

assessed in the Y-maze. *In vivo* signals were confirmed by autoradiography and immunohistochemistry in brain sections from scanned mice. **Results:** A progressive, age-dependent reduction in  $^{18}\text{F}$ -BCPP-EF uptake was observed in hippocampal and forebrain regions of tauTg mice, coinciding with the development of tau lesions detected by  $^{11}\text{C}$ -PBB3 PET. A strong association was observed between MC-I signals detected by PET, hippocampal volume assessed by MRI, and learning and memory performance in the Y-maze task. *In vivo* findings were confirmed by  $^{18}\text{F}$ -BCPP-EF autoradiography and immunohistochemistry for AT-8 (tau phosphorylation), GFAP (astrocytes), IBA-1 (microglia), NeuN (neurons). **Conclusions:** MC-I PET may provide a useful non-invasive imaging biomarker for the real-time identification of early-stage mitochondrial abnormalities associated with tau-induced neurodegenerative cascades.

**IC-P-023** **CEREBRAL PERFUSION IN THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE**



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**Background:** The need for early, definitive diagnosis of Alzheimer's disease (AD) is imperative for disease management, and will increasingly rely on improved neuroimaging techniques. Functional neuroimaging with  $^{99\text{m}}\text{Tc}$ -hexamethylpropylamino-oxime ( $^{99\text{m}}\text{Tc}$ -HMPAO) SPECT has been used as an ancillary test in AD to evaluate cerebral blood flow. Specific patterns of hypoperfusion and hypometabolism have been established in human AD using  $^{99\text{m}}\text{Tc}$ -HMPAO-SPECT and  $^{18}\text{F}$ FDG-PET, respectively. Hypometabolism has been observed in the 5XFAD mouse; however, it is unknown whether hypoperfusion signatures of AD are also present in 5XFAD, often used for diagnostic/therapeutic drug development. We seek to assess baseline perfusion in the 5XFAD mouse using  $^{99\text{m}}\text{Tc}$ -HMPAO SPECT and determine whether perfusion signatures of human AD are recapitulated in this model. **Methods:** Male 5XFAD (n=3) and age-matched wild-type (WT) (n=2) mice at 12 months underwent SPECT scanning 20min after  $^{99\text{m}}\text{Tc}$ -HMPAO administration and subsequently imaged using CT/MRI. Whole brain standardized uptake values (SUVs) were compared. **Results:** Preliminary results indicate that, in the 5XFAD brain, patterns of hyperperfusion, rather than hypoperfusion are seen with significantly greater (60%) whole brain SUVs observed in 5XFAD compared to WT (p=0.009). **Conclusions:** Early evidence suggests an apparent disconnect between cerebral blood flow and glucose metabolism (neurovascular decoupling) in the 5XFAD brain. A full study to establish regional patterns of perfusion in 5XFAD mice is warranted to further evaluate disease progression in this model. Establishing these baseline perfusion patterns is extremely valuable and identifying discrepancies from human AD should be taken under advisement in pre-clinical diagnostic and therapeutic drug discovery programs.

**IC-P-024** **INVESTIGATING GLYMPHATIC FUNCTION DURING EARLY TAU PATHOLOGY USING DYNAMIC CONTRAST-ENHANCED MRI**



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**Background:** The glymphatic system describes the cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange pathway that facilitates efficient clearance of solutes and waste from the brain [1]. Because waste solutes, such as amyloid- $\beta$  and tau, can depend on the glymphatic pathway for clearance, we proposed that failure of this clearance system may contribute to tau accumulation and Alzheimer's disease (AD) progression. Using dynamic contrast-enhanced MRI, we visualised CSF-ISF exchange across the mouse brain following subarachnoid contrast agent administration. We previously provided evidence that glymphatic clearance is impaired during the later stages of tauopathy[2]. Here we investigate glymphatic function in the early stages prior to the onset of mature tangle formation and neurodegeneration to identify the stage at which glymphatic clearance becomes impaired during the pathological tau accumulation in the mouse brain. **Methods:** Glymphatic clearance in rTg4510 and litter-matched wildtype mice at 2.5 months and 5 months of age was captured using contrast-enhanced MRI. Gadolinium was infused intracisternally and its whole brain distribution was dynamically imaged in real-time using T1-weighted MRI. Histological assessment of astrocytes surrounding blood vessels and quantification of aquaporin-4 expression was also performed, as derangement of this water channel in glymphatic impairment was previously found in rTg4510 aged mice [2]. **Results:** Glymphatic CSF-ISF exchange was not impaired in 2.5 month old rTg4510 mice prior to mature tangle formation, compared to wildtype animals. However, there was a marginal elevation of CSF-ISF exchange at 5 months of age in rTg4510 mice with the presence of mature tangles. **Conclusions:** In the context of our previous findings at 8.5 months in rTg4510 mice [2], impaired glymphatic clearance from the brain is dependent on the onset of neurodegeneration and is not influenced by intracellular tangle formation. This suggests that glymphatic impairment is a consequence rather than a contributor to tau pathology in this tauopathy model. This is in line with elevated CSF tau in AD patients. Changes in expression and polarisation profiles of astrocytic aquaporin-4 may highlight possible roles of this protein in preceding impaired glymphatics in this mouse model. References: [1] Iliff, J.J. et al. (2012), *SciTransMed*, 4(147):p.147. [2] Harrison, I.F. et al., (2015), *Alz&Dementia*, Supplement IC-P-160. 11 (7):p.P107.

**IC-P-025** **THALAMIC CONNECTIVITY CONTRIBUTES TO EPISODIC MEMORY IN MILD COGNITIVE IMPAIRMENT**



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**Background:** The medial temporal lobe has traditionally been viewed to instigate episodic memory loss. However, a more extended memory circuit might be involved, in particular the limbic thalamus with its rich hippocampal connections. In addition, the topology of whole-brain networks has been related to cognitive decline. We investigated how hippocampal and thalamic connectivity, as well as whole-brain structural network topology, are related to episodic memory in mild cognitive