Dementia 13: 152-167), block this nutrient-induced mitochondrial activity (NiMA) by a mechanism dependent on tau. Remarkably, AβO-mediated inhibition of NiMA was completely restored when mTORC1 was forced to lysosomes by expressing a Raptor construct fused to the lysosomal targeting signal of Rheb15. Furthermore, NiMA was found to be insensitive to nutrient stimulation when lysosomal mTORC1 was constitutively activated by antisense-mediated reduction of Tsc2 or Nprl3, the main components of two lysosomal negative regulators of mTORC1, the TSC and GATOR1 complexes. NiMA was also found to suppress mitochondrial DNA synthesis, which can be overridden by AβO-mediated activation of mTORC1 at the PM. Finally, evidence for NiMa *in vivo* was provided by MP-PAM analysis of brain blood flow following local application of amino acids to the cortex via a cranial window. **Conclusions:** Our collective results indicate that lysosomal mTORC1 functionally couples nutrient availability to mitochondrial metabolism, and mechanistically links mitochondrial dysfunction to AD. Moreover, they reinforce evidence that AβOs and soluble forms of tau work coordinately to drive AD pathogenesis.

O2-12-03 MUTATIONS IN PSEN GENES ASSOCIATED WITH FAMILIAL FORM OF ALZHEIMER'S DISEASE DISPLAY AN IMPAIRED BLOOD-BRAIN BARRIER PHENOTYPE IN VITRO

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Background: Mutations in presenilin genes PSEN1 and PSEN2 constitute the second and third common gene mutations associated with the familial form of Alzheimer's disease (FAD). Yet, the impact of such mutations on the blood-brain barrier function and Aβ clearance remains unknown. In this study, we investigated the impact of PSEN1 and PSEN2 mutations on the blood-brain barrier function. **Methods:** Induced pluripotent stem cells (iPSCs) from two patients suffering from FAD and harboring a mutation in PSEN1 (A246E) or PSEN2 (N414I) were used in this study, as well as two respective iPSCs from parental controls. iPSCs were differentiated into astrocytes and brain microvascular endothelial cells following established differentiation protocols. Barrier function was assessed using trans endothelial electrical resistance (TEER) and permeability to fluorescein. BBB markers expression was assessed by immunofluorescence and immunoblot. Cell metabolic activity was assessed using MTT assays. Glucose uptake was assessed using [14C]-glucose. **Results:** PSEN1 but not PSEN2 patient-derived BMECs showed impaired barrier function compared to their respective parental controls, as measured by lower TEER and higher permeability. We also noted differences a lower expression of tight junction proteins in PSEN1-derived BMECs. We noted a decreased expression and activity in MRP1 and P-gp activity in PSEN1 and PSEN2 iPSC-derived BMECs compared to their respective controls. Furthermore, both FAD-derived astrocytes and BMECs showed lower glucose uptake and lower cell metabolic activity compared to controls. No differences in barrier induction by astrocytes were noted. **Conclusions:** FAD-associated PSEN mutations appear associated with dysfunctions in the blood-brain barrier tightness, drug efflux activity and glucose metabolism. We are currently assessing the presence of a difference in Aβ clearance.

O2-12-04 STALLED BLOOD FLOW IN BRAIN CAPILLARIES IS RESPONSIBLE FOR REDUCED CORTICAL PERFUSION AND IMPACTS COGNITIVE FUNCTION IN MOUSE MODELS OF ALZHEIMER'S DISEASE

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Background: A reduction of ~30% in cerebral blood flow is observed in patients and animal models of Alzheimer's disease (AD). Although this hypoperfusion likely contributes to cognitive impairment and disease progression, no physiological explanation for this phenomenon has emerged. We observed that leukocytes often occlude capillaries in the brains of AD mouse models, thereby stopping blood flow in the smallest brain blood vessels. Here, we tested the hypothesis that these leukocytes stalls contribute to the blood flow reduction and cognitive impairment. **Methods:** Using in vivo two-photon excited fluorescence imaging in transgenic AD mice (APP/PS1), we quantified the number of flowing and stalled cortical capillaries, and measured blood flow speed in penetrating arterioles as well as

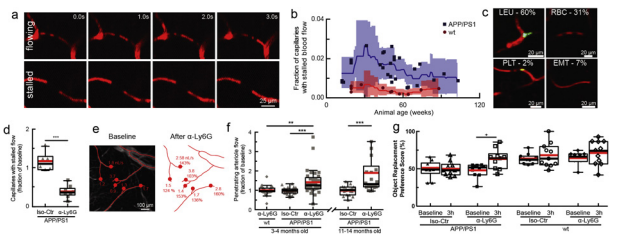

Fig.1. Stalled capillaries occured at increased incidence in mouse models of Alzheimer's disease, were caused by adhered neutrophils, and contributed to blood flow and cognitive deficits, (a) Individual brain capillaries were scored as flowing or stalled based on the motion of unlabeled blood cells (black) within the fluorescently labeled blood plasma (red), (b) Fraction of capillaries with stalled blood flow in APP/PS1 and wt mice as a function of age. One outlier not shown: APP/PS1, 42 weeks, 4.4% stalled. Shaded regions indicate 95% confidence intervals, (c) 2PEF images of capillaries stalled by a leukocyte (LEU), red blood cells (RBCs), and platelet aggregates (PLT), or found empty of blood cells (EMT), distinguished by fluorescent labels (red: Texas Red-labeled blood plasma; yellow: rhodamine 6G-labeled leukocytes and platelets; green: Hoechst-labeled leukocyte nuclei).The percentage of stalled capillaries due to each cause in the APP/PS1 mice is indicated in each image, (d) Number of capillaries with stalled blood flow ~1 hr after administration of antibodies against Ly6G (α-Ly6G) or isotype control antibodies (Iso-Ctr) shown as a fraction of the number of stalled capillaries at baseline, (e) Projection of 2PEF image stack of brain surface vasculature, with surface (red lines) and penetrating (red dots) arterioles identified. For each penetrating arteriole, volumetric blood flow is indicated at baseline (left) and after α-Ly6G administration (right), along with the percentage of baseline flow, (f) Volumetric blood flow in penetrating arterioles measured 60-90 min after α-Ly6G or Iso-Ctr antibody administration in young and old APP/PS1 mice and wt control animals shown as a fraction of baseline arteriole flow, (g) Preference score in object replacement task for APP/PS1 and wt mice at baseline and at 3 hr after a single administration of α-Ly6G or Iso-Ctr antibodies.

performance on memory tasks before and after treatment with antibodies that reduce the incidence of capillary plugging. **Results:** About 1.5% of cortical capillaries were transiently stalled in AD mice, leading to an overall reduction in cerebral blood flow (CBF). These stalls were released using an antibody against the neutrophil cell surface protein Ly6G, resulting in an immediate ~25% increase in CBF and an immediate improvement in performance on short-term memory tasks. Mice treated with an isotype control antibody showed no improvement in CBF or memory performance. In a second set of experiments we deterimend that reducing capillary stalls and increasing CBF led to improved cognitive performance in mice with relatively advanced AD pathology (17 month old APP/PS1 mice, first cognitive impacts detectible at 8 months). **Conclusions:** In this study we uncovered leukocyte adhesion in brain capillaries as a mechanism contributing to reduced CBF in AD mouse models and showed that blocking this adhesion leads to immediate cognitive benefits even in advanced stages of disease development.

O2-12-05 **WITHDRAWN**

O2-12-06 **NEUROPATHOLOGICAL FINDINGS DRIVEN BY AN APOEε4 LIVER PHENOTYPE**

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Background: Presence of the APOE4 allele is the main risk factor for neurodegenerative diseases like Alzheimer's disease (AD) and dementia with Lewy bodies. APOE4-carriers exhibit low plasma levels of apolipoprotein E (apoE). A higher relative ratio of apoE4 to apoE3 plasma levels in healthy APOE3/4 carriers were previously associated with reduced gray matter volume and glucose hypometabolism in several brain areas relevant to AD. The peripheral pool of apoE, which is mainly produced by the liver, may be directly associated with the increased risk of neurodegenerative disease in APOE4-carriers. **Methods:** FRGN-mice with humanized livers through hepatocyte transplantation exhibit a human-like plasma profile including human apoE and serve as a proof-of-principle model to study the effect of a liver APOE4 phenotype on the brain. Neuropathological changes including synaptic degeneration and inflammation as well as levels of APP and alpha-synuclein were assessed in synaptosomal preparations using western blot. **Results:** No human apoE levels were detected in the FRGN mouse brains whereas several changes in synaptic markers were observed in mice that harbored human APOE4/4 hepatocytes compared to APOE2/3 hepatocytes. In the cortex, APOE4/4-harboring mice exhibited astrocytosis and increased levels of TNF-a alongside altered levels of PSD-95 and NMDA receptors. The hippocampi of the same animals demonstrated altered levels of APP, alpha-synuclein, GFAP and CD11b. **Conclusions:** A liver APOE4 phenotype is clearly linked to neuroinflammation and synaptic alterations despite the fact that apoE does not cross the blood-brain-barrier, and may be the risk determinant for neurodegenerative disease in APOE4-carriers.

ORAL SESSIONS
O2-13
NEUROIMAGING: VASCULAR DISEASE IN THE AGING BRAIN

O2-13-01 **INCIDENCE OF CEREBRAL MICROBLEEDS AND AMYLOID BURDEN: THE MAYO CLINIC STUDY OF AGING**

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Background: Cerebral microbleeds (CMBs) are associated with underlying cerebral amyloid angiopathy (CAA) when located in a lobar distribution, and hypertensive arteriopathy when located in deep regions. However, the temporality of the association between amyloid PET and CMBs has not been examined. The objectives of this study were to determine the incidence of CMBs and whether amyloid burden on PET is associated with incident CMBs. **Methods:** We analyzed 567 Mayo Clinic Study of Aging participants age 50 years and older (54% male) with 3T MRI scans with at least two separate T2* GRE sequences from October 2011-August 2017. 489 (86%) underwent C-11-Pittsburgh Compound-B (PiB) PET scans at the time of the baseline MRI scan. We performed logistic regression analyses to examine the relationship between demographic factors and odds of incident CMBs (having developed on subsequent neuroimaging). We stratified by location to examine the relationship between PiB SUVR and lobar versus deep CMBs. **Results:** The mean age (SD) of participants was 69.4 (9.8) years at baseline. 84 participants (15%) had at least one baseline CMB. The mean (SD) of the time interval between scans was 2.6 (0.9) years. The incidence of any CMB over the follow-up period was 9%. CMB incidence increased with age, from 5% in persons aged 50 to 59 years to 15% in participants of 70 years and older. Male sex (odds ratio (OR) (95% confidence intervals [CI]) (2.12 [1.15, 3.91], p= 0.02) and greater PiB SUVR (2.65 [1.45, 4.83], p<0.001) were associated with increased odds of having an incident CMB while APOE ε4 carrier status was not (1.29 [0.71, 2.34]p=0.41). In a subsequent logistic regression analysis adjusting for age, sex, and APOE ε4 carrier status, greater PiB SUVR was associated with incident CMBs (1.48 [1.00, 2.17]p=0.048). When stratified by location, greater PiB SUVR was associated with lobar (1.62 [1.07, 2.45]p=0.02), but not deep CMBs (1.22 [0.59, 2.53] p=0.59). **Conclusions:** The frequency of new CMBs in the Mayo Clinic study of aging was 9% over an average of 2.6 years of follow-up. Greater amyloid PET burden was associated with the development of lobar, but not deep CMBs supporting CAA as the underlying pathophysiology.