Functional and structural connectivity impairments precede plaque deposition in a transgenic mouse model of Alzheimer's disease

Joanes Grandjean[1], Pan He[2], Aileen Schröter[1], and Markus Rudin[1,3]

[1]*Inst. f. Biomedizinische Technik, ETH and University Zürich, Zürich, Switzerland,* [2]*ETH Zürich, Zürich, Switzerland,* [3]*Institute of Pharmacology and Toxicology, University of Zürich, 8057, Switzerland*

Purpose: Functional MRI studies in ArcAbeta [1] and other mouse models of Alzheimer's disease (AD) [2] have revealed decreased responses to stimuli with impairments increasing in severity as the disease progressed. In this study we question, whether the genetically induced amyloidosis in the ArcAbeta mouse model translates into alterations in functional connectivity (FC) and structural connectivity. Resting-state functional MRI (rs-fMRI) was used to measure FC in ArcAbeta mice, a mouse of model of AD presenting aspects of cerebral amyloid angiopathy. Diffusion tensor imaging (DTI) was used to measure fractional anisotropy (FA).

Method : ArcBeta mice [3] were imaged in three groups, at 5 months (N=9 wild-type, 8 transgenic), 8 and 11 months (N=9, 9), and 19 and 21 months (N=9,10). The animals were anaesthetized with isoflurane 1.5% in 4:1 air to oxygen mix with a face mask. Measurements were done on a 9.4T Bruker system equipped with a 2x2 phased-array cryogenic coil, using an echo planar imaging (EPI) sequence (TR/TE/FA=1500ms/9.3ms/50°, 500 repetitions, matrix 90x70, pixel dimension=220x250 µm², 12 slices) and DTI sequence (TR/TE/FA=3000ms/23.5ms/90°, 36 directions of diffusion encoding, matrix 128x128, pixel dimension=156x137 µm², 12 slices). EPI imaged were realigned, corrected for slice timing and normalized to an in-house EPI template with SPM05 and frequency drift, motion and signal from the ventricles was regressed. Network correlations were computed with an EPI mask containing 42 regions-of-interest (ROIs). Mixed model analysis was performed to test for the effect of the gender, age and genotype for each brain region pairs and for fractional anisotropy. Statistical significance was set at p<=0.001 and with false discovery rate correction of 10%. Error bars show 1 standard deviation.

Results: Analysis of FC matrix reveals in general reduced values for the Pearsons correlation coefficient in ArcAbeta as compared to their wild-type littermates (Fig.1a), effects reaching statistical significance between several regions of interest (Fig1b). FC was reduced between the sensory-motor cortex with the visual cortex, auditory cortex, retrospinal and cingulate cortex, and parts of the basal ganglia. Changes in FC were detected as early as at 5 months of age and persisted throughout the duration of the study (until months 21) as illustrated for the significantly reduced FC across the sensory-motor cortex compared to littermate wild-type controls with a mixed model analysis (Fig.1C). Reduced FA (Fig.1E) occurred in the corpus callosum from 5 months in transgenic mice compared to wild-type (genotype effect: p=0.00001), while there was a decrease over time in FA in the forceps minor of the corpus callosum detectable from 8 months in the wild-type mice (genotype effect: p=0.000002). We did not find age or gender related effects in the mixed model analysis for any of response variables.

Discussion: ArcAbeta mice have intracellular Abeta detectable at 3 months of age, declining cognition detectable at 6 months old and plaque deposition at 7 months of age [3]. Our data revealed reproducible changes in FC as well as in FA in the corpus callosum of the ArcAbeta as compared to wild-type littermates. Changes in FC precede amyloid plaque deposition. Interestingly, these effects remain unchanged throughout the development of amyloid pathology, suggesting that in this mouse model, the functional and structural changes are not due to amyloid plaque. ArcAbeta mice have been shown to develop astrogliosis at early stages of the pathology, as well as astrocytes endfeet retraction, leading to impaired neurovascular coupling [4]. Reduction of nerve fiber in the corpus callosum and elsewhere may also explain the reduced functional connectivity observed in this study.

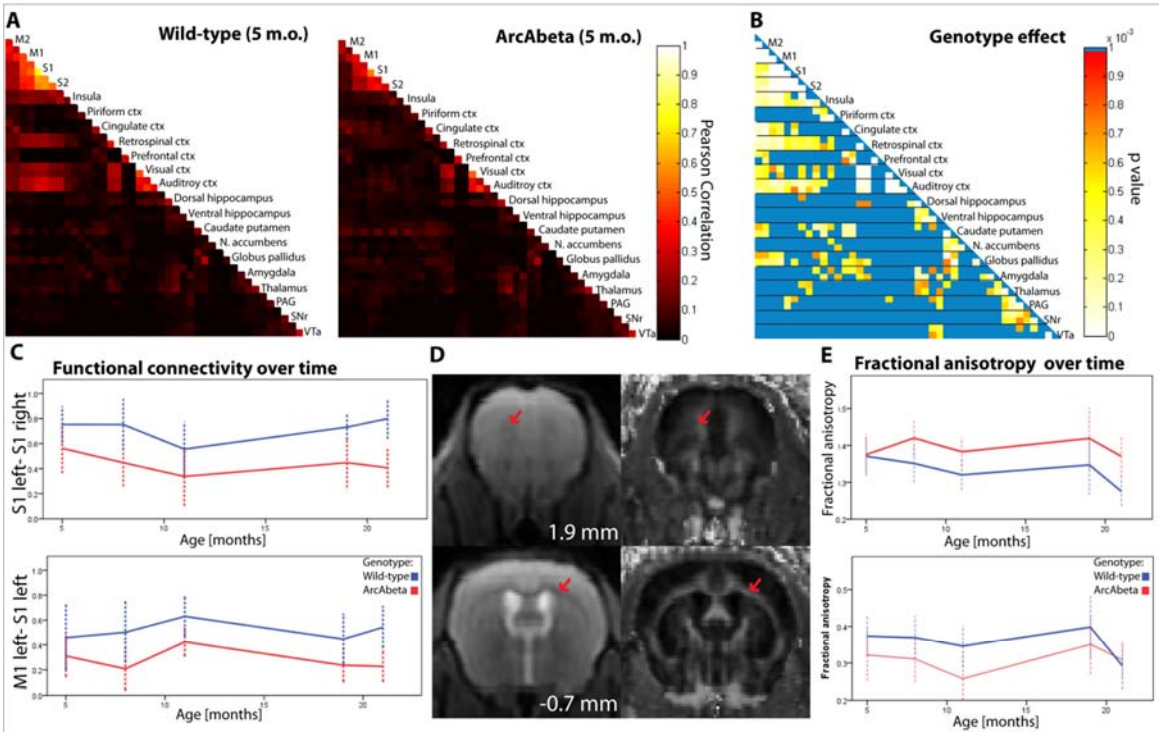

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Figure 1 A Network map of wild-type and ArcBeta mice aged 5 months show early alteration of functional connectivity (FC). **B** Statistical map of genotype effect in the mixed model analysis show statistically significant changes in cortical and basal ganglia functional connectivity. **C** Bilateral FC between sensory cortices S1 (upper panel) and FC of S1 and M1 (lower panel) reveal an early reduction of the correlation coefficient in ArcAbeta mice (shown in red) that persisted as the disease progressed. **D** Proton density and fractional anisotropy images showing the ROI for fractional anisotropy analysis. Distance is indicated from Bregma. **E** Fractional anisotropy in the minor forceps of the corpus callosum is progressively decreased in wild-type animals (upper panel). ArcAbeta mice shows reduced fractional anisotropy values in the corpus callosum compared to wild-type (lower panel).