intensive period of treatment from 3.03 [3.03-3.2] % at baseline up to 11.37% [11.37%-14.45%] (median-IQR; $p<0.05$) before the last PE; while untreated group did not show any change. This effect was associated with the treatment intensity and, interestingly, correlated with Aβ mobilization observed in plasma after TPE in the same Phase II study ($r=0.6022$; $p<0.0001$). **Conclusions:** Albumin from AD patients is impaired, at least in its antioxidant capacity, in comparison with healthy subjects. TPE with albumin replacement in AD patients seems to have an effect on albumin oxidation status that correlates with plasma Aβ mobilization. Further investigation is warranted to better understand the mechanisms underlying AD therapy based on TPE followed by albumin replacement.

P2-068 RATIONAL DESIGN OF APOE4 MUTANTS AS A TOOL FOR CELLULAR STUDIES IN ALZHEIMER'S DISEASE

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Background: The incidence rate of Alzheimer's disease (AD) is rising, thus, there is an urgent need for new therapeutic avenues. In this regard, the ApoE4 genotype is considered the most important genetic risk factor for AD. One leading hypothesis is that the ApoE4 protein accesses an intermediate conformational state, which may cause mitochondrial stress, beta-amyloid aggregation, and tau protein post-translational modifications, ultimately leading to AD. However, ApoE4 amphipathic properties constitute a major hurdle for comprehensive protein folding, and structural studies, as well as for structure-based drug design campaigns. Currently, an NMR-derived structure of a monomeric ApoE mutant, and a computational model of an ApoE4 intermediate state have been reported in literature. These two structural models may provide insight into the ApoE4 pathological mechanisms implicated in AD. The goal of this study is to rationally design mutations that alter the structural stability of the native and intermediate conformations of ApoE4 with the aim to clarify the role of these specific states in AD onset. **Methods:** Models for the native and intermediate conformations of wild type (WT) ApoE4 have been derived using NMR spectroscopy data and discrete molecular dynamics simulations, respectively. Mutations altering the structural stability of the two ApoE4 conformations have been modeled using Eris, an in-house developed software that evaluates the relative thermodynamic stability ($\Delta\Delta G$) of potential mutations in a given protein structure. **Results:** Several mutations, computationally introduced throughout the WT-ApoE4 structure, exhibited $\Delta\Delta G$ values that specifically alter the conformational stability of the ApoE4 intermediate state. In particular, the hydrophobic mutations R213Y, K242I and E231I, are directly responsible for the further stabilization of N- and C-terminal domain interactions, which characterize the ApoE4 intermediate conformation. Additionally, destabilizing mutations such as W210P and R90F are found within regions of intra-domain protein interactions or in ApoE4 distal helices. **Conclusions:** The set of predicted mutations suggests the possibility to control the stability of different conformational states of ApoE4. This data can provide useful information on the role of an ApoE4 intermediate state in AD pathogenesis, and provide a tool for the future development of conformation-driven in-cell studies.

P2-069 RESTING-STATE ABNORMALITIES IN AMNESTIC MILD COGNITIVE IMPAIRMENT: A META-ANALYSIS

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Background: Amnestic mild cognitive impairment (aMCI) is a prodromal stage of Alzheimer's disease (AD). Once diagnosed, AD is irreversible and there is currently no effective drug that can cure this disease. Therefore, early diagnosis and intervention for aMCI are urgently needed. The standard diagnostic procedure of aMCI primarily relies on subjective neuropsychological examinations that required the judgment of experienced clinicians. It is necessary for the development of other objective and reliable aMCI markers, such as neural markers. Previous neuroimaging studies revealed abnormalities in regional resting-state activity in MCI patients, however, the findings are being inconsistent. The current study provided an updated activation likelihood estimation (ALE) meta-analysis of resting-state functional magnetic resonance (fMRI) data on aMCI. **Methods:** The authors searched on the MEDLINE/PubMed databases for whole-brain resting-state fMRI studies on aMCI published until March 2015. Twenty-one wholebrain resting-state fMRI studies that reported a total of 156 distinct foci in either Montreal Neurological Institute (MNI) or Talairach coordinates were included. Studies were excluded if (1) only non-amnestic MCI or only subtypes of aMCI were included and without a control group; (2) subjects had a history of neurological, psychiatric, or any systemic disease that could influence cognitive functions (e.g., stroke, depression, alcoholism, drug abuse); (3) a priori region of interest (ROI) analysis or a seed-based functional connectivity analysis was conducted; or (4) the effects of medication were tested without reporting fMRI data at baseline. **Results:** Significant regional resting-state differences were consistently found in the posterior cingulate cortex (PCC), right angular gyrus, right parahippocampal gyrus, left fusiform gyrus, left supramarginal gyrus and bilateral middle temporal gyri in patients with aMCI relative to controls. **Conclusions:** Our findings support that abnormalities in resting-state of these regions may serve as neuroimaging markers for aMCI.

P2-070 SEEAB^3: A NOVEL METHOD FOR VOLUMETRIC ANALYSIS OF AMYLOID PLAQUES

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Background: One of the main neuropathological hallmarks of Alzheimer's disease (AD) is the presence of plaques which consist of aggregated extracellular amyloid beta (Aβ) protein. Patients with early onset or familial AD (FAD) often harbor genetic mutations that bias processing towards this amyloidogenic outcome, accelerating disease onset and worsening disease severity. Elevated levels of Aβ peptides are thought to be a key component of the disease state; thus, characterizing the spatial and temporal profile of amyloid plaque deposition may yield important insights into the mechanisms that cause and

exacerbate AD pathology. Therefore, we have developed a new method which permits high throughput, detailed analysis of plaque deposition on entire intact brain regions. **Methods:** In order to more easily and precisely quantify amyloid plaque deposition, we have developed a new method which permits high throughput, detailed analysis on entire intact brain regions. This method relies on the use of the lipophilic dye BTA-1, which was developed as an in vivo biomarker to detect amyloid plaques with PET imaging, combined with an optical clearing method called SeeDB in which the refractive index of the sample is altered to minimize light scatter during imaging. As a result, amyloid plaques can be visualized throughout significanlty thicker sections of tissue (up to 1 mm), and because SeeDB does not cause sample swelling, z-stack images rendered in 3D yield much more accurate size, shape, and volume measurements. In addition, vascular architecture can be analyzed in the same sections by using a fluorescently conjugated (Dylight 594) form of Lycopersicon Esculentum (tomato lectin) which is injected iv prior to sacrifice. **Results:** Our preliminary studies demonstrate that this approach provides high resolution detection of amyloid plaques as well as quantitative analysis of vascular networks in the 5xFAD mouse model of AD. **Conclusions:** We anticipate that the use of this method will afford a more complete and accurate characterization of amyloid plaque deposition throughout the progression of AD.

P2-071 SUPER RESOLUTION MICROSCOPY OF INTACT BRAIN WHITE MATTER

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Background: The wavelength of visible light imposes a size limit (approx. 250 nm) on the objects that can be resolved with light microscopy. Super resolution microscopy methods have recently permitted greater spatial resolution using light microscopy. These include stochastic optical reconstruction microscopy (STORM) and super-resolution optical fluctuation imaging (SOFI). Here we applied super resolution methods to histological sections of brain white matter. **Methods:** Frozen sections of subcortical white matter were mounted on coverslips and immuno-labelled by standard methods. Primary antibody labelling was visualised with Alexafluor647-labelled secondary antibodies and YOYO-1 nuclear DNA stain. Coverslips were imaged in standard STORM buffer, using a 640 nm laser (676/37 nm band-pass filter) and 488 nm laser (525/30 nm band-pass filter). **Results:** We report STORM and SOFI imaging of white matter sub-cellular structures (<1 micron) in rodent and human subcortical white matter. These include axonal filaments (immuno-labelled for neurofilament NF200), myelin sheaths (myelin-associated glycoprotein) and astrocytic filaments in fibrous astrocytes (GFAP). **Conclusions:** Sub-cellular structures can be resolved by STORM and SOFI in frozen sections of brain white matter. Future studies will explore whether other algorithms can retrieve higher-resolution images, e.g. Bayesian methods, deconSTORM.

P2-072 CORRELATION AMONG DNA METHYLATION STATUS AND LINE-1 EXPRESSION IN RAT BRAIN

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Background: LINE 1 is an autonomous, non-LTR retrotransposon and the L1 retrotransposons constitute around 17%, of the human, mouse and rat genomes respectively. Under normal physiological conditions, the retroelements remain by and large transcriptionally silent but are activated in response to biotic and abiotic stress conditions. Our objectives were to study the transcriptional expression of L1Rn elements in different brain regions and correlate with corresponding DNA methylation levels. **Methods:** Real time PCR analysis using RNA isolated from various brain regions and various tissues from old and young wistar rats was carried out to determine the change in L1 transcripts. DNA methylation assay was performed using COBRA method (Yang et al, 2004). **Results:** There was no significant change in the expression of L1Rn in various brain regions of 2 month old and 18 month old rats except cerebral cortex. **Conclusions:** In conclusion, the degree of hypomethylation in promoter CpG islands in LINE-1 repetitive sequences do play essential role in LINE-1 element expression. Besides tissue specific factors do play pivotal role in LINE-1 expression.

P2-073 EPIGENETIC REGULATION OF BRCA1 IN ALZHEIMER'S DISEASE: EVALUATION OF POSTMORTEM BRAIN AND MODEL MICE REVEALS IMPORTANCE OF AGGREGATED TAU

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Background: We performed neuron-specific methylome analysis of AD brains and found significant hypomethylation in *BRCA1* promoter region. BRCA1 is known to play an important role in DNA repair and its mutation is risk factor of hereditary breast cancer, while its role has been seldom studied in neurodegeneration. We analyzed *in vitro* and *in vivo* models of AD to elucidate the role of BRCA1 in Alzheimer's disease pathomechanism. **Methods:** We first analyzed the effect of Aβ on BRCA1 expression and DNA damage in N2a swe.10 cells. We further tested expression pattern and solubility of BRCA1, and the balance between DNA damage and repair in post-mortem AD, 3×Tg-AD and APP/PS1 mice brains. **Results:** N2a swe.10 cells showed increased soluble BRCA1 expression which was attenuated at the presence of γ-secretase inhibitor. They were positive for DNA double strand break (DSB) marker γ-H2ax but showed no detectable DNA fragmentation, which suggested BRCA1 was functional in effective repair. BRCA1 was mislocalized at the cytoplasm in neuronal cells of AD and 3×Tg-AD brains and was found mostly at detergent insoluble fractions. However, in APP/PS1 mice it was only found at soluble fraction and cytoplasmic BRCA1 was not observed. Comparing between 3×Tg-AD and APP/PS1 mice, positive DNA fragmentation was only observed in 3×Tg-AD brains, which strongly suggested that aggregated tau impaired the function of BRCA1. In AD brains, BRCA1 staining pattern correlated with tau distribution. In Braak stage 3 AD brains, cytoplasmic staining of BRCA1 was limited to the hippocampal