modifying agents, sensitive biomarkers of early FTD are crucial. Previous cross-sectional studies already demonstrated imaging abnormalities in presymptomatic FTD. Our present study investigates longitudinal neuropsychological and imaging alterations in presymptomatic FTD. **Methods:** Healthy *MAPT* or *GRN* mutation carriers (n=40) and related non-carriers (n=37) underwent neuropsychological assessment and MRI at baseline and two-years follow-up. Grey matter volume, white matter integrity, and functional connectivity were analyzed over time using voxel-based morphometry, tract-based spatial statistics, and seed-based analyses. To investigate group differences in association with expected onset age, and to explore individual data, grey matter volumes were extracted for the insula and anterior and posterior cingulate cortex and FA values were extracted for the uncinate fasciculus, and forceps minor and major. **Results:** Longitudinal analyses revealed a significant decline in executive and social cognition tasks, stronger right insular atrophy, and stronger white matter impairment in the uncinate fasciculus over a two-year period in carriers within five before estimated symptom onset compared to controls. Two mutation carriers converted to clinical FTD during follow-up. Interestingly, they already showed the worst DTI values at baseline (Figure 1B) as well as the strongest grey matter atrophy over time (Figure 1A). The total group of mutation carriers differed from controls regarding longitudinal alterations in frontoinsula and posterior cingulate functional connectivity - that cannot be driven by the two converters, as their values cannot be distinguished from those of other subjects at baseline, follow-up or longitudinally (Figure 1C). **Conclusions:** We demonstrated longitudinal changes in neuropsychological performance, grey matter volume, white matter integrity, and functional connectivity in presymptomatic FTD. This study suggests that DTI might provide a baseline predictor for disease conversion, and that the first DTI changes might reflect the optimal starting point for a disease-modifying intervention. Moreover, grey matter volume and white matter integrity could serve as sensitive biomarkers in future therapeutic trials at the individual level.

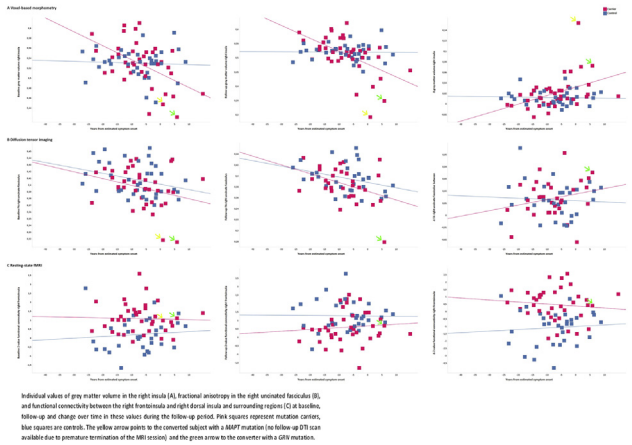

Figure. Individual values of grey matter volume in the right insula (A), fractional anisotropy in the right uncinated fasciculus (B), and functional connectivity between the right frontoinsula and right dorsal insula and surrounding regions (C) at baseline, follow-up and change over time in these values during the follow-up period. Pink squares represent mutation carriers, blue squares are controls. The yellow arrow points to the converted subject with a *MAPT* mutation (no follow-up DTI scan available due to premature termination of the MRI session) and the green arrow to the converter with a *GRN* mutation.

## O2-01-03 AMYLOID LOAD INCREASE AND CEREBRAL MICROBLEED PREVALENCE DIFFER AS A FUNCTION OF THE POSITION OF THE MUTATION WITHIN THE PSEN1 CODING SEQUENCE

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**Background:** Autosomal dominant Alzheimer's disease (ADAD) is a rare familial form of AD caused by mutations that alter metabolism of the $\beta$-amyloid protein. Most ADAD mutations concern the *PSEN1* gene with more than 185 mutations currently reported. Mann and colleagues have reported histological differences in terms of amyloidosis and angiopathy when *PSEN1*mutations are located before or after the codon 200 (Mann et al., 2001). The Dominantly Inherited Alzheimer Network (DIAN) aims to understand the changes occurring in the ADAD population. Here, we investigated amyloid PiB-PET retention and prevalence of microbleeds as imaging biomarkers, taking into account the mutation position relative to the codon 200. **Methods:** Carriers of a mutation on the *PSEN1*gene (n=119), before (n=34) or after (n=85) codon 200, underwent PiB-PET scan to quantify amyloid brain deposition, susceptibility-weighted imaging MR scan to detect microbleeds, and volumetric MRI. The volumetric MRI was used to register the PET images and calculate standardized uptake values ratio (SUVR) from segmented regions. Cross-sectional analyses with linear models were performed to evaluate the amyloid retention in function of estimated year of onset (EYO) of the symptoms. Prevalence of microbleeds in the participants and per group of mutation position was also analyzed. **Results:** Cross-sectionally estimated slopes of amyloid accumulation differed as a function of the mutation position. The group with mutations before codon 200 showed greater slope of amyloid accumulation at the mean cortical and caudate levels (p-value$<$0.005 and p-value$<$0.0005, respectively). Concerning microbleed evaluation, 12% of our cohort displayed one or more microbleeds. The percentage of carriers with microbleeds was up to 75% in the group carrying a mutation located after codon 200 compare to 25% in the group carrying a mutation located before codon 200. **Conclusions:** Our imaging findings are concordant with the previous histological description of particular phenotypes due to the position of the *PSEN1* mutation. They give new insights into the ADAD population who often display high subcortical, basal ganglia amyloidosis. These outcomes can be taken into account to address specific treatment trial designs, including screening participants likely to develop microbleeds during clinical trials.

## O2-01-04 WHITE MATTER HYPERINTENSITIES ARE A CORE FEATURE OF ALZHEIMER'S DISEASE: EVIDENCE FROM THE DOMINANTLY INHERITED ALZHEIMER'S NETWORK

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