BORDEAUX neurocampus

5th BORDEAUX NEUROCAMPUS CONFERENCE

LabEx BRAIN

Bordeaux, September 26th - 28th, 2018

Aging of Memory Functions: Where are we now?

Invited Speakers

Hélène Amieva, FR
Carol Barnes, US
Audrey Branch, US
Gaëlle Chételat, FR
Neal J Cohen, US
John Disterhoft, US
Emrah Duezel, DE
Anders Fjell, NO
Chantal Mathis, FR
Lars Nyberg, SE
Peter Rapp, US
Laure Rondi-Reig, FR
Embla Steiner, SE
Sandrine Thuret, UK
Thomas Wolbers, DE
Michael Yassa, US

Scientific Organizers

Nora Abrous
Gwenaelle Catheline
Aline Marighetto

université de BORDEAUX

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Aging is generally accompanied by a progressive cognitive decline particularly in memory functions. The progressive decline of episodic memory, ranging from benign Forgetfulness to sever amnesia, is the main cause of loss of autonomy of the old subject. Memory disorders related to aging concern a large part of the population and have a very high human and financial cost, and make the promotion of healthy “memory” and the treatment of memory diseases a problem of increasing priority on the western world.

During this conference, we aim to bring together world-leading experts in the field of brain aging from invertebrates to humans.

Contents

Speakers

Invited speakers

Hélène Amieva	University of Bordeaux, Bordeaux - France
Carol Barnes	University of Arizona, Tucson - USA
Audrey Branch	Johns Hopkins University, Baltimore - USA
Gaël Chételat	University of Caen-Normandie, Caen - France
Neal J Cohen	University of Illinois, Urbana-Champaign - USA
John Disterhoft	Northwestern University, Chicago - USA
Emrah Duezel	University of Otto Von Guerick Magdeburg, Magdeburg - Germany
Anders Fjell	University of Oslo, Oslo - Norway
Chantal Mathis	University of Strasbourg, Strasbourg - France
Lars Nyberg	Umeå University, Umeå - Sweden
Peter Rapp	National Institute on Aging, Baltimore - USA
Laure Rondi-Reig	Institute of Biology Paris Seine, Paris - France
Embla Steiner	Karolinska Institute, Solna - Sweden
Sandrine Thuret	King's College London, London - United-Kingdom
Thomas Wolbers	German Center for Neurodegenerative Diseases, Magdeburg - Germany
Michael Yassa	University of California, Irvine - USA

Scientific organizers

Nora Abrous	Bordeaux Neurocampus, Bordeaux - France
Gwenaëlle Catheline	Bordeaux Neurocampus, Bordeaux - France
Aline Marighetto	Bordeaux Neurocampus, Bordeaux - France

Supports

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Programme

WEDNESDAY, SEPTEMBER 26TH

8:30 - REGISTRATION

9:00 - INTRODUCTION by Christophe Mulle and Nora Abrous

SESSION 1 HIPPOCAMPUS AND MEMORY FUNCTION

Chairs: Aline Desmedt, Christelle Robert

In tribute to Howard Eichenbaum:

9:15-10:00 **Neal J Cohen** - University of Illinois, Urbana-Champaign, USA
Relational memory theory

10:00-10:30 **Aline Marighetto** - Bordeaux Neurocampus, Bordeaux, France
A model of age-related decline of declarative memory based on the relational theory : identification of temporal binding as a key process

10:30-11:00 Coffee break and posters

11:00-11:45 **Carol Barnes** - University of Arizona, Tucson, USA
Normal lifespan changes in brain circuits critical for memory

11:45-12:15 **Chantal Mathis** - University of Strasbourg, Strasbourg, France
Separating the similar in mouse models of aging and Alzheimer's disease

12:15-14:30 Lunch time and posters

SESSION 2 HIPPOCAMPUS AND MEMORY FUNCTION : NEURAL MECHANISMS

Chairs: Mylène Potier, Nicole Etchamendy

14:30-15:15 **John Disterhoft** - Northwestern University, Chicago, USA
Cellular mechanisms of age-associated learning deficits in hippocampus and lateral entorhinal cortex

15:15-15:45 **Peter Rapp** - National Institute on Aging, Baltimore, USA
Neurocognitive aging: synapses to neural networks

15:45-16:15 Coffee break and posters

16:15-16:45 **Audrey Branch** - Johns Hopkins University, Baltimore, USA
Individual differences in aging outcomes: contributions of neurocognitive aging to risk and resilience

16:45-17:15 **Michael Yassa** - University of California, Irvine, USA
Computations supporting episodic memory in aging and Alzheimer's disease

18:00–20:00 Wine and cheese around the posters

THURSDAY, SEPTEMBER 27TH

SESSION 3 INDIVIDUAL DIFFERENCES, SUCCESSFUL AGING

Chairs: Ernesto Sanz-Arigita, Daniel Béracochea

9:15-10:00 **Lars Nyberg** - Umeå University, Umeå, Sweden
Memory aging and brain maintenance

10:00-10:30 **Hélène Amieva** - University of Bordeaux, Bordeaux, France
Concepts of reserve and frailty in cognitive aging: data from epidemiology

10:30-11:00 Coffee break and posters

11:00-11:30 **Anders Fjell** - University of Oslo, Oslo, Norway
Role of sleep for memory consolidation in aging

11:30-12:00 **Thomas Wolbers** - German Center for Neurodegenerative Diseases, Magdeburg, Germany
What neural mechanisms can explain navigational decline in old age?

12:00-14:00 Lunch time and posters

SESSION 4 ADULT HIPPOCAMPAL NEUROGENESIS

Chairs: Muriel Koehl, Joachim Mazère

14:00-14:30 **Nora Abrous** - Bordeaux Neurocampus, France
Individual differences in adult neurogenesis and memory

14:30-15:00 **Sandrine Thuret** - King's College London, London, England
Neural stem cells as biomarkers of cognitive aging and dementia

15:00-15:30 **Embla Steiner** - Karolinska Institute, Solna, Sweden
Adult Neurogenesis in Human

15:30-16:00 Coffee break and posters

16:00-18:00 **SELECTED TALKS**

Chairs: Olivier Nicole, Klaus Petry

Pascal Bielefeld - *Circadian Glucocorticoid Oscillations Preserve a Population of Adult Hippocampal Neural Stem Cells in the Aging Brain*

Rodrigo Cunha - *Adenosine neuromodulation is imbalanced in the aging hippocampus – restoring memory performance by blocking adenosine A2A receptors*

Kasia Radwanska - *CaMKII-dependent elimination of PSD-95 with learning is impaired in aged animals*

Beatriz Rodriguez-Grande - *A single mild traumatic brain injury at juvenile age accelerates brain aging phenotype*

Vincent Planche - *Evolution of hippocampal-to-cortical volume ratio during aging predicts long-term cognitive decline and incident Alzheimer's disease*

Aniket Mishra - *Genetic link between dementia and regional sulci morphology*

Adrien Folville - *Older adults do not always rely on the amount of episodic details when considering the subjective vividness of their memories*

Christine Bastin - *A manipulation of processing fluency to attenuate age-related differences in recognition memory*

19:30-2:00 Gala dinner

FRIDAY, SEPTEMBER 28TH

SESSION 5 LOOKING BEYOND THE HIPPOCAMPUS

Chairs: Jacques Micheau, Ernesto Sanz-Arigita

9:30-10:15 **Gaël Chételat** - University of Caen-Normandie, Caen, France
From reserve to preventive interventions – example of the European project MEDITAGEING

10:15-10:45 **Gwenaëlle Catheline** - Bordeaux Neurocampus, Bordeaux, France
Cognitive decline in aging and multimodal imaging

10:45-11:15 Coffee break and posters

11:15-11:45 **Emrah Duezel** - University of Otto Von Guerick Magdeburg, Magdeburg, Germany
Specific associations of CSF tau and amyloid levels with object and scene memory in old age and preclinical AD : data from the DELCODE study

11:45-12:15 **Laure Rondi-Reig** - Institute of Biology Paris Seine, Paris, France
How cerebellum can impact hippocampal activity

12:15-12:35 Closing remarks by Nora Abrous

12:35-14:30 Lunch time

Oral presentations

Invited speakers

IS1 - Neal J Cohen	*Relational memory theory*
IS2 - Aline Marighetto	*A model of age-related decline of declarative memory based on the relational theory : identification of temporal binding as a key process*
IS3 - Carol Barnes	*Normal lifespan changes in brain circuits critical for memory*
IS4 - Chantal Mathis	*Separating the similar in mouse models of aging and Alzheimer's disease*
IS5 - John Disterhoft	*Cellular mechanisms of age-associated learning deficits in hippocampus and lateral entorhinal cortex*
IS6 - Peter Rapp	*Neurocognitive aging: synapses to neural networks*
IS7 - Audrey Branch	*Individual differences in aging outcomes: contributions of neurocognitive aging to risk and resilience*
IS8 - Michael Yassa	*Computations supporting episodic memory in aging and Alzheimer's disease*
IS9 - Lars Nyberg	*Memory aging and brain maintenance*
IS10 - Hélène Amieva	*Concepts of reserve and frailty in cognitive aging: data from epidemiology*
IS11 - Anders Fjell	*Role of sleep for memory consolidation in aging*
IS12 - Thomas Wolbers	*What neural mechanisms can explain navigational decline in old age?*
IS13 - Nora Abrous	*Individual differences in adult neurogenesis and memory*
IS14 - Sandrine Thuret	*Neural stem cells as biomarkers of cognitive aging and dementia*
IS15 - Embla Steiner	*Adult Neurogenesis in Human*
IS16 - Gaël Chételat	*From reserve to preventive interventions – example of the European project MEDITAGEING*
IS17 - Gwenaëlle Catheline	*Cognitive decline in aging and multimodal imaging*
IS18 - Emrah Duezel	*Specific associations of CSF tau and amyloid levels with object and scene memory in old age and preclinical AD : data from the DELCODE study*
IS19 - Laure Rondi-Reig	*How cerebellum can impact hippocampal activity*

IS1 - Relational Memory Theory

Neal COHEN

Department of Psychology, Beckman Institute, Carle Illinois College of Medicine, and Interdisciplinary Health Sciences Institute - University of Illinois

Relational memory theory holds that representations of experience mediated by the hippocampus, in interaction with neocortical networks, are fundamentally relational. Hippocampal representations capture the spatial, temporal, and other contextual relations among the constituent elements of experience, that is, among the people, objects, places, actions, etc. that populate events as they unfold in their particular temporal-spatial context, as well as the relations among successive events as they unfold over the course of an extended episode. The hippocampus organizes experiences into a flexible, multidimensional memory space that supports a range of memory performances and memory-guided choice behaviors in navigating space, time, and life in all its rich complexity. This talk shows how relational memory theory can reconcile data across species, tasks, methods, & disciplines, and pays tribute to the profound contributions of Howard Eichenbaum to our understanding of memory and the brain.

IS2 - A model of age-related decline of declarative memory based on the relational theory: identification of temporal binding as a key process

Aline MARIGHETTO

INSERM U1215, Neurocentre Magendie, Bordeaux, France
Université de Bordeaux, Bordeaux, France

One major component of cognitive aging is the degradation of declarative memory (DM), the conscious and verbally expressible memory of facts and episodes that depends on the hippocampus. To identify underlying mechanisms of DM degradation occurring in aging, we have developed a radial-maze model of DM impairment in aged mice based on the relational theory, according to which non-verbal characteristic of DM is its flexible expression and this flexibility relies on a relational representation of past events. Using our radial-maze task in mice and its virtual analog in humans, we recently demonstrated that the age-related loss of flexible memory expression, i.e. of DM, was due to a degradation of temporal binding, the capability to associate temporally discontiguous events into a relational memory representation, and shown to rely on CA1 activity across brief temporal intervals between events.

IS3 - Normal lifespan changes in brain circuits critical for memory

Carol A. BARNES

Regents' Professor, Psychology and Neurology
Evelyn F. McKnight Chair for Learning and Memory in Aging
Director, Evelyn F. McKnight Brain Institute
Director, Division of Neural Systems, Memory and Aging

Aging is associated with specific impairments of learning and memory, some of which are similar to those caused by damage to temporal or frontal lobe structures. For example, healthy older humans, monkeys and rats all show poorer spatial, recognition and working memory, than do their younger counterparts. Rats and monkeys do not develop age-related pathology such as Alzheimer's or Parkinson's diseases, which makes them good models for assessing functional alterations associated with normal aging in humans. While many cellular properties of medial temporal lobe cells appear to be intact in aging animals, age-related impairments in synaptic function, plasticity and gene expression have been observed. Because information is represented by activity patterns across large populations of neurons, an understanding of the neural basis of cognitive changes in aging requires the examination of the dynamics of behaviorally-driven neural networks. Ensemble recording experiments are described that suggest fundamental changes in the storage and retrieval of information, as well as in high level perceptual processing in aging hippocampus and perirhinal cortical circuits. In addition, frontal lobe correlates of age-related changes working memory are discussed. The data presented are congruent with recent suggestions that rather than uniform deterioration, the aging brain shows region and cell-specific changes consistent with adaptation and compensation in these altered memory circuits.

IS4 - Separating the similar in mouse models of aging and Alzheimer's disease

Céline HERAUD, Karine HERBEAUX, Caroline MURSCH, **Chantal MATHIS**

LNCA, UMR 7364 CNRS, Université de Strasbourg, Neuropôle de Strasbourg, 12 rue Goethe, Strasbourg, France

Performance in separating overlapping memories is thought to rely on a pattern separation computational process occurring within the medial temporal lobe. Older adults show reduced performance in pattern separation demanding recognition tasks using similar objects or object locations. Alzheimer patients show profound deficits at a very early stage when neurodegeneration spreads through the medial temporal lobe. This is consistent with several studies showing that pattern separation performance depends on the integrity of the dentate gyrus (DG)-CA3 region and its inputs from cortical regions of the temporal lobe. Animal studies further suggest a role for adult-born DG neurons. In a pattern separation task based on subtle changes in object location, we showed a progressive decrease in performance from mild to severe between the age of 7 to 21 months in C57BL/6J mice. Aged mice were also impaired in a pattern separation task based on subtle changes in object appearance. In the APP SWE model of Alzheimer's disease, object location based performance drops very rapidly between 3 and 4 months of age. Interestingly, brain levels of amyloid peptide are known to increase around this age in APP SWE mice. We hypothesized that pattern separation deficits in APP SWE mice and in aged mice had different origins. Accordingly, chronic treatment with m266 (antibody against amyloid peptide, gift from Boehringer Ingelheim, Germany) completely rescued

pattern separation performance in APP SWE mice, whereas a deep deficit remained in aged C57BL/6J mice. Preliminary results suggest that performance improvement in APP SWE mice was not mediated through a beneficial effect on quantitative aspects of DG neurogenesis. Our ongoing studies focus on functional activation of neuronal populations thought to participate in some pattern separation-like processing. Grant from Association France Alzheimer and Groupe Intérialе.

IS5 - Aging and Learning Alters Neuron Function in Hippocampus and Lateral Entorhinal Cortex

John DISTERHOFT, Matthew OH M., Carmen LI., Kyle KELLY

Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, IL 60611

Increases in intrinsic excitability of hippocampal neurons via a reduction in calcium-activated potassium currents (postburst afterhyperpolarization, AHP) have been demonstrated to be a cellular hallmark of successful associative learning (e.g., trace eyeblink conditioning, fear conditioning and spatial water maze learning) in young adult subjects. Notably, these currents are enlarged at baseline in neurons from aging animals, contributing to impaired learning. However, those aging animals that can learn (aging unimpaired or AU) demonstrate CA1 pyramidal neurons with increased excitability as compared to learning-impaired aging (AI) animals. Moreover, pharmacological (e.g., cholinergic agonists) or genetic (e.g., CREB overexpression) manipulations that enhance neuronal excitability of CA1 pyramidal neurons to a 'young-like' state have been proven to rescue aging-related learning deficits. Using calcium imaging with two-photon laser scanning microscopy, we demonstrated that calcium influx following a train of action potentials is increased in aging neurons, contributing to the enhanced calcium-activated potassium currents observed in aging animals. Surprisingly, we observed increased calcium transients caused by bath application of cholinergic agonist carbachol that abolished the postburst AHP in CA1 neurons from behaviorally naïve animals. This carbachol-induced increase in calcium transients appears to be abolished (occluded) in CA1 neurons from AU rats after learning, indicating that the cholinergic signaling pathway has been used for successful learning in the AU rats. The lateral entorhinal cortex (LEC) is known to be a vital pathway of information flow into the hippocampus and is among the first areas of the brain to exhibit AD pathologies prior to the observation of behavioral deficits. As in the hippocampus, neurons from layer III (origin of temporo-ammonic pathway) and layer V (receives hippocampal output from CA1) of the LEC exhibit an aging-related decrease in cellular excitability, and an increase in cellular excitability following acquisition of trace eyeblink conditioning. One of the prominent features of layer III and V LEC pyramidal neurons is their ability to exhibit persistent firing activity, a cholinergic dependent property that is a potential cellular mechanism to bridge multimodal stimuli across time for associative learning, such as the conditioned stimulus and unconditioned stimulus across the temporal gap in trace conditioning. We have recently observed that both layer III and layer V LEC neurons from aged animals are less likely to persistently fire and are less able to maintain the frequency of their firing, potentially stemming from a loss of cholinergic tone, and thereby contributing to age-associated learning and memory impairments.

Supported by NIH R37 AG008796, RF1 AG017139, T32 AG020506 and F31 AG055331.

IS6 - Neurocognitive Aging: Synapses to Neural Networks

Peter R. RAPP

Laboratory of Behavioral Neuroscience, Neurocognitive Aging Section, National Institute on Aging, Baltimore, MD, USA

Deficits in memory and other domains of cognitive function are among the most troubling signs of aging. Alongside the devastating impairments of Alzheimer's disease and related neurodegenerative disorders, a much larger proportion of older individuals experience milder decline in cognitive health that nonetheless compromises the quality of life and capacity for independent living. An earlier view was that neuron death in memory-related brain regions is an inevitable consequence of growing older and the proximal cause of age-related cognitive impairment. Marked and distributed neuronal degeneration, however, is now understood to be a signature of pathological aging, and considerable evidence suggests instead that the brain changes associated with normal aging are regionally selective, involving relatively subtle alterations in connectivity and a blunted capacity for dynamic neural network plasticity. The specific pattern of change varies substantially across individuals, and growing interest has centered on the idea that optimally healthy cognitive outcomes arise from a lifecourse neuroadaptive trajectory rather than compensatory mechanisms or a slower rate of aging. This perspective has encouraged a search for strategies to promote neuroadaptive aging, including the possibility that noninvasive brain stimulation and other novel approaches might shift the fundamental course of growing older away from neurodegenerative disease. Basic research in experimental animal models has provided a valuable window on these issues.

IS7 - Individual Differences in Aging Outcomes: Contributions of Neurocognitive Aging to Risk and Resilience

Audrey BRANCH[1,2], Rebecca Haberman[1], Michela Gallagher[1].

1. *Johns Hopkins University, Department of Psychological and Brain Sciences.*
2. *Johns Hopkins University, Kavli Neuroscience Discovery Center.*

Like aging humans, aged outbred rats exhibit individual differences in cognitive outcomes. We have found substantial evidence for a distinct signature of hyperactivity in both medial temporal lobe and cortical circuits in animals displaying age-dependent cognitive decline[1, 2]. A subset of these aged animals behaves on par with young subjects in hippocampal memory tasks, providing a window into mechanisms supporting cognitive resilience. In our recent pharmacological and behavioral work, we show that aged unimpaired animals retain young-like expression of behaviorally induced activity and plasticity related genes. However, they do so alongside a unique upregulation of inhibitory markers. This finding is consistent with earlier observations showing greater recruitment of inhibitory control in aged intact, relative to impaired rats [3], and may represent an adaptive adjustment in homeostatic control of excitatory/inhibitory balance in the face of aging.

1. Wilson, I.A., et al., Age-associated alterations of hippocampal place cells are subregion specific. J Neurosci, 2005. **25**(29): p. 6877-86.
2. Haberman, R.P., M.T. Koh, and M. Gallagher, Heightened cortical excitability in aged rodents with memory impairment. Neurobiol Aging, 2017.
3. Haberman, R.P., et al., Behaviorally activated mRNA expression profiles produce signatures of learning and enhanced inhibition in aged rats with preserved memory. PLoS One, 2013. 8(12): p. e83674.

IS8 - Episodic Memory in the Aging Brain

Michael YASSA

Center for the Neurobiology of Learning and Memory, University of California, Irvine

Memory is the bridge to our past and future. Without memory, we would be stuck in a constant present, unable to learn from our experiences and unable to plan for the future. Memory loss can have catastrophic impact on life and livelihood. Memory degrades to some extent in everyone as we get older. It is completely ravaged in dementing illnesses such as Alzheimer's disase, placing a tremendous burden on individuals, families, and global public health. This talk will discuss our approach to understanding the neural mechanisms underlying episodic memory (memory for 'what', 'where' and 'when'), and how this approach can inform our understanding of age-related memory loss. I will highlight recent advances in determining the functional division of labor in the medial temporal lobes using a combination of targeted behavioral paradigms for what, where and when memory and high-resolution functional MRI. This fundamental understanding is then applied to examining memory in older adults and assessing susceptibility to Alzheimer's disease, providing potential avenues for clinical intervention.

IS9 - Memory aging and brain maintenance

Lars NYBERG[1], Ulman LINDENBERGER[2].

1. MPI Berlin, Germany
2. Umeå University, Sweden

The aging brain undergoes many changes that can impact memory and cognition, but some older adults display brain maintenance, or lack of senescent brain changes and age-related brain pathology. General brain maintenance remains a possibility, but at present selective maintenance of some brain systems along with age-related decline in others appears more likely. This presentation is focused on structural and functional maintenance of the hippocampus complex, as hippocampal maintenance is a key determinant of well-preserved episodic-memory functioning in old age. Several potential neural and non-neural mechanisms promoting hippocampal maintenance will be considered, including neuronal survival and neurogenesis, intact neuronal morphology, and vascular integrity. Evidence will be reviewed that suggest that correlated genetic and environmental factors influence the operation of these maintenance mechanisms, partly through lifestyle choices. Finally, some ideas for future work on brain maintenance will be discussed, including contributions of specific connections, transmitter systems, and subregions to hippocampal maintenance.

IS10 - What neural mechanisms can explain navigational decline in old age?

Thomas WOLBERS

Aging & Cognition Research Group, German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany
Center for Behavioural Brain Sciences (CBBS), Otto-von-Guericke University Magdeburg, Germany

While decades of research into cognitive aging have focused on functions such as memory and attention, spatial navigation has been understudied. This is surprising because key structures of the brain's navigation circuit are particularly vulnerable to the deleterious consequences of aging. In addition, deficits with spatial orientation are often among the first noticeable symptoms in patients with Alzheimer's Disease. Given the recent breakthroughs in understanding the cellular components of basic navigational circuits in rodents and primates, we are now in the position to identify changes in the navigation network that occur as a result of normative aging processes and specific neuropathological conditions.

In this talk, I will outline recent studies that have begun to elucidate age-related changes in human navigational processing, using advanced virtual reality paradigms and high-resolution neuroimaging. By targeting specific spatial computations, these experiments have revealed mechanisms of altered positional coding in the hippocampal formation and beyond. Importantly, our findings also offer novel insights into general mechanisms of brain ageing that could affect processes beyond the spatial domain. Finally, I will conclude with a discussion on how navigational indicators could aid early detection of neuropathological conditions and support behavioral interventions to maintain cognitive wellbeing.

References

Lester AW, Moffat SD, Wiener JM, Barnes CA, Wolbers T (2017) The Aging Navigational System. Neuron 95:1019–1035.

Stangl M, Achtzehn J, Huber K, Dietrich C, Tempelmann C, Wolbers T (2018) Compromised Grid-Cell-like Representations in Old Age as a Key Mechanism to Explain Age-Related Navigational Deficits. Curr Biol CB 28:1108-1115.e6.

Vieweg P, Stangl M, Howard LR, Wolbers T (2015) Changes in pattern completion--a key mechanism to explain age-related recognition memory deficits? Cortex 64:343–351.

IS11 - Role of sleep for memory consolidation in aging

Anders Martin FJELL

Center for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo, Oslo, Norway
Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway

On a group level, episodic memory function is reduced in higher age. Previous research has shown that age may affect both encoding and retrieval processes. However, also the third major process of memory – consolidation – may be affected by age. Still, consolidation has received much less attention in previous research. There are theoretical and empirical reasons to expect that also changes in consolidation are important in aging: brain structures critical for memory consolidation are vulnerable to aging, the connections between these structures change with age, and sleep quality – critical for memory consolidation – is generally reduced. Still, we have only superficial understanding of the

contributions of consolidation to episodic memory decline in aging. A major reason for this lack of focus may be methodological – in contrast to encoding and retrieval, consolidation is not associated with a conscious experience or an explicit cognitive attribute. Thus, one cannot easily distinguish between consolidation and retrieval processes, as an inherent problem with the behavioral approaches is that reminders and cues can either create new engrams or fortify connections themselves. This makes consolidation difficult to measure and the neural correlates hard to pin-point. In this talk, I will present tentative behavioral evidence suggesting that episodic memory consolidation should also be a target for memory aging research, and how future research could try to address the inherent methodological challenges described above. Sleep is critical for memory consolidation, and changes in sleep patterns are often observed with age. Thus, the role of sleep in memory consolidation in aging will be addressed.

IS12 - Concepts of reserve and frailty in cognitive aging: results from epidemiology

Hélène AMIEVA

Bordeaux Population Health Center INSERM U1219, Team Psychoepidemiology of aging and chronic diseases, University of Bordeaux

A deeper knowledge of the pre-dementia phase of Alzheimer's disease is important to allow earlier and better management of this ominous disease. This prodromal period has been investigated in the French epidemiologic PAQUID cohort by analysing change in cognitive performances of a large sample of older adults over a 20-year period. Neuropsychological measures including global cognitive functioning, visuo-spatial memory, verbal fluency and cognitive speed were assessed in 3777 older adults among whom about 400 developed Alzheimer's disease along the follow up. The results show how early cognitive symptoms may emerge before the full clinical diagnosis of Alzheimer dementia particularly in higher-educated individuals, for whom decline occurred up to 16 years before dementia. Lower educated participants presented a shorter and different pattern of cognitive trajectory. Hence, the results illustrate the protective role of education in the clinical trajectory preceding dementia.

Another predicting strategy consists in focusing not exclusively on a particular syndrome but on negative brain outcomes more generally. Syndromes like dementia, stroke, depression and disability have in common high frequency in late life. Even though each of these disorders relies on specific pathogenic processes, a common clinical manifestation of these disorders is psychomotor slowing. Psychomotor slowing is a fundamental and multi-composite marker of brain functioning. It reflects overall efficiency of cognitive operations, which in turn plays a critical role in maintaining higher-order functions. A second study showed that low psychomotor speed is associated with an increased risk of developing negative neurocognitive outcomes such as not only Alzheimer's disease, but also stroke, depression, disability and marginally Parkinson's disease in a 10-year delay. Therefore, one could conclude that cognitive slowing reflects a state of brain frailty. An alternative view would postulate that low cognitive speed may not necessarily be secondary to subtle brain impairment, but rather could be a marker of cognitive reserve since prior studies have suggested that differences in psychomotor speed are detectable in childhood and persist through adulthood. Future research having access to assessments all along the life span should determine if early life psychomotor speed is a significant predictor of later life negative cognitive outcomes and should be viewed as a factor of resilience to the adverse effects of brain aging or a marker of brain frailty.

IS13 - Adult hippocampal NEUROGENESIS and spatial memory during aging

Nora ABROUS

INSERM U1215, Neurocentre Magendie, Bordeaux, France
Université de Bordeaux, Bordeaux, France

Aging is associated with cognitive dysfunction, which has been correlated to an alteration of hippocampal functioning Indeed, the hippocampal formation (HF) plays a crucial role in controlling a wide array of cognitive functions, and is the brain region most vulnerable to ageing processes. The mammalian HF, in particular the dentate gyrus (DG), is an important site for the production of new neurons during adulthood. The aim of our work is to determine the relationship between the production and activity of these newborn neurons throughout life and the appearance of age-related cognitive deficits. We have found that cognitively-impaired senescent rats display lower rate of neurogenesis than cognitively-unimpaired old rats. These inter-individual differences are link to the activity of the pituitary hypothalamo-pituitary-adrenal (HPA) axis. Indeed, we have shown that 1) the magnitude of HPA axis activity in old animals is correlated with their rate of neurogenesis and memory ability, 2) natural individual differences in the activity of the HPA axis in young adult animals predict the extent of age-induced alterations; 3) increasing the activity of the HPA axis by prenatal stress impairs adult neurogenesis and memory throughout life, 4) lowering corticosterone secretion from midlife onward reduces the decline in neurogenesis observed in old rats and prevents age-related memory disorders. 5) More recently, by tagging neurons born in adult, middle-age and old rats, we found that these neuronal cohorts are recruited by learning only in old rats with good memory abilities. These results suggest that a preservation of the synaptic inputs onto adult born neurons may be responsible for preserved memory abilities of aged rats**.** Altogether these data strengthen the idea that alterations in adult hippocampal neurogenesis play a pivotal role in the development of pathological aging and reinforce the hypothesis of an early neurodevelopmental origin for psychopathological vulnerabilities in aging.

IS14 - Neural stem cells as biomarkers of cognitive aging and dementia

Sandrine THURET

King's College London, Institute of Psychiatry, Psychology & Neuroscience, Department of Basic and Clinical Neuroscience, London, United Kingdom.

Age-related declines in stem cell function in the body and central nervous system of rodents can be reversed by exposure to a youthful systemic milieu. Conversely, the old milieu inhibits stem cell function in young rodents. In this study, allogeneic human serum from old healthy individuals induced an increase in apoptotic cell death of human hippocampal progenitor cells when compared to serum from young subjects. General Linear Models revealed variability in markers of proliferation and differentiation was partly attributable to intake of antihypertensive medication and very mild cognitive decline among older subjects. An endophenotype approach revealed upregulation of established and novel ageing molecular hallmarks in response to old serum following whole-genome expression arrays. interestingly, serum from older subjects induced a wide range of cellular and molecular phenotypes, likely reflecting the cumulative effect of health exposures and inequalities during a lifetime. Data will also be presented on how serum of mild cognitively impaired patients differentially alters human hippocampal progenitor cell fate to predict conversion to Alzheimer's Disease.

IS15 - Adult Neurogenesis in Human

Embla STEINER1, Hagen HUTTNER [2], Olaf BERGMANN[1], Kanar ALKASS[1,3], Mehran SALEHPOUR[4], Samuel BERNARD[5], Göran POSSNERT[4], Henrik DRUID[3], Jonas FRISÉN[1]

1. Department of Cell and Molecular Biology, Karolinska Institute, SE-171 77 Stockholm, Sweden
2. Department of Neurology, University of Erlangen-Nuremberg, Schwabachanlage 6, 91054 Erlagen, Germany
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4. Department of Physics and Astronomy, Ion Physics, Uppsala University, SE-751 20 Uppsala, Sweden
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It was thought for a long time that the nervous system was incapable of regeneration. Although most neurons are generated before birth, it is now established that new neurons are generated continuously throughout life in discrete areas of the brain. In most mammals, adult neurogenesis is limited to two areas of the brain during physiological conditions; the dentate gyrus of the hippocampus and the olfactory bulb, where immature neurons migrated from the subventricular zone are integrated as mature neurons. Adult neurogenesis appears to be altered in models of neurological and psychiatric diseases. Depression is associated with reduced hippocampal neurogenesis and antidepressant drugs stimulate neuronal turnover in rodents. After stroke, reactive neurogenesis in the neurogenic niches, as well as cortex has been demonstrated in rodent. In Alzheimer's disease and Parkinson's disease the results are more contradicting.

Most studies on adult neurogenesis are performed in animal models, because studying adult neurogenesis in humans is technically challenging. In the late 90s Eriksson et al. established adult neurogenesis in the human hippocampus, however the dynamics and the extent of adult neurogenesis remained unknown. A retrospective birth dating method, developed in our laboratory, allows us to investigate the turnover of cell populations in human tissues, by measuring the concentration of nuclear-bomb-test-derived ^{14}C in genomic DNA. Recent work from our group has shown that humans are unique among mammals in that there is no detectable neurogenesis in the olfactory bulb but substantial neurogenesis in the striatum. In order to investigate the function and clinical relevance of adult neurogenesis, we have set out to investigate the neuronal turnover dynamics in the pathologies associated with altered neurogenesis.

IS16 - From reserve to preventive interventions: example of the European project MEDITAGEING

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Cognitive decline, dementia (e.g. Alzheimer's disease, AD), sleep disturbances and depression – all related to psychological distress and anxiety – are significant drivers of reduced quality of life in older adults. A third of AD cases may be attributable to potentially modifiable risk factors, the main ones being cardio-vascular risk factors, depression and physical and cognitive inactivity. Current large scale long-term preventive non-pharmacological trials target most of these risk factors with multidomain approaches including physical activity, cognitive activity, diet and prevention cardio-vascular risks but do not directly target depression and psychoaffective factors at large. Mental training for the reduction of stress, the regulation of attention and the cultivation of positive emotions through meditation practice

appears as a promising way to take care of the emotional dimension of ageing. Thus, meditation practice has the potential to down-regulate several of the adverse factors cited above and, thereby, to have a positive impact on mental health and wellbeing – notably in the ageing population. This talk will illustrate the interest for meditation in ageing populations by showing preliminary evidences from previous studies. We will also present the design of a European project MEDITAGEING aiming at assessing the effects of meditation on mental health and well-being in the ageing population. Ten partners from 6 countries (France, Spain, Germany, UK, Switzerland and Belgium) are involved in this collaborative project including two clinical trials sponsored by Inserm. Results are expected to foster the development of preventive strategies in ageing reducing the negative impact of mental conditions and disorders

IS17 - Cognitive decline during aging : a multimodal neuroimaging contribution.

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Aging is associated to both structural and functional cerebral changes. Although these grey and white matter alterations have been described since the 19th century by post-mortem studies, the development of neuroimaging technique over the past 20 years has enabled in vivo descriptions on elderly subjects. Moreover, the safety of Magnetic Resonance Imaging (MRI) has allowed longitudinal studies with repeated MRI over large population cohorts. These longitudinal studies, providing a promising framework for the study of the asymptomatic phases of age-related neurodegenerative, is a specificity of the Bordeaux epidemiological center for a long time. Based on two cohorts of this kind (3City-Bordeaux and AMImage) we have revealed that age-related decline in episodic memory is associated with an early atrophy of the hippocampus followed by the atrophy of the posterior cingulate cortex. From a functional point of view, age-related episodic memory decline is associated with a loss a functional connectivity of the posterior cingulate cortex. In a second set of studies, we were interested to the sleep/wake cycle as a factor of cognitive vulnerability in the elderly. Sleep/wake cycle data are collected in the environment of the subjects through wrist actimeters. We have observed that not only sleep but also 24-h cycle disturbances were associated with altered structural connectivity revealed through DTI parameters. This alteration of structural backbone networks related to activity/rest cycle disturbances in aging might constitute a cerebral frailty factor for the development of cognitive impairment.

IS18 - Specific associations of CSF tau and amyloid levels with object and scene memory in old age and preclinical AD : data from the DELCODE study

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IS19 - How Cerebellum can impact Hippocampal Activity: Space, Time and Aging

Laure RONDI-REIG

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Over the last decades, an increasing number of researches have reported the role of the hippocampus beyond space representation, in particular highlighting its role in the representation of time. Complex behavioral paradigm offers an ideal framework to evaluate brain activity in time and space. In particular, spatio-temporal navigation offers suitable paradigms to probe for episodic memory in animal models and humans. We previously proposed that the ability to remember an ordered sequence of choices during spatial navigation could be one of the episodic memory properties shared by human and rodent models. We thus developed the Starmaze paradigm that allow to test a new and objective experimental memory of a personal past experience. The use of Virtual Reality increases the active engagement of the subject during learning and avoids verbal report. We previously demonstrated that the ability to learn the correct sequence of choices is associated with the co-activation of both the hippocampus and the cerebellum and is particularly sensitive to age-related decline in both rodents and humans. Using such sequence strategy associated with neuropsychological tests, we were also able to differentially diagnose Alzheimer patients from fronto-temporal dementia ones and normal aging controls with a 100% sensibility and specificity. These different findings clearly point up navigation paradigms as powerful tools to diagnose memory deficits. However, major challenges remained and my group is currently tackling two points. First, how the different functions involved in navigation (i.e. memory, executive function and sensory-motor processing) are captured by navigation scores. Second, how hippocampal activity can be modulated by other structures of the navigation network. Here, we particularly focus on how the cerebellum may impact the hippocampal code.

Oral presentations

Selected talks

ST1 BIELEFELD Pascal
Circadian Glucocorticoid Oscillations Preserve a Population of Adult Hippocampal Neural Stem Cells in the Aging Brain

ST2 CUNHA Rodrigo
Adenosine neuromodulation is imbalanced in the aging hippocampus – restoring memory performance by blocking adenosine A2A receptors

ST3 RADWANSKA Kasia
CaMKII-dependent elimination of PSD-95 with learning is impaired in aged animals24

ST4 RODRIGUEZ-GRANDE Beatriz
A single mild traumatic brain injury at juvenile age accelerates brain aging phenotype

ST5 PLANCHE Vincent
Evolution of hippocampal-to-cortical volume ratio during aging predicts long-term cognitive decline and incident Alzheimer's disease

ST6 MISHRA Aniket
Genetic link between dementia and regional sulci morphology

ST7 FOLVILLE Adrien
Older adults do not always rely on the amount of episodic details when considering the subjective vividness of their memories

ST8 BASTIN Christine
A manipulation of processing fluency to attenuate age-related differences in recognition memory

ST1 - Circadian Glucocorticoid Oscillations Preserve a Population of Adult Hippocampal Neural Stem Cells in the Aging Brain

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A decrease in adult hippocampal neurogenesis has been linked to age-related cognitive impairment. While this age-related reduction may result from a division-coupled depletion of a pool of neural stem/precursor cells (NSPC), the mechanisms involved remain elusive. Glucocorticoid hormones (GC) are important regulators of NSPC proliferation. GC are released from the adrenal glands in ultradian secretory pulses that generate characteristic circadian oscillations. Interestingly, GC oscillations are affected by aging. Here, we investigated the hypothesis that GC oscillations prevent NSPC activation and preserve a quiescent NSPC pool in the aging hippocampus. We found that hippocampal NSPC populations lacking expression of the glucocorticoid receptor (GR) decayed exponentially with age, while GR-positive populations decayed linearly and predominated in the hippocampus from middle age onwards, when NSPC proliferation is lowest. Importantly, GC oscillations controlled NSPC activation and GR knockdown reactivated NSPC proliferation in aged mice. We show that, when modelled in primary hippocampal NSPC cultures, GC oscillations control cell cycle progression and induce specific genome-wide DNA methylation profiles. GC oscillations induced lasting changes in the methylation state of a group of gene promoters associated with cell cycle regulation and the canonical Wnt signaling pathway. Our results indicate that GC oscillations preserve a population of GR-expressing NSPC during aging, preventing their activation possibly by epigenetic programming through methylation of specific gene promoters. These observations indicate a novel mechanism mediated by GC that controls NSPC proliferation and preserves a dormant NSPC pool, thereby possibly contributing to a neuroplasticity reserve in the aging brain.

ST2 - Adenosine neuromodulation is imbalanced in the aging hippocampus – restoring memory performance by blocking adenosine A2A receptors

Rodrigo CUNHA

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The adenosine modulation system in the brain mostly operates through inhibitory A1 (A1R) and facilitatory A2A receptors (A2AR). The activity-dependent release of adenosine acts as a brake of excitatory transmission through A1R, which are enriched in glutamatergic terminals. Adenosine actually sharpens salience of information encoding in neuronal circuits: high-frequency stimulation triggers ATP release in the 'activated' synapse; ATP is locally converted by ecto-nucleotidases into adenosine to selectively activate A2AR; A2AR switch off A1R and CB1R, bolster glutamate release and NMDA receptors to assist increasing synaptic plasticity in the 'activated' synapse; the parallel engagement of the astrocytic syncytium releases adenosine further inhibiting neighboring synapses, thus sharpening the encoded plastic change.

The adenosine modulation system in the brain is modified upon aging: there is a decrease density and efficiency of inhibitory A1R in parallel with an increased density and efficiency of A2AR, observed both in rodents and in humans. There also seems to be a modification of the extracellular metabolism of adenosine and a modification of the transducing system(s) operated by A2AR in aged rodents. Notably, the over-activation of hippocampal A2AR is actually sufficient to trigger memory impairment, as shown both upon pharmacological activation of A2AR or opto-activation of the A2AR transducing system in the hippocampus during performance of spatial memory tasks (collaboration with Jiang Fan Chen). This over-activation of hippocampal A2AR seems to be a hallmark of brain diseases involving memory dysfunction, such as Alzheimer's disease, epilepsy, depression, ADHD or diabetic encephalopathy, probably as an attempt to bolster synaptic stability, which is a key role of A2AR during development (collaboration with Sabine Levi and Christophe Bernard).

This prompts the proposal that the over-functioning of hippocampal A2AR might actually be responsible for memory impairment upon aging. In accordance with this contention, A2AR blockade restores the abnormal hippocampal long-term potentiation (LTP) upon aging and an LTD-to-LTP shift characteristic of memory impairment upon aging (collaboration with Luisa V. Lopes). Furthermore, both the regular intake of caffeine (a non-selective adenosine receptor antagonist) and selective A2AR antagonists restore the performance of reference spatial memory in aged mice and rats.

Overall, these observations herald the concept that adenosine A2AR over-function might be a critical contributing factor for memory deterioration associated with aging, as well as for the greater susceptibility of brain diseases in the elderly. Furthermore, this imbalance of the adenosine modulation system upon aging also provides a rationale to understand the particular ability of caffeine to normalize mood and memory performance in aged compared to younger adult subjects and prompts the suggestions that: i) A2AR polymorphisms might be predictors of memory deterioration upon aging; ii) PET analysis of A2AR density might be an ancillary biomarker of memory function upon aging; iii) A2AR antagonists might be of particular interest as cognitive bolsters in aged individuals.

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ST3 - CaMKII-dependent elimination of PSD-95 with learning is impaired in aged animals

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The molecular mechanisms involved in formation of memory are still poorly understood. Here, we analysed interactions between the scaffold protein, PSD-95, and CaMKII in the area CA1 of the hippocampus, during formation of spatial memory in young adult and old mice. Our data indicate that in young mice formation of memory about spatial location of reward induces elimination of PSD-95 protein from dendritic spines that also contain CaMKII. CaMKII-dependent phosphorylation of PSD-95 on serine 73, which controls LTD-induced elimination of PSD-95, is necessary for early phase of memory formation. Later, for the memory to be stabilised, new PSD-95 protein is required, as memory stabilization is disrupted by shRNA targeting PSD-95. In old mice, training-induced elimination of PSD-95 from dendritic spines is excessive, and leads to the perforation of post-synaptic densities. Because elimination of PSD-95 occurs only in CaMKII-negative spines, we conclude that in old mice alternative mechanisms of synaptic remodelling are required for the memory to be formed. Overall, our data implicate CaMKII-driven phosphorylation of PSD-95 on serine 73 in memory formation in young, adult mice. We also conclude that this process is impaired in old mice possibly contributing to the altered morphology of dendritic spines and less stable spatial memory observed with aging.

ST4 - A single mild traumatic brain injury at juvenile age accelerates brain aging phenotype

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Traumatic brain injury (TBI) is a major public health issue with at least one million-hospital admissions/year. TBI hits the pediatric population particularly hard, and its mild form, juvenile (j) mild (m)TBI represents most of the cases of juvenile TBI (80%) seen in the emergency room. Mild TBI is clinically defined with a Glasgow coma score of 13-15, no or transient (< 30 min) loss of consciousness, no skull fracture, no visual alterations on CT scans, and no apparent short-term cognitive deficits. It is more widely recognized that moderate/severe jTBI causes significant morbidity over years after the initial event. We have previously shown that moderate/severe TBI promotes age-related pathology during the first months after the injury in pre-clinical models (e.g. amyloid beta deposition and cognitive impairment). A growing body of clinical evidence suggests that repetitive mild TBI, such as that occurring to athletes or soldiers, can lead to profound structural brain changes and cognitive impairment such as chronic traumatic encephalopathy. However, whether a single mild TBI sustained during childhood can produce long-lasting damage and accelerate the aging process, is highly discussed. Therefore, we aimed to explore the consequences of a single jmTBI in the aging process by evaluating: a) cognitive function with a battery of behavioral tests, b) neuroimaging alterations using diffusion tensor imaging (DTI) and c) histological changes (gliovascular and neuronal alterations) at 12 months after one jmTBI sustained at postnatal day 17 in mouse.

Significant impairment in spatial learning and memory during the Morris water maze test were observed in the jmTBI compared to the sham group. This cognitive impairment was accompanied by DTI changes in both white and grey matter: decreased fractional anisotropy (FA) was observed in the corpus callosum and most parts of the dorsal and ventral hippocampus. In addition, a significant decrease of AD was observed in the substantia innominata/nucleus basalis (SI/NB), a region that has also been involved in memory. Interestingly, changes in diffusion metrics in the hippocampus and SI/NB significantly correlated with cognitive dysfunction. There was a significant decrease in NeuN staining in jmTBI compared to sham group in the dorsal hippocampus, accompanied by altered astrocyte phenotype with increased AQP4 water channel in astrocyte perivascular end-feet and processes. In contrast, Iba1 staining was increased, in the jmTBI group compared to sham group suggesting increase of microglia in the SI/NB. However, GFAP and AQP4 levels were reduced in the SI/NB of jmTBI mice, concomitant with a reduction in blood vessel diameter.

Changes in astrocyte AQP4 and vascular morphology have been previously linked to the aging process. Therefore our results show for the first time that a single mild TBI during the juvenile period exacerbates an aging phenotype (cognitive impairment, white and grey matter DTI alterations, hippocampal neurodegeneration) 12 months after the injury, accompanied by neurovascular alterations. The development of region-specific pathologies is for the first time explored long-term after jmTBI and suggests that jmTBI is a complex multifactorial disorder, which calls for the development of sophisticated long-term treatments.

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ST5 - Evolution of hippocampal-to-cortical volume ratio during aging predicts long-term cognitive decline and incident Alzheimer's disease

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Background: MRI patterns of "typical", "hippocampal sparing" or "limbic predominant" atrophy are known to be surrogates of tau neurofibrillary tangles distribution in Alzheimer's disease. However, it is currently unknown whether these MRI patterns are clinically relevant in aging and prodromal Alzheimer's disease.

Methods: Participants (n=368) from a population-based cohort of non-demented older adults received longitudinal neuropsychological assessments every 2 years during 12 years. MRI scans at baseline and 4 years later were used to define participants with: "hippocampal predominant atrophy", "cortical predominant atrophy", "homogenous atrophy" and "no evidence of brain subtype atrophy" based on the dynamics of hippocampal-to-cortical volume ratio evolution.

Results: After adjustment on age, gender, educational level and ApoE4 genotype, participants with "hippocampal predominant atrophy" during the first 4 years declined faster than all other groups regarding global cognition (MMSE, p=0.013), verbal fluency (IST-30, p=0.030 and IST-60, p=0.011) and verbal episodic memory (FCSRT free recall, p=0.023 and FCSRT total recall, p=0.009). In Cox proportional hazards models, "hippocampal predominant atrophy" was associated with an increased risk of developing Alzheimer's disease over time (HR=5.73; IC95% 2.71–12.15), independently of age and ApoE4 genotype, the two other significant predictive factors (respectively HR=1.19; IC95% 1.08–1.30 and HR=2.56; IC95% 1.27–5.16).

Interpretation: While previous works studying Alzheimer's disease patients with cross-sectional "hippocampal sparing" atrophy reported faster cognitive decline, we found in a population-based study of older adults based on longitudinal MRI analyses that "hippocampal predominant atrophy" predicted future cognitive decline and incident Alzheimer's disease. As a surrogate of confined tauopathy and early Alzheimer's disease pathology, future studies should consider hippocampal-to-cortical volume ratio evolution rather than hippocampal volume alone.

ST6 - Genetic link between dementia and regional sulci morphology

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MRI-markers for cortical atrophy assessment such as sulcus opening and thickness can be used as quantitative endophenotypes of dementia. Here we report the first study testing the association between genetically predicted dementia risk and sulci morphology measurements in older persons of European origin.

The study population to derive the polygenic risk score (PRS) comprised 6,489 participants from the French population-based 3C cohort, with 1000 genomes imputed genome-wide genotype data, and of whom 810 had a diagnosis of prevalent or incident dementia cases. Using genome-wide association study summary data on 17,008 Alzheimer's disease (AD) cases and 37,154 controls from the International Genomics Alzheimer Project (IGAP) consortium we created the polygenic risk score (PRS) profile of the 6,489 3C participants, using the PRSice-2 software. The parameters for the PRS analysis were optimized such that the highest predictive power was achieved for dementia diagnosis in 3C (R2=0.332).

The association of the PRS with sulci opening and thickness was then tested in a subset of 2,218 3C participants with brain MRI and sulci measurements derived using the MORPHOLOGIST software. A total of 111 sulci measurements were available after quality control. Using linear regression we identified significant association of the AD PRS profiles for 9 sulci opening and 2 sulci thickness parameters after multiple testing corrections using the permutation approach.

In conclusion, we report genetic link between Alzheimer's disease and sulci morphology in older community persons.

ST7 - Older adults do not always rely on the amount of episodic details when considering the subjective vividness of their memories

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Although healthy aging has been related to a decline in recollection as indexed by objective measures (e.g., source memory or free-recall), the subjective experience of recollection (e.g., vividness of memory) seems to remain stable. To date, however, behavioral studies have only examined these age-related effects using aggregated data across trials, such that the relationship between subjective and objective measures of recollection on a trial-by-trial basis remains unknown. In this study, we conducted two experiments in which young and older adults performed a cued recollection task with pictures associated with descriptive labels at encoding. At retrieval, participants were cued with the labels and were asked to rate the vividness of their memory of the associated picture and to recall as many details of the picture as they could. In Experiment 1, multilevel analyses revealed that, across trials, the relationship between subjective (global vividness) and objective (free recall) recollection was greater in young than in older participants. Experiment 2's results replicated and extended this finding by showing that, when requested to rate the vividness of more specific memory dimensions (e.g., persons and objects), older adults still did not calibrate their subjective judgements on the amount of retrieved episodic details to the same extent as young adults. These results provide direct evidence that, compared to young individuals, older adults rely to a lesser extent on the amount of retrieved episodic details to judge their subjective experiences while remembering.

ST8 - A manipulation of processing fluency to attenuate age-related differences in recognition memory

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Normal aging is characterized by decreased recollection, but better preserved familiarity. Memory tasks that facilitate the use of familiarity should allow attenuating age-related differences in memory. The study tested two hypotheses: (1) the reliance on familiarity during recognition memory should be promoted by increasing the difference in perceptual processing fluency between old and new items; (2) this manipulation should reduce age-related difficulties in episodic memory. Twenty-four young and 24 older adults performed two verbal recognition memory tasks. In the No-Overlap task, target words and new words did not share any letter. Prior exposition to the target words thus induced increased processing fluency of the words and letters, so that fluency difference was a salient and reliable cue to discriminate between old and new words. In the Overlap task, target and new words had letters in common, so fluency cues were less useful. Recollection and familiarity was assessed with the Remember/Know/Guess paradigm. The results showed an age effect on recollection but intact familiarity. Moreover, (1) memory performance was better in the No Overlap than the Overlap task, with a greater hit rate and a smaller false alarm rate associated with familiarity. And, (2) age-related differences in recognition accuracy (hits – false alarms) were significantly attenuated in the No Overlap task compared to the Overlap task. These findings suggest that minimizing the perceptual similarity between targets and distractors, and thus increasing processing fluency differences, allowed to reduce the effect of age on recognition memory performance by facilitating the use of familiarity.

Posters

P1 - Older adults' adaptation to time constraint in verbal fluency tasks

P2 - Emotional orthographic neighborhood effects in memory for young and older adults as function of study list composition

P3 - Stability of SuperAgers over three years

P4 - Inflammation, oxidative stress and Alzheimer disease: a preliminary gene expression study

P5 - FILTER IT: application for the training of visual selective attention

P6- The contributions of representational quality and strategic retrieval processes to individual differences in recognition memory in older adults

P7 - Active lifestyle and cognitive performance in older adults

P8 - Organotypic hippocampal slices as an *in vitro* model of AD-linked tau pathology

P9 - Behavioural tagging and capture: memory persistence and memory-related neuronal ensembles in young and middle-aged rats

P10 - Auditory sensory memory encoding is sensitive to context precision

P11 - Are synapses in the aging brain too large to learn?

P12 - Exploring age-related changes in the precision of episodic memory

P13 - Memory of low-arousal emotional words in young and older adults

P14 - Potential role of NRF2 in Alzheimer's disease as a crucial modulator of the innate immune suppression

P15 - Effects of age on long-term memory for objects and object-name pairs following "fast-mapping" learning

P16 - Are odors, musical pieces and faces equal to evoke episodic memories? A new encoding approach using virtual reality

P17 - Word frequency effects on free recall in young and older adults: Influence of study list composition

P18 - Navigation paradigms to assess memory and executive functions in mice

P19 - Alpha-Mangostin Prevents Scopolamine-induced Cognitive Deficit through Inhibition of Caspase-3

P20 - Investigating the role of noradrenaline in olfactory discrimination during aging

P1 - Older adults' adaptation to time constraint in verbal fluency tasks

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Verbal fluency tasks are widely used to assess semantic memory and strategic retrieval. While semantic fluency (i.e., generating words from a given category) and action fluency (i.e., giving as many things one can do) generally decrease in older adults, letter fluency data are rather mixed, showing a decrease or no age-related effect (e.g., Kemper & Sumner, 2001; McDowd et al., 2011). Production time is generally of one minute, although the influence of increasing production time has been shown in verbal fluency tasks (e.g., Holtzer, Goldin & Donovick, 2009). Importantly, the effect of time constraint instruction (i.e., the time given explicitly to the participants) has not been investigated. The aim of the present study was to investigate whether the effect of time constraint might influence verbal fluency tasks according to age during the first minute of production. Forty young adults (24.2 years old) and 40 older adults (66 years old) performed semantic, letter, and action fluency tasks. One of the two following time instructions was given to each participant: to produce as many words as possible in one or three minutes. In both time conditions, only the first minute of production has been transcribed. An ANOVA was run on the number of words produced in one minute, with age (young, old) and time instruction (1 min., 3 min.) as between factors and fluency (semantic, letter, action) as a within factor. Results showed an interaction between age and time instruction. Older adults produced more words in one minute when the time instruction was of one minute rather than three. That difference did not occur in younger adults. Planned comparisons indicated that the effects of time instruction in older adults occurred in letter and action fluencies only, and was not retrieved when the effect of vocabulary was controlled. The data suggest age-related strategical effect, with older adults relying on their level of vocabulary to adapt their production to time constraint.

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P2 - Emotional orthographic neighborhood effects in memory for young and older adults as function of study list composition

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Previous studies have shown that the influence of emotional words in memory differs across age. Indeed, young adults would show a preference toward negative words whereas older adults would not (Murphy & Isaacowitz, 2008). Other studies have found that orthographic similarity between words (i.e., orthographic neighborhood) also influences memory performance in young adults (Cortese, Fugett, Watson, & Wang, 2004). Here, we examined whether emotional orthographic neighborhood of words, a factor that combines both emotional and orthographic characteristics, influences memory performance across age. Although the emotional content of orthographic neighbors has never been investigated in memory tasks, this factor has been shown to influence visual word recognition (Gobin & Mathey, 2010) and color categorization tasks (Camblats & Mathey, 2016). Two experiments in which list composition was varied (pure vs. mixed lists) were conducted. List composition was considered since lexical effects on memory performance in young adults have been shown to depend on whether same words are presented in separate lists (i.e., pure lists) or in the same list (i.e., mixed list). Words to be memorized had a negative higher-frequency orthographic neighbor (e.g., truelle [trowel]-CRUELLE [cruel]) or a neutral one (e.g., monceau [heap]-MORCEAU [piece]). In Experiment 1, 52 young (M = 21.8 years) and 52 older (M = 65.7 years) adults studied pure word lists (words with either a negative or a neutral neighbor) for free recall and recognition. An effect of emotional orthographic neighborhood was found in both free recall and recognition tasks. More words were correctly recalled and recognized when they had a negative neighbor than a neutral one. This effect was similar across age. In Experiment 2, 47 young (M = 20.1 years) and 47 older (M = 67.53) adults performed the same tasks with the same words presented in mixed lists (with words of both conditions). The facilitatory effect of emotional neighborhood was found for both age groups in recognition but not in free recall. The results are discussed with regard to memory processes and emotions during aging, and also to the differences between memory processes involved in the two types of lists.

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P3 - Stability of SuperAgers over three years

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Objective: In older age, cognitive performance decreases, however, some individuals grow to be "SuperAgers" (SA), who are resistant to this decline, are aged 80 and over, and have episodic memory performance at least as good as normative values for 50- to 65-year-olds. One longitudinal study presented the relative stability of the cognitive performance of SA after 18 months (Cook et al., 2017). The aim is to assess the stability of SA over 3 years.

Participants: 101 persons aged 80 and older, participants of NANOK study (2012-2015) were divided into two groups: the SA and non-SA groups. The SA were defined following the criteria of Harrison et al. (2012): older adults who recalled ≥ 9 words on the delayed recall (normative mean for 60 years old adults) of Philadelphia Verbal Learning Test and had performance within or above one standard deviation from the age-appropriate average in the non-memory tasks such as the 30-item Boston Naming Test (15-item in year 2), the Trail-Making Test Part B and Category Fluency (Animals). Cognitive performance was assessed in years 1, 2 and 4.

Methods: Mann-Whitney U test and Fisher's exact test were used to assess the difference in demographic variables (age, gender, education) for SA and non-SA groups. Cochran's Q and McNemar's test were used to assess the change in proportions between SA and non-SA in years 1, 2 and 4.

Results: In year 1, SA criteria were met by 19 individuals; by 31 individuals in year 2; in year 4, by 16 individuals. Cochran's Q test found statistically significant change in the proportions of individuals in the SA and non-SA groups. McNemar's test specified that significant changes were between years 1 and 2, and 2 and 4. There was no significant change between years 1 and 4. There was no difference between demographic variables among groups, except for age in year 2 (non-SA slightly older). Only 9.9 % of participants met the SA criteria consistently in all three assessments, 7.9 % twice (3 % year 2 and 4, 4.9 % year 1 and 2), 20.8 % once (4 % year 1, 13.8 % year 2, 3 % year 4), 61.4 % of participants were classified as non-SA consistently.

Conclusions: In our study, the stability of SA defined by Harrison et al. (2012) is influenced by an interval between the assessments. The short interval is mainly influenced by practice effect and the long interval by cognitive decline. SA should be evaluated prospectively to define sustained, stable SA, which suggests that one time results without further context are not reliable indicators in this case. In our study, at least 50 % of SA are sustained SA. Long-term observation may lead to the identification of factors that influence the potential trajectory of successful cognitive aging ("cognitive maintenance"). Our study may help to plan adequate sample sizes for next longitudinal superaging studies.

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P4 - Inflammation, oxidative stress and Alzheimer disease: a preliminary gene expression study

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Alzheimer disease (AD) is the most common cause of dementia and represents an enormous disease burden in terms of human suffering and economic cost. Mild cognitive impairment (MCI) has come to be recognized as an intermediate state of clinical impairment and a high percentage of MCI patients develops AD.

In this study we aimed to detect biomarkers in blood useful for the early diagnosis and prognosis of MCI. We analyzed the gene expression levels of 168 genes related to oxidative stress and inflammation in peripheral blood from a cohort of 18 MCI and 27 non-demented controls (CTRL) by qRT-PCR. After diagnosis patients were divided in the two groups according to the Mini-Mental State Examination (MMSE) score. The average of the MMSE score in the CTRL group was 28.72±1.18 and in the MCI group was 21.88±4.69. The two cohorts were age matched (CTRL=74.31±7.09, MCI=76.18±5.54, p=0.36). Our preliminary results on this small cohort showed a significant impairment ($p<0.05$ and $-1.5>FR>1.5$) in the levels of CD40, CSF2, EGR1, IKBKE, RHOA, TICAM1, TNFRSF10A (NFKB signaling pathway) and GSTZ1, SFTPD, GLA (Oxidative stress pathway) in patients. Interestingly, EGR1 levels correlate with the MMSE score. Our results that inflammation and oxidative stress are early indicators of MCI progression. These results will be validated in a larger and longitudinal cohort of MCI and AD patients.

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P5 - FILTER IT: application for the training of visual selective attention

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The ability to process information and retain in the episodic buffer for a short period is indispensable for performing everyday activities. The capacity of this buffer is limited and individual, however, can be enhanced. As one gets older, the capacity to process information decreases. One of the reasons is the decreased ability to inhibit irrelevant information and focus on the important successfully. Selective attention or so-called distractor filtering efficiency thus determines our working memory (WM) and to a great extent co-determines its content. Persons with greater WM capacity more successfully inhibit irrelevant information than people with low WM capacity.

Distractor filtering efficiency and the WM capacity can be examined with the "Change Detection Task" (CDT), which is also used as a training task in research. The task is to identify whether the set of stimuli is identical to a set that was presented just previously. Thus it gives many possibilities to design the task and to choose adaptive aspects (a type of stimuli, number of stimuli, presentation/retention time, etc.).

Research studies have suggested that training of selective attention has an impact on the WM capacity and decision-making ability. However, they have focused only on younger adults, and the extent to which this training is effective in older adults yet needs to be researched. For this purpose, we have developed an application "FILTER IT" for tablets (OS Android). The main aim of our poster is to present our adaptation of CDT for tablets.

The application can be used for assessment or training and has four parts (Instructions, Trial mode, Training, Results). Our CDT consists of three paradigms (change detection in color, orientation, and shape). The task is to focus on the target visual information (stimuli on the cued side indicated by arrow) in the presence of irrelevant information (items located on opposite side) in a display set. Following a short retention interval (900 ms) participants are asked to determine whether the stimuli on the cued side of new display set have changed or not. Each paradigm consists of 7 sequences, and one sequence has 20 trials. The efficiency is evaluated after every sequence and based on it the number of stimuli presented (from 2 to 7 stimuli on each side of the screen) is changed or remained. Thus the task for training and assessment is adaptive.

The application FILTER IT will be described in detail in the poster.

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P6 - The contributions of representational quality and strategic retrieval processes to individual differences in recognition memory in older adults

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Introduction. Recognition memory declines with age, particularly when targets and foils are perceptually similar. By contrasting recognition memory performance in a Yes/No (YN) and Forced Choice (FC) recognition test format, the contributions of strategic retrieval processes and ability to form detailed stimulus representations can be teased apart because simultaneous presentation of targets and foils in the FC test minimises demand on strategic retrieval processes. Using this approach, previous studies have shown that declines in both representational quality and strategic retrieval processes contribute to worse memory performance in old age. Given high individual variability in performance, the present study expands on this literature by adopting an individual differences approach to assess the contributions of representational quality and strategic retrieval processes to YN and FC object recognition using multivariate regressions.

Methods. 110 older and 55 young adults performed FC and YN object recognition memory tests, neuropsychological tests measuring executive functioning (EF; as proxy for strategic retrieval abilities), and object and scene perceptual discrimination tasks with conditions of low and high feature overlap (as proxy for representational quality).

Results. Older adults performed worse on both high ambiguity object and scene discrimination even when controlling for low-level perceptual abilities. Older adults also had lower scores on FC and YN tasks with the age effect being equivalent across formats. In two multivariate hierarchical regression models for FC and YN performance, age, MoCA score, and scene and object discrimination ability under low feature ambiguity were entered as control variables and EF score and scores on the high ambiguity conditions of scene and object discrimination were the main variables of interest. The final model for FC revealed that memory performance could be predicted based on age, EF, and high ambiguity object discrimination. YN scores could best be explained by a model containing age and EF. Even when controlling for both FC scores and age in the YN model, EF still emerged as a significant predictor.

Conclusions. The present findings strengthen the evidence base for decline in strategic retrieval processes and representational quality as two major factors underlying age-related memory decline even when controlling for age and general cognitive ability. Their relative contributions further depend on task demands, with high representational quality being insufficient to achieve high performance when target and foil cannot be directly compared and demands on strategic retrieval increase. The effects of representational quality appear to be content-selective such that object but not scene perceptual discrimination ability predicted individual differences in memory performance.

P7 - Active lifestyle and cognitive performance in older adults

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Level of education is known to correlate with cognitive performance in some tests and it is considered a part of the cognitive reserve. Type of profession (manual/mental) and mentally demanding leisure activities are also included in the cognitive reserve concept. Our aim is to find whether the type of profession and number of regularly performed activities during productive adulthood and retirement (attending a course at a university of third age, attending other courses such as language or ICT, physical exercise, aerobic activity of medium intensity at least 2,5 hours per week, a hobby, using a computer, reading books, reading newspapers and magazines, doing crossword puzzles or quizzes) predict cognitive performance in older age.

We assessed 324 cognitively normal community-dwelling older adults (60–74 years of age) without serious neurological or psychiatric disorder who are retired and not economically active for minimum 2 years. Three composite scores (CS) were created from the administered neuropsychological tests: CS Memory – Story, Boston Naming Test-15; CS Visuo-graphomotor – Trail Making Test A and B, Digit Symbol Coding; CS Verbal – Prague Stroop Test (Dots, Words, Colors), Rey Auditory-Verbal Learning Test Trial 1, Category Verbal Fluency – Animals.

Groups with performance above the 75th percentile for each composite score were identified. Binary logistic regression analysis was performed to know whether the type of profession and number of activities predicted cognitive performance above the 75th percentile. The level of education was added in block 1, then in block 2 type of profession and a number of activities (past and current) were added.

The level of education was a significant predictor (all ps < 0.001; OR = 2.38 – 4.01) of better cognitive performance in all three cognitive domains (memory, visuo-graphomotor, and verbal). However, after adding the type of profession and number of activities (past and current) in the analysis, its effect disappeared (all ps > 0.05; OR = 1.79 – 1.95). In block 2, more current activities were significant predictor of better performance in memory ($p < 0.05$; OR = 1.25) and verbal ($p < 0.01$; OR = 1.41) tests. On the other hand, more activities in the past significantly predicted better performance in visuo-graphomotor tests ($p < 0.05$; OR = 1.29). Type of profession did not significantly predict better performance in any composite score (all ps > 0.05; OR = 1.21 – 2.05).

Even though the probability of better cognitive performance rises with more activities only slightly, we may conclude that there is a potential positive effect of active lifestyle on the cognitive performance in older age. Thus, it could be an optimistic message that it is possible to escape from the predicament of lower education.

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P8 - Organotypic hippocampal slices as an *in vitro* model of AD-linked tau pathology

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Abnormal aggregation of the microtubule-associated protein Tau is a classical hallmark of Alzheimer's disease and other tauopathies. Several mouse models expressing different pathological forms of tau have been engineered. Although they constitute precious tools to study the pathology, they come with their lot of constrains for the synaptic physiologist. One of them is that tau aggregation only occurs in relatively old animals, which is challenging for slice electrophysiology and imaging. In addition, following the progression of the disease requires the sacrifice of cohorts of animals at multiple time points, which is time consuming and ethically questionable.

Here we developed an in vitro model of Alzheimer's disease using hippocampal organotypic slices. Organotypic slices can be maintained in culture for weeks, allowing the pathology to develop in vitro. They keep the main synaptic connections of the hippocampal circuit, which makes them a reliable model for synaptic studies. Organotypic slices were made from mice bearing the human P301S mutant tau protein. The addition, at DIV 3, of K18 seeds, tagged with either a Myc- or a HA-tag, induced tau aggregation 10 days after. The number of tau aggregates increased over time in different regions of the hippocampus. Seeding efficiency relies mostly on the level of expression of the mutant protein. It was higher in homozygous compared to heterozygous animals- and the type of seeds –Myc-tagged or HA-tagged seeds.

In conclusion, we were able to develop a reliable and progressive model of tau pathology in organotypic slices. We are currently investigating the specific progression of tau aggregation in different neuronal cell types of the hippocampus.

P9 - Behavioural tagging and capture: memory persistence and memory-related neuronal ensembles in young and middle-aged rats

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Decline in the cognitive functions including memory is one of the most common observations in ageing (Burke & Barnes 2006). During ageing, the hippocampus shows a number of structural changes and alteration, linked to impairments in learning and memory consolidation. Our daily memories of insignificant events fade away quickly. However, when a memory-modulating event is introduced before or after memory encoding, memories can persist longer. We investigated this phenomenon in a rodent spatial task in which weak memories persist longer if a novel event is introduced around the time of memory encoding (Wang et al. 2010; Salvetti et al. 2014). Linking to the synaptic tagging and capture theory (Redondo & Morris 2011), it is likely that a weak or strong stimulation leads to synaptic tagging while only strong stimulation triggers synthesis of the plasticity-related synaptic proteins that enable the lasting synaptic changes and memory. To understand how these two processes change over aging, we trained rats when they were young (3 to 5 months) and next at mid-age (10 to 13 months) with a spatial memory task described before (Salvetti et al. 2014). We found, first, that the long-term memory persistence (24h) declined at the mid-age in this task. Second, a novel event effectively improved persistence of weak memory in young rats but not in mid-aged rats. Furthermore, if encoding was reminded, the memory could persist in mid-aged rats. These results point that the synaptic tagging mechanisms is impacted by ageing and already vulnerable at the mid-age of the lifespan. Finally, using fluorescence in situ hybridization (FISH), we explored the activation of neuronal ensembles in the hippocampus in this task. We found that in young rats, the neurons activated by the encoding overlapped with neurons activated by the memory-modulating event in CA1 and CA3.

P10 - Auditory sensory memory encoding is sensitive to context precision

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Auditory sensory memory maintains a low-level representation of past sounds for a brief period of time, which is fundamental for most auditory functions. Previous research suggested that components of the midlatency auditory responses are putative biomarker for the encoding of auditory sensory memory (Näätänen & Picton, 1987; Jääskeläinen et al., 2007). However, it remains an open question whether the encoding mechanism is sensitive to context precision, which is known to modulate sensory processing in auditory cortex (Friston, 2005, 2009; Feldman & Friston, 2010; Schröger et al., 2015; Hsu et al., 2015, 2018). The current study used magnetoencephalography (MEG) to examine the encoding of auditory sensory memory in context of different precision. We presented 21 participants (average age 23; 6 males; 19 right-handed) with repetition of predicted probes and two non-predicted probes embedded in context of high and low precision, namely mispredicted and unpredicted probes. While mispredicted probes followed the primes arranged in ascending pattern, unpredicted probes followed the primes determined by pseudorandom sampling where there was no existing pattern. We reported the novel finding that the encoding of auditory sensory memory in context of different precision started to dissociate on early components of the midlatency auditory responses (i.e., P1m and N1m time windows). In P1m time window, repetition of predicted probes triggered neuronal enhancement (over left temporal region). Meanwhile, repetition of mispredicted probes elicited neuronal enhancement (over bilateral temporal region), whereas repetition of unpredicted probes did not. In N1m time window, repetition of predicted probes still triggered neuronal enhancement (over left temporal region). However, repetition of mispredicted probes elicited neuronal suppression (over left temporal region), whereas repetition of unpredicted probes did not. The results suggest that the encoding of auditory sensory memory is dependent on context precision, which likely involves temporal-frontal interaction (Grunwald at el., 2003) across the hemispheres. Its implications for research on how auditory sensory memory deteriorates in aging are discussed.

P11 - Are synapses in the aging brain too large to learn?

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Augmentation of LTP is a current model for the advantages of spaced versus massed learning. In the adult rat hippocampus, LTP can be saturated after one round of repeated bursts of high-frequency stimulation, namely theta-burst stimulation (TBS). Further potentiation, or augmentation of LTP, can only be achieved after a refractory period of at least 90 minutes and requires 4 hours for augmentation to be reliable. In spaced learning, memory consolidation is greatly improved if training is spread across spaced trials rather than clumped together in one “cram session.” Spaced learning is better than massed learning for memory consolidation and enhancement of LTP. Interestingly, prior studies in humans used spaced vs massed training protocols to test word-word association recall and found that both older adults (mean age of 65 years) and young adults (mean age of 19 years) show improvement in memory recall when spaced training was used. However, the amount of improvement compared to massed training protocols in older adults was significantly less than in young adults, indicating spaced learning loses efficacy as we age.

In models of age-related cognitive decline, LTP is surprisingly intact; however, augmentation of LTP has not been tested. Our preliminary data demonstrate a reduced capacity for augmentation of LTP in aged rats (25-26 months). Aged rats were assessed for cognitive impairment in concurrent experiments alongside young adults using the Morris Water Maze (MWM). Tissue from young adult control animals and cognitively impaired aged rats was processed for 3D reconstruction from serial section electron microscopy (3DEM). Initial findings revealed the distribution of synapse size was shifted right (larger) for aged relative to the young adults. These findings suggest the intriguing possibility that synapses of cognitively impaired aged animals are unable to be augmented because their synaptic weight is already saturated.

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P12 - Exploring age-related changes in the precision of episodic memory

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Healthy ageing is associated with declines in episodic memory. However, it is unclear whether these deficits reflect a reduction in the amount of information remembered, or decreased quality, or precision, of the retrieved memories. In two experiments, we used a continuous report task in combination with computational modelling of participants' retrieval responses to separate the effects of ageing on the probability of successful memory retrieval, and the precision of the retrieved information. Young and older participants studied stimuli displays consisting of everyday objects varying along different perceptual features (e.g., location, colour, orientation). At retrieval, participants recreated features of studied objects using a continuous response dial, allowing for detailed assessment of memory fidelity. Across all task conditions, we observed significant age-related declines in the precision of episodic memory retrieval, whereas age differences in retrieval success were limited to the most challenging task condition, indicating that ageing can differentially affect these two components of episodic memory retrieval. Furthermore, age-related impairments in episodic memory precision persisted after controlling for variability in the precision of perception and working memory, suggesting that this deficit was primarily attributable to long-term memory processes. The results indicate impoverished precision of memory representations as one factor contributing to episodic memory decline in older age, and highlight the benefit of continuous report paradigms for gaining a more detailed understanding of the specific basis of age-related memory impairments.

P13 - Memory of low-arousal emotional words in young and older adults

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Numerous studies have shown that emotions influence memory. A negativity bias resulting in higher memory performance for negative rather than neutral words has been demonstrated in memory for young adults. However, the benefits for negative words in memory seem to decrease during aging and a positivity effect would appear for the older adults (e.g., Murphy & Isaacowitz, 2008). To our knowledge, only one study showed that the positivity effect in memory only emerges for low-arousal words (Kensinger, 2008). Moreover, stability of this effect over time has never been tested. In this study, we attempt to test the effect of valence on the memory of low-arousal words in young and older adults using an emotional word memory paradigm including immediate free recall, recognition and delayed free recall tasks.

Fifty-five young adults (M = 20.0 years) and 45 older adults (M = 69.2 years) native French speakers participated.
Thirty-six low-arousal French words, including 12 negative (e.g., égout), 12 positive (e.g., lagune) and 12 neutral (e.g., notion) words were selected from an emotional lexical database containing valence and arousal assessments from adults aged 18 to 82 (Gobin, Camblats, Faurous, & Mathey, 2017). For the recognition task, 36 new words were selected to serve as distractors.

At first, participants had to learn two lists of words presented on a computer screen and then to orally recall them. Then, they had to perform a recognition task. Finally, they performed a delayed recall of the words they had previously learned.

Results showed a significant effect of emotional valence in both immediate and delayed free recall tasks, and also in the recognition task ($p<.001$). More positive words were recalled and recognized than neutral words ($p<.001$), indicating a positivity bias. The same pattern was observed for negative words ($p<.05$), indicating a negativity bias. A significant interaction between emotional valence and age was also found in both immediate and delayed free recalls ($p < .05$). Negativity bias was lower in older than in young adults ($p < .01$).

This study reveals a long lasting memory positivity effect in aging for low-arousal words, consistent with previous findings (Kensinger, 2008). Further multimodal MRI study will allow us to describe the brain correlates of this effect.

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P14 - Potential role of NRF2 in Alzheimer's disease as a crucial modulator of the innate immune suppression

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Clinical observations reveal that Alzheimer disease (AD) patients exhibit increased susceptibility to secondary infections. One possible explanation is that chronic inflammation specific to AD induces a refractory state of monocytes/macrophages (Mϕ) similar to Endotoxin Tolerance (ET). Upon activation with an endotoxin (first hit) Mϕ are driven to a transiently refractory state, being unable to fully respond to further infectious challenges (second hit). In line with this, a partial suppression of the immune system was found in AD-patients at the level of Mϕ, henceforth highlighting the importance of understanding the molecular mechanisms involved in ET. Here we describe an immunomodulatory role for the transcription factor NRF2 (Nuclear factor (erythroid-derived 2)-like 2), classically considered as the master regulator of the antioxidant response. We have found that it is activated in response to lipopolysaccharide (LPS). Interestingly, an even higher NRF2 activity was observed in tolerant human and mouse Mϕ, suggesting a potential role of this transcription factor in maintaining the hypo-responsive state of Mϕ. Moreover, we have observed that deficiency in NRF2 leads to a reduced tolerogenic state in mouse Mϕ, which is accompanied by their switch towards a marked pro-inflammatory phenotype after LPS stimulation. Altogether, our data suggest that NRF2 might be a drug target candidate for modulating Mϕ reactivity in AD patients.

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P15 - Effects of age on long-term memory for objects and object-name pairs following "fast-mapping" learning

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The “fast-mapping” (FM) learning paradigm has been recently proposed as an interesting tool for adults’ long-term acquisition of novel object-name pairs (Coutanche & Thompson-Schill, 2015). In the FM paradigm, an unknown object is introduced in context with a familiar object along with a question that mentions the name of the unknown object. The novel object-name pair is therefore encoded incidentally through exclusion of the familiar object and inference on the unknown object. Results in amnesic patients with hippocampal damage suggest that FM learning may permit long-term memory for object-name pairs independently of the hippocampus (Sharon et al. 2011), although challenging results suggest that hippocampal volume would predict recognition performance after FM learning (Greve et al. 2014). We aimed to test long-term object memory and object-name associative memory in adults of various ages, following either FM learning or intentional episodic encoding (EE).

Young (19-30 years, n=17), middle-aged (36-51 years, n=9) and older (58-81 years, n=13) adults underwent a learning session of 48 object-name pairs. Half pairs were presented with an FM paradigm, whereas the other half were learned explicitly (EE paradigm). Participants were told that they would be further tested on explicitly learned items. A recognition session was conducted after 1 month in all participants. Moreover, several participants (6 young, 6 middle-aged, 8 older) underwent a second recognition test 5-6 months post-learning.

All age groups had recognition scores for objects and object-name pairs above chance levels after a 1-month delay, showing that both learning paradigms resulted in effective long-term memory. Following EE, older adults had slightly lower object recognition scores relative to other groups ($p=0.04$) and lower object-name pair recognition ($p=0.002$). When comparing object-name pair vs. object recognition scores, older subjects showed greater decrease in associative vs. item memory (significant age × recognition task interaction, $p=0.01$), in agreement with specific associative memory deficit with age (Naveh-Benjamin, 2000). In contrast, following FM learning, object and object-name pair recognition scores were equivalent in the 3 age groups ($p>0.05$). Moreover, age groups had similar decrease in recognition scores for associative vs. item memory ($p>0.05$), showing that associative memory was not particularly impaired in older participants. Re-test after a delay of 5-6 months showed that object recognition improved with time ($p=10^{-8}$) with greater improvement for objects learned through FM ($p=0.005$). Object-name pair recognition was stable across time ($p>0.05$) for objects learned through both FM and EE. Our results suggest that the age-related deficit in associative vs. item memory may be reduced with incidental learning such as FM. Moreover FM learning may result in efficient long-term object memory, especially in older adults.

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P16 - Are odors, musical pieces and faces equal to evoke episodic memories? A new encoding approach using virtual reality.

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Odors are often presented as a privileged gateway to the recollection of past events. However, the mechanisms of this phenomenon are still rather unknown, and there is an ongoing debate about whether or not olfaction provides better cues for an emotional and vivid recollection compared to other sensory modalities (Larsson and Willander, 2009).

Our study addresses this question by analyzing the characteristics of episodic memory evoked by ecologically relevant cues from three different sensory modalities well known to trigger vivid recollection: odors, musical pieces and faces (Barsics and Brédart, 2012; Janata et al., 2007; Saive et al., 2014). For this purpose, we developed a new approach using virtual reality, to allow participants to encode multi-sensory episodes presented in laboratory conditions, and to retrieve them through the presentation of a unimodal sensory cue.

Results showed that participants significantly recognized all sensory cues, but musical pieces and faces were recognized more accurately than odors. Importantly, only odors and faces were able to evoke episodic memories: music-evoked episodic memory performance was not different from chance. It appeared that recognition and episodic memories may have been influenced by emotions carried by the sensory cues. Actually, odors' and musical pieces' recognition were linked to pleasantness: recognition score was better when odors were unpleasant than pleasant, and when musical pieces were pleasant than unpleasant. Odors' unpleasantness also tended to lead to higher episodic memory scores. Moreover our results linked episodic memory score to participants' behavior at encoding, where participants reported us they paid more attention to faces than odors, and to odors than musical pieces. Our results at retrieval tended further to show that decreased attention to a stimulus type at encoding was related to a lower episodic memory score, and this could explain the surprising music-evoked episodic memory score. The encoding and emotion effect will be investigated in another experiment in which emotional cues will be used.

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P17 - Word frequency effects on free recall in young and older adults: Influence of study list composition

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Although it seems well established that healthy aging leads to deficits in episodic memory, only a few studies has examined whether age deficit in episodic memory is influenced by word frequency, a lexical characteristic known to influence memory performance in younger adults (e.g., Ozubko & Joordens, 2007). Furthermore, the literature provides mixed data regarding word frequency effects in memory during aging (e.g., Almond, Morrison & Moulin, 2013; Badham, Whitney, Sanghera & Maylor, 2017). The aim of our study was to examine whether age deficits in episodic memory could be influenced by manipulations of word frequency and study list composition. Study list composition was considered here since word frequency effects on memory performance in young adults have been shown to depend on whether low- and high-frequency words are presented in separate lists (i.e., pure lists) or in the same list (i.e., mixed list). Here, 20 young (M = 19.5 years) and 20 older adults (M = 68.5 years) studied four word lists for free recall. Two lists were pure frequency lists (of low vs. high-frequency words) and the two others were mixed lists (with both low- and high-frequency words). Results indicated a main age-group effect ($p<.001$), young adults recalling more words than older ones. A list effect was also found ($p<.001$), with a higher proportion of words recalled for mixed than for pure lists. Interestingly, there was an interaction between age and list composition ($p=.001$), with a significant list effect in older adults only. Also, list composition interacted with word frequency ($p=.001$). High-frequency words showed a recall advantage in pure lists, which was reversed in randomly mixed lists. Finally, a marginal interaction between word frequency and age was found ($p=.067$), with a higher word frequency effect in older adults. Taken together, our results indicate that age-related memory deficits are sensitive to word frequency and list composition.

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P18 - Navigation paradigms to assess memory and executive functions in mice

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Research into the diagnosis of Alzheimer's disease (AD) focuses on the discovery of new biomarkers. However, these biological markers do not directly estimate memory and executive function disorders, which ultimately induce autonomy loss in AD patients. Thus, there is a real need to develop diagnostic tests able to objectify the alteration of these cognitive functions as well as quantify their possible improvement when using pharmacological agents.

To investigate episodic memory, Laure Rondi-Reig invented the Starmaze, a navigation task that relies on spatiotemporal memory (Rondi-Reig et al., 2006). Navigation tasks have several additional advantages: they allow the creation of new specific memory that can be experimentally evaluated, they are ethological, do not require language and are translational across species. Thus, the Starmaze is available for memory evaluation in both humans (virtual reality maze; Igloi et al., 2009, 2010) and mice (aquatic maze; Fouquet et al., 2011). By using the virtual reality Starmaze in humans, we were able to distinguish between early AD patients, frontotemporal lobe degeneration patients and normal aged subjects (Bellassen et al., 2012). This differential diagnosis is based on their spatiotemporal memory performances.

However, there is growing evidence that executive functions may be altered even sooner than memory in AD patients (see Kirova et al., 2015 for review). Our objective was therefore to assess executive functions using different navigation tasks. We thus developed a new paradigm including the Starmaze task followed by an aquatic Y-maze in order to assess cognitive flexibility and working memory alongside with spatiotemporal memory. To assess those functions, we also developed new behavioral scores in the Starmaze guided by different specific tests already existing in the assessment of one function.

Three different models of mice were used: a model of the familial form of the AD (APPPS1 mice with C57Bl6 mice as control), a model of risk factor of the sporadic AD (ApoE4 mice with ApoE3 mice as control) and a model of normal aging (C57Bl6 mice of 6 and 14 months). Executive and memory functions were preserved in 6 and 14 month-old C57Bl6 mice. However, we found spatiotemporal and working memory disorders in APPPS1 mice of 14 months. In 6 month-old ApoE4 mice, we found a flexibility deficit in the aquatic Y-maze task but no memory deficit in the Starmaze task. Interestingly, the deficit observed in the ApoE3 mice at 6 months was observed in ApoE4 mice at 14 months. Altogether these results reveal how navigation tasks allow the evaluation of memory and executive function during aging.

P19 - Alpha-Mangostin Prevents Scopolamine-induced Cognitive Deficit through Inhibition of Caspase-3

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The expression of apoptosis related proteins as active caspase-3, procaspase-9, and PARP were increased by scopolamine which play a role in the pathogenesis of neurodegenerative diseases. Caspase-3, procaspase-9, and PARP served as markers for apoptosis were markedly increased in the brain which is associated with neurotoxicity. As such, inhibition of caspases is considered as a tool for prevention and compensation of various synaptic pathologies leading to cognitive deficit and Alzheimer's disease pathogenesis. The extract from the pericarp of mangosteen (*Garcinia mangostana L.*) was previously reported to protect against cytotoxicity *in vitro* and improve spatial memory in scopolamine (SCOP)-induced amnesic rats. We therefore examined the ability of α-mangostin (α-MG), an aprenylated xanthone derivative from the extract, to attenuate SCOP-induced neurotoxicity in rat brains. Eight groups (n=8 each) of 8-weeks-old male Wistar rats were i.p. injected with donepezil (2 mg/ml/kg), α-MG (50 mg/ml/kg), α-MG (100 mg/ml/kg), or vehicle (1 ml/kg) followed by SCOP (2 mg/ml/kg, i.p.) or NSS (1 ml/kg, i.p.). Thirty minutes later, the learning and memory performances were assessed using Morris water maze test. All rats received four trials per day. These procedures were repeated for 7 days. On day 7, all rats were tested in the probe trial. After trials, the animals were sacrificed and three brain regions (basal forebrain, cerebral cortex, and hippocampus) were dissected and homogenized for biochemical analysis to investigate caspase-3 activity. The results showed that donepezil and α-MG (50 and 100 mg/ml/kg) given to rats before SCO-administration could improve learning and memory in Morris water maze test by decreasing time to find platform on training session and increasing both time spent and number of entries into the target quadrant in probe-trial session when compared to their control groups. In biochemical analysis, no significant difference was found between groups in NSS treatment in all studied brain regions. SCOP significantly elevated caspase-3 activity in all brain regions, compared to their respective NSS groups ($P<0.05$). Pretreatment of donepezil and α-MG (50 mg/ml/kg), but not α-MG (100 mg/ml/kg), significantly attenuated the increase of caspase-3 activity induced by SCOP in cerebral cortex and hippocampus ($P<0.05$). In basal forebrain, all pretreatments had no effect on the increase of caspase-3 activity induced by SCOP. The results demonstrated neuroprotective effect of α-MG against SCOP neurotoxicity. The present study is the first report on α-MG as a potential neuroprotective candidate. Its underlying mechanisms by which α-MG improves learning and memory may be involved in ameliorating scopolamine-induced neurotoxicity via activation and subsequent expression of apoptotic enzymes.

P20 - Investigating the role of noradrenaline in olfactory discrimination during aging

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Normal aging is accompanied by structural changes in the brain and by sensory and cognitive declines. However, some aged individuals maintain unexpectedly good cognitive abilities in spite of brain alterations while others are largely affected. The concept of cognitive reserve proposes that the degree of intellectual stimulation throughout the adult life contributes to these individual differences. NA has been recently proposed as a candidate link between cognitive activities and neuronal plasticity during the cognitive reserve buildup.

My project investigates the role of NA in the cognitive reserve build-up and its contribution to the maintenance of structural plasticity and cognitive abilities during aging. To do so, we use the model of olfactory perceptual learning that induces an improvement in discrimination between perceptually close odorants after repeated exposure to these odorants. This learning is dependent on Noradrenaline release and aged mice are deficient in perceptual learning. We thus stimulated local Noradrenaline release within the olfactory bulb by optogenetic stimulation of the noradrenergic fibers in young and aged mice. Our results show that optogenetic stimulation of Noradrenaline release in the olfactory bulb improved olfactory discrimination in both young and aged mice, thereby mimicking olfactory perceptual learning. However, aged mice required a longer duration of stimulation in order to improve olfactory discrimination performances (20 days), compared to young adults (10 days). These results suggest that Noradrenaline is involved in the maintenance of olfactory discrimination learning during aging. Ongoing studies investigate the structural plasticity of adult-born neurons in the olfactory bulb, in order to identify the cellular basis of the improved olfactory discrimination performances.

This project is funded by ARC2 Region Auvergne Rhône-Alpes.

Name index

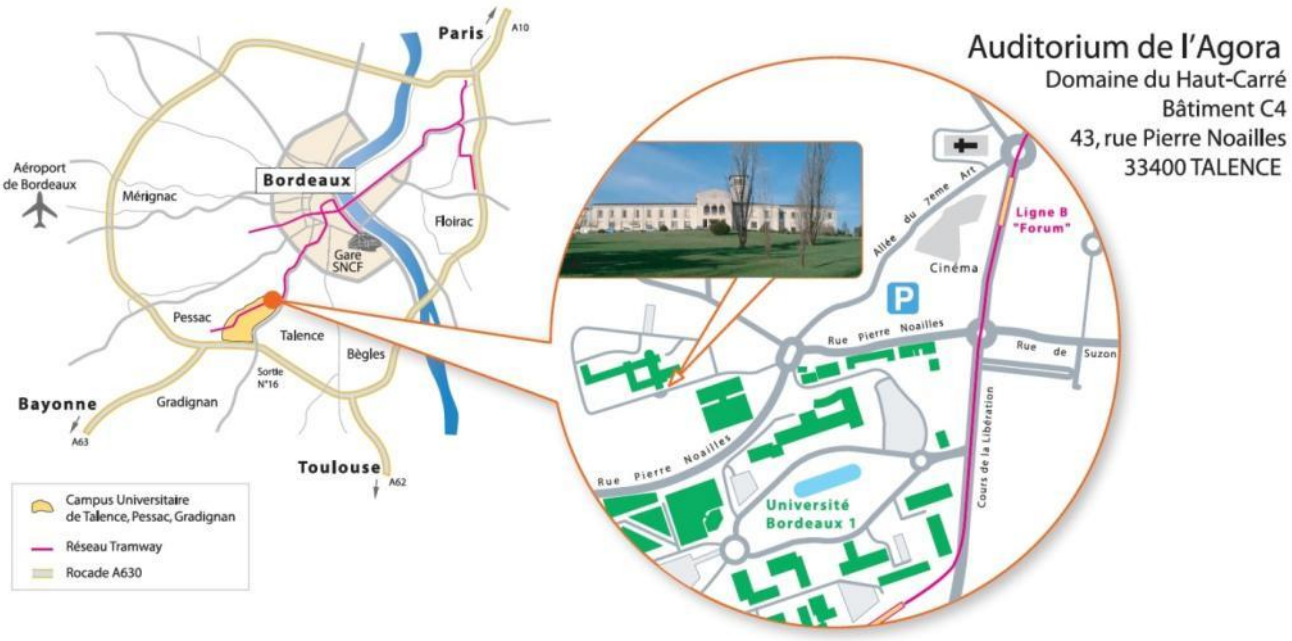
Practical information

Where and when

The conference will take place **from 26 to 28 September 2018** in l'Agora du Haut-Carré (Espace AGORA, Domaine du Haut Carré, Campus de l'Université de Bordeaux, 43 rue Pierre Noailles, TALENCE).

Agora du Haut-Carré is an unusual setting, being housed in a former convent built in the 1950's. It is located in the southwest of the city on the Bordeaux University campus, it has a direct access to Bordeaux city center by the tramway in less than 25 minutes.

Haut Carré is on the line B of the tramway. Station name : Forum



GPS: Latitude 44.810012 - Longitude -0.59645

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Security

Due to « vigipirate » safety,

- Please wear your badge all the time,
- Please avoid to come with your luggage,
- Bags will be checked at the entrance.

Thank you for your understanding.

Wifi

Choose the ’REAUMUR’ wireless network

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Choose ’Conferences/Invites’

Identify yourself with:

Login: NEUROCAMPUS−n−1

Password: YAat=hL

Gala dinner

Thursday, September 27th
only for participants registered to the gala dinner

Château Luchey-Halde is located in the heart of Bordeaux, in the prestigious Pessac-Léognan appellation, and benefits from an exceptional terroir.
It is constituted of several ridges which contain gravel, pebbles and fine soil deposited by the Garonne River and its tributaries between the end of the Tertiary and the beginning of the Quatenary periods. It is a poor but well-drained soil perfectly adapted to winegrowing in the oceanic climate of Bordeaux.

How to get there ?

By tram : line A – Stop: "fontaine d'Arlac" stop
By taxi : adresse is "17 avenue du Maréchal Joffre – Mérignac »

https://www.google.com/maps?ll=44.81992,-0.630384

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