal regions, and for New vs. Old words in the right frontal region in all time windows. Our results suggest the presence of behavioural and EM-ERP signatures of preclinical AD in cognitively normal at-risk participants. This study shows that EEG, a non-invasive cost-effective technique, may contribute to mitigate the current underdiagnosis challenge, and help developing earlier, more effective, tailor-made treatments.

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