P4-151 EFFECTS OF THE APOLIPOPROTEIN E GENOTYPE ON INTRINSIC FUNCTIONAL CONNECTIVITY IN YOUNG, HEALTHY ADULTS

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Background: The Apolipoprotein E4 (ApoE4) genotype is a strong genetic risk factor for sporadic Alzheimer's Disease (AD). Regional brain volume reductions have been observed in healthy E4 carriers relative to non-carriers in brain areas that are known to be particularly affected by AD pathology, such as the medial temporal lobe and the posterior cingulate cortex. Moreover, the ApoE4 genotype has been associated with altered functional connectivity between areas of the default-mode network (DMN). In the search of diagnostic and prognostic biomarkers of AD it is of interest, whether structural and functional alterations can be detected sufficiently long before the onset of clinical symptoms, thus providing a critical time window for preventive measures. The aim of the present study is to assess the effect of the ApoE4 genotype on brain volume, microstructure and function in young healthy adults. **Methods:** 22 ApoE4 carriers (mean age: 26.8. $\pm$ 5.3 years) and 22 non-carriers, matched in age and education, underwent resting-state fMRI, high-resolution 3D-anatomical MRI imaging, diffusion tensor imaging (DTI) and neuropsychological assessment. Functional connectivity analysis of resting-state activity was performed with the left hippocampus as a seed region (corrected fMRI for nuisance variates) using Matlab and BrainVoyager QX 2.2. Voxel based morphometry (VBM) was used to identify areas of ApoE4 related differences in brain volume. Additionally, DTI data was analyzed with Tract-Based Spatial Statistics (TBSS) to reveal possible differences in fractional anisotropy (FA) between groups. **Results:** ApoE4 carriers showed reduced connectivity between the left hippocampus and several regions of the DMN compared to non-carriers ($p < 0.05$, corrected). Structural analysis with VBM and DTI did not reveal any significant differences in gray matter and white matter volume or in FA between groups. Also, there were no significant differences between E4 carriers and non-carriers in measures of memory and attention. **Conclusions:** The results indicate that ApoE4 modulates brain function long before any clinical or morphological changes can be detected. Resting-state functional connectivity seems to be very sensitive to subtle changes in brain function associated with risk factors of AD and thus could serve as a possible biomarker of early disease processes in AD.

P4-152 EPIGENETIC MECHANISMS OF NITRIC OXIDE AND *IN VIVO* BRAIN FUNCTIONAL IMAGING

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Background: Some functional neuroimaging methods such as functional magnetic resonance imaging (fMRI), widely used to explore large-scale brain function in health and disease, are based on task-dependent modulation of cerebrovascular function. The blood oxygenation level dependent (BOLD) signal, assessed with fMRI, results from changes in local concentrations of deoxygenated and oxygenated haemoglobin, which in turn is modulated by regional changes in cerebral blood flow (CBF). While first studies linking genetic influence on functional imaging patterns have successfully been performed and helped to identify genetically-based endophenotypes, the role of epi genetics for large scale brain function has not been investigated. Here, we propose a rationale for future studies linking epigenetic factors with functional neuroimaging. **Methods:** Literature search in Medline databases with search items: "epigenetics", "neurovascular coupling", and "functional magnetic resonance imaging". **Results:** An important key factor to functional neuroimaging is cerebrovascular coupling. Neurons, glia cells, and cells of vascular vessels interact with each other in a "neurovascular unit". In particular, astrocytes are able to adjust the diameter and resistance of arterioles and capillaries by releasing vasoactive factors such as nitric oxide (NO), a reactive gaseous molecule. Recently, NO has been assumed to be an "epigenetic molecule". Evidence in support of this statement comes from observations that NO exerts its function on chromatin components - DNA and histones - and gene expression patterns via biochemical reactions targeting nuclear and non-nuclear proteins. Moreover, a model system based on endothelial nitric oxide synthase (eNOS) gene has been proposed to demonstrate the existence of epigenetic pathways that control gene expression in vascular endothelial cells. eNOS promoter region exhibits lack of DNA methylation and enrichment of post-translational histone modifications. As a result, the chromatin architecture assumes an open conformation enabling the recruitment of the transcriptional machinery and the transcription process. **Conclusions:** In light of these findings, epigenetic mechanisms of eNOS and NO may offer new insights on transcriptional control paradigms in vascular endothelial cells and on CBF regulation. Studies assessing both epigenetic molecular markers and functional neuroimaging may help to unravel interactions between epigenetic signalling and neurovascular physiology underlying functional neuroimaging.

P4-153 ELEVATED PIB PRECEDES DEMENTIA IN AUTOSOMAL-DOMINANT ALZHEIMER'S DISEASE: PIB, FDG AND ATROPHY IN THE DIAN COHORT

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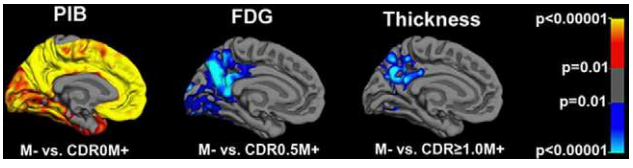
Background: DIAN (Dominantly Inherited Alzheimer's Network) is an international longitudinal study of autosomal dominant Alzheimer's Disease (ADAD). In addition to clinical, cognitive and psychometric testing, participants undergo serial multi-modal imaging. **Methods:** 120 participants representing a mix of non-carrier and carriers in both the presymptomatic and symptomatic stages of AD underwent PIB, FDG PET and MRI. Cohorts were determined based on genetic status, dementia severity (Clinical Dementia Rating, CDR), and estimated time to dementia onset (TDO, based on parental age of onset). All imaging exams were transformed and processed in a common atlas space using a combination of in-house software and FreeSurfer. Regions of interest were applied to

Table 1

	Non-carriers (M-) CDR 0	Carriers (M+)CDR 0	Carriers (M+) CDR 0.5	Carriers (M+) CDR >=1
n	43	44	18	15
Age*	39.90 (9.02)	34.84 (9.08)	42.17 (10.95)	47.67 (8.63)
Estimated time to dementia*	-5.48 (12.33)	-12.02 (8.47)	-1.72 (8.75)	+2.27 (8.02)
Gender	M=43%	M=36%	M=56%	M=60%
Education*	15.05 (2.49)	14.61 (2.62)	13.50 (2.31)	12.27 (1.98)

*Mean (standard deviation) in years

volumetric T1-weighted MRI, FDG and PIB data. For each modality and cohort, a linear regression analysis was used to determine the effects of TDO on a vertex-by-vertex basis. **Results:** Differences in PIB binding between carriers (M+) and non-carriers (M-) start to diverge up to 20 years prior to symptom onset (conversion to CDR 0.5). PIB retention in non-demented carriers were significantly different from the non-carrier cohort in the caudate, putamen and thalamus and in every cortical grey matter region (Figure 1). The first areas of significant amyloid deposition include the caudate, the occipital lobe, and the frontal lobe. Significant findings for grey matter volumes, cortical thickness, and FDG were limited to those carriers with dementia (CDR >=0.5) and did not reach significance in the pre-symptomatic population. **Conclusions:** DIAN represents the largest cohort of families with ADAD studied to date. Similar to findings in sporadic AD, elevated PIB retention precedes detectable atrophy and metabolic changes by decades. Unlike sporadic AD, there is particular involvement of the caudate, and occipital lobe/visual cortex.Figure 1: Lateral surface projection of cluster corrected p-values from linear regressions for PIB, FDG, and cortical thickness, when differences first appear. With PIB, non-demented carriers (CDR0M+) demonstrate widespread amyloid deposition (left). With FDG, differences are identified in the carriers with very mild cognitive changes (CDR 0.5, M+, middle). Changes in cortical thickness are only identified in the cohort with mild dementia (CDR>=1, M+).



P4-154 PROGRESSIVE WHITE MATTER ABNORMALITIES IN AUTOSOMAL-DOMINANT ALZHEIMER'S DISEASE: RESULTS OF THE DIAN STUDY

Tammie Benzinger[1], Tyler Blazey[1], Robert Koeppe[2], Clifford Jack[3], Marc Raichle[1], Beau Ances[1], Abraham Snyder[1], Daniel Marcus[1], John Ringman[4], Paul Thompson[5], Bernardino Ghetti[6], Andrew Saykin[6], Yi Su[7], Reisa Sperling[8], Stephen Salloway[9], Keith Johnson[10], Steve Correia[11], Peter Schofield[12], Nick Fox[13], Christopher Rowe[14], Krista Moulder[1], Randall Bateman[15], Chester Mathis[16], Eric McDade[17], Michael Weiner[18], Alison Goate[1], Virginia Buckles[1], Richard Mayeux[19], Colin Masters[20], Victor Villemagne[21], Morris John[1], *[1]Washington University School of Medicine, St. Louis, Missouri, United States; [2]University of Michiagan, Ann Arbor, Michigan, United States; [3]Mayo Clinic, Rochester, Minnesota, United States; [4]Easton Center for Alzheimer's Disease Research, Los Angeles, California, United States; [5]University of California, Los Angeles, Los Angeles, California, United States; [6]Indiana University School of Medicine, Indianapolis, Indiana, United States; [7]Washington University School of Medicine, St Louis, Missouri, United States; [8]Harvard University, Boston, Massachusetts, United States; [9]Brown University, Providence, Rhode Island, United States; [10]MGH HMS, Boston, Massachusetts, United States; [11]Brown University, Providence, Rhode Island, United States; [12]Neuroscience Research Australia, Newcastle, Australia; [13]The National Hospital for Neurology and Neurosurgery, London, United Kingdom; [14]Neuroscience Research Australia, Melbourne, Australia; [15]Washington University, St. Louis, Missouri, United States; [16]University of Pittsburgh, Pittsburgh, Pennsylvania, United States; [17]University of Pittsburgh, Pittsburgh, Pennsylvania, United States; [18]University of California, San Francisco, San Francisco, California, United States; [19]University of Columbia, New York, New York, United States; [20]University of Melbourne, Melbourne, Australia; [21]Austin Health, Melbourne, Australia.*

Background: DIAN (Dominantly Inherited Alzheimer's Network) is an international longitudinal study of autosomal dominant Alzheimer's disease, including individuals affected with, or at risk for, AD. In late onset AD it is often difficult to separate white matter disease associated with aging and diseases of aging (hypertension, diabetes, etc) from that of AD. In this young cohort, we quantified WM pathology using volumetric MRI and diffusion tensor imaging (DTI) in order to evaluate WM disease in ADAD. **Methods:** 71 participants from the DIAN study underwent DTI. Participants were classified into four groups based upon mutation (M+ and M-) and dementia status (CDR, Table 1). DTI was acquired using a 64 direction sequence at 3T. Image analysis was conducted with Tract Based Spatial Statistics (TBSS), a part of FSL. Group-level differences were assessed with a general linear model controlling for age, gender, and education and corrected for multiple comparisons using Threshold-Free Cluster Enhancement. Volumetric T1 (MPRAGE) studies were processed with FreeSurfer to generate white matter volumes. **Results:** White matter volumes decrease with carrier status and progressive dementia (Figure 1). Associated loss of fractional anisotropy (FA, Figure 2) and elevated mean diffusivity (MD, not shown) are widespread. Periventricular white matter is particularly involved at very mild (CDR 0.5) and mild (CDR 1.0) dementia (Figure 2). **Conclusions:** These findings support the hypothesis that widespread white matter abnormalities are associated with dementia in ADAD, and that these abnormalities precede the development of dementia.

Table 1

	Non-carriers (M-) CDR 0	Carriers (M+) CDR 0	Carriers (M+) CDR 0.5	Carriers (M+) CDR >=1
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