autosomal dominant samples. In addition, one sporadic patient consistently showed aberrant levels of secreted Aß in neurons, a phenotype not observed in the parental primary cells, suggesting the possibility of a cell type-specific aberration. **Conclusions:** This study demonstrates a method of modeling AD pathogenesis in live, human neurons using reprogrammed patient samples. Our results suggest that reprogrammed neurons can provide new insights into autosomal dominant and sporadic AD pathogenesis, and a platform for therapeutic development.

P4-056 ASSOCIATION OF SERUM LEPTIN LEVELS WITH COGNITIVE DECLINE IS DEPENDENT ON BODY MASS INDEX

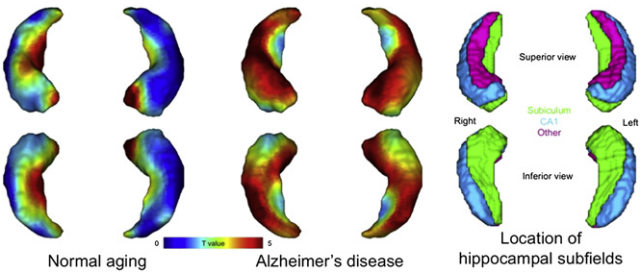
David J. Llewellyn[1], Katarina Kos[1], Kenneth M. Langa[2,3], Luigi Ferrucci[4], William E. Henley[1], Iain A. Lang[1], Robert Clarke[5], Helen Chiu[6], Juan Li[7], Antonio Cherubini[8], David Melzer[1], *[1]Peninsula Medical School, Exeter, United Kingdom; [2]University of Michigan, Ann Arbor, MI, USA; [3]Veterans Affairs Center for Practice Management and Outcomes Research, Ann Arbor, MI, USA; [4]National Institute on Aging, Bethesda, MD, USA; [5]University of Oxford, Oxford, United Kingdom; [6]Chinese University of Hong Kong, Hong Kong, China; [7]Chinese Academy of Sciences, Beijing, China; [8]Perugia University Hospital and Medical School, Perugia, Italy. Contact e-mail: david.llewellyn@pms.ac.uk.*

Background: Low levels of the adipokine leptin have been identified as a potential risk factor for incident Alzheimer's disease and cognitive decline. A significant interaction between leptin and body mass index was noted previously, possibly due to central leptin resistance which is well recognized in satiety signaling. Our objective was to relate baseline circulating leptin levels in a population-based sample of older adults to substantial cognitive decline. **Methods:** We determined whether high levels of serum leptin were associated with a reduced risk of substantial cognitive decline in the InCHIANTI study conducted in Italy between 1998 and 2006 with follow-up assessments every 3 years. 752 adults aged 65 years or more completed interviews, cognitive assessments, medical examinations, and had valid serum leptin measurements. Cognitive decline was assessed using the Mini-Mental State Examination (MMSE; substantial decline defined as $\geq$3 points) and the Trail Making Tests A and B (substantial decline defined as worst 10% of the distribution of decline or if testing discontinued). **Results:** Higher leptin levels were associated with a reduced risk of substantial cognitive decline on the MMSE in multivariate adjusted models (relative risk [RR] per 1-SD increment in sex-standardized log leptin was 0.81 [95% CI, 0.66-0.98]). There was a significant interaction between leptin levels and BMI ($P = 0.01$). The association was significant in non-obese participants (RR = 0.76, 95% CI = 0.60-0.96), although there was little evidence for an association in obese participants (RR = 1.10, 95% CI = 0.65-1.87). Elevated leptin was also significantly associated with a lower risk of substantial decline on both Trail Making Tests A and B. The same pattern of results was observed when adjusting for self-reported weight (kg) at 50 years of age or change in weight from 50 years of age to baseline (kg/year). Degree of cognitive decline was not associated with leptin levels at the 6-year follow-up or change in leptin levels in multivariate adjusted models. **Conclusions:** High serum leptin levels are associated with a reduced risk of substantial cognitive decline in the elderly over a six year period. In lean older adults leptin treatment may have therapeutic potential, whereas in obese older adults leptin resistance should be addressed.

P4-057 A NEW MR SEQUENCE ON A 3T SCANNER TO ASSESS THE VOLUME OF HIPPOCAMPAL SUBFIELDS: CONTRASTED EFFECTS OF NORMAL AGING AND ALZHEIMER'S DISEASE

Renaud La Joie[1], Béatrice Desgranges[2], Florence Mezenge[1], Brigitte Landeau[1], Audrey Perrotin[1], Alice Pèlerin[2], Vincent de la Sayette[2], Francis Eustache[2], **Gael Chételat**[1], *[1]Inserm - EPHE - Université de Caen/Basse-Normandie, Caen, France; [2]Inserm - EPHE - Université de Caen/Basse-Normandie, Caen, France. Contact e-mail: chetelat@cyceron.fr.*

Background: Recent neuroimaging advances have stressed the interest of assessing hippocampal subfields separately rather than considering the hippocampus as a whole, notably to highlight specific effects of diseases on this structure. Whereas the pattern of hippocampal atrophy in Alzheimer's disease (AD) is relatively well-known (involving an early and marked atrophy of the CA1 subfield), the effect of normal aging is still a source of debate as discrepant findings have been reported. **Methods:** To further investigate this question, we developed a new high-resolution proton-density weighted magnetic resonance sequence using a 3-Tesla scanner, together with tracing guidelines to delineate hippocampal subfields. Three regions of interest (ROI) were manually drawn on both hippocampi of 50 healthy subjects between 18 and 68 years old and 10 patients with AD: CA1, Subiculum and Other (including CA2-3-4 and Dentate Gyrus). We also applied a simpler and less time-consuming method based on the widely-used automatic Voxel-Based Morphometry (VBM) technique onto standard T1-weighted images obtained in the same subjects. The effect of age was assessed with both methods in the healthy controls using correlation analyses, and patients with AD were compared to healthy elderly. **Results:** A significant effect of age was observed on the volume of the subiculum with CA1 and Other subfields being relatively spared with age, while a decrease in the volume of CA1 was found in AD. Although less precise than the ROI technique, the VBM method led to consistent findings, showing a stronger effect of age on the medial border of the hippocampus corresponding to the subiculum while AD preferentially affected the lateral portions mainly superposing to the CA1 subfield (see figure below). The VBM automatic technique thus appears as a reliable alternative to assess volumetric changes within the hippocampus, especially to distinguish CA1 and subiculum subfields. **Conclusions:** Our finding of a specific effect of age on the subiculum are consistent with the developmental hypothesis ("last-in first-out" theory) and contrasts with the predominant vulnerability of the CA1 subfield in AD. Those results suggest that assessing the volume of hippocampal subfields may improve the discrimination between normal and pathological aging.



P4-058 PRESENILIN 2 IS THE PREDOMINANT GAMMA-SECRETASE IN MICROGLIA AND REGULATES CYTOKINE RELEASE

Suman Jayadev, Amanda M. Case, Alison J. Eastman, Wiley C. Jesse, Thomas Moeller, Richard S. Morrison, Gwenn A. Garden, *University of Washington, Seattle, WA, USA. Contact e-mail: sumie@u.washington.edu.*

Background: Mutations in Presenilins (PS) cause early onset familial Alzheimer's disease (AD) by mechanisms that have not been fully elucidated. Modulating the activity of PS and the gamma-secretase complex is a possible therapy for AD, and thus a better understanding of PS function in the central nervous system (CNS) is needed. PS1 and PS2 are expressed in many CNS cell types including microglia, the innate immune cell of the brain. We sought to investigate the impact of gamma-secretase inhibition and specific PS deficiency in microglia. **Methods:** We measured Lipopolysaccharide (LPS) induced cytokine release by primary murine microglia exposed to the pharmacological gamma-secretase inhibitor, DAPT. Similar