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Background: White matter hyperintensities (WMH) have shown to be associated with increased risk of dementia. However, studies reporting the association of specific WMH locations with brain aging and dementia are scarce. We sought to investigate the association of WMH appearance in predefined anatomical brain regions and cardiovascular risk with brain atrophy patterns related to brain aging (BA), throughout adulthood in the general population, leveraging state of the art pattern analysis methods and structural equation modeling. **Methods:** We delineated WMH using a fully automated segmentation method in a large population-based sample (n=2,367) covering most of the adulthood life span (range 20-90 years, median=53 years), from the Study of Health in Pomerania, Germany. We automatically quantified WMH volume within four anatomical WM regions of interest i) frontal, ii) parietal -temporal, iii) deep structures including fornix and internal capsule and iv) occipital, using a multi-atlas segmentation method. Using machine-learning methods, we calculated the SPARE-BA score, a subject-specific index that captures and quantifies age-related brain atrophy patterns. The Framingham cardiovascular disease risk score (CVD-RS) was used to summarize the individual cardiovascular risk profile. We used four structural equation models independently; we modelled the SPARE-BA index as dependent variable, age as independent variable as well as CVD-RS and WMH volume within each region of interest as mediators. **Results:** Structural equation modeling showed that the age effect on brain aging patterns captured by the SPARE-BA score was mediated by WMH volume in frontal (8.7% Variance explained (VE), P<0.0001), parietal-temporal (9.5% VE, P<0.0001), deep WM structures including fornix and internal capsule (2.8%, VE, P<0.0001) and occipital (6.6% VE, P<0.0001) regions. The cardiovascular risk score was associated with WMH in frontal (P<0.0001), occipital (P<0.0001) and parietal-temporal (P<0.0001) regions but not in deep structures. **Conclusions:** Our results indicate that, regardless of their location, WMH might accelerate the brain aging process throughout adulthood in the general population as a result of vascular risk factors, but also independent of them. Preventive strategies against WMH could help to delay brain aging.

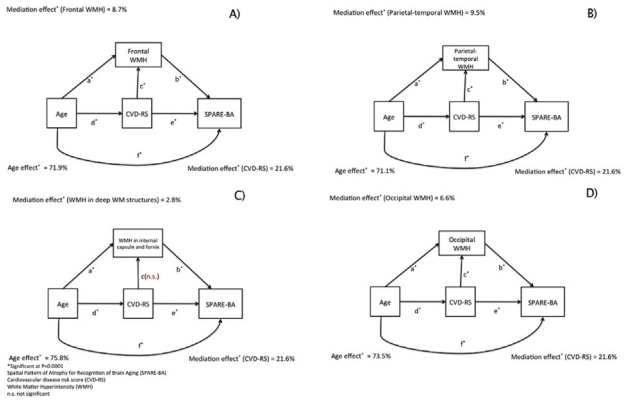

Figure 1. Four structural equation models showing potential causal association of regional WMH in the A) frontal, B) parietal -temporal, C) deep structures including fornix and internal capsule and D) occipital regions, with brain aging patterns of atrophy (SPARE-BA) across the adulthood life span from the SHIP sample (range 20-90 years, median = 53 years).

IC-03-04

WHITE MATTER HYPERINTENSITIES IN GENETIC FRONTOTEMPORAL DEMENTIA: A GENFI STUDY

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Background: Around a third of frontotemporal dementia (FTD) is caused by mutations in three main genes: progranulin (*GRN*),

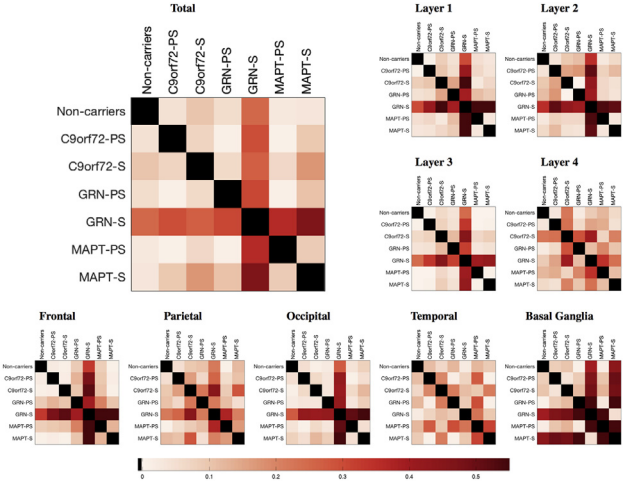

Figure 1. Effect sizes of observed differences between groups at local (layers and lobes) and global scales; PS - Presymptomatic ; S - Symptomatic.

Table 1
Comparison of global WMH volumes (mL) across mutation groups corrected for age, TIV, sex, scanner type, year before expected onset

	NC		PS		S		
	Mean	CI	Mean	CI	Mean	CI	p-values
C9orf72			0.50	[0.35 0.71]	0.44	[0.28 0.67]	NC vs PS 0.99 NC vs S 0.60 PS vs S 0.87
GRN	0.50	[0.40 0.62]	0.56	[0.39 0.81]	1.51	[0.77 2.94]	NC vs PS 0.60 NC vs S 0.0030 PS vs S 0.012
MAPT			0.53	[0.27 1.06]	0.59	[0.34 1.02]	NC vs PS 0.87 NC vs S 0.60 PS vs S 0.87
p-values	NA		*C9orf72* vs GRN 0.86 *C9orf72* vs *MAPT* 0.99 *GRN* vs *MAPT* 0.86		*C9orf72* vs *GRN* 0.0048 *C9orf72* vs *MAPT* 0.67 *GRN* vs *MAPT* 0.012		

Acronyms: NC - Non-carriers; PS - Presymptomatic; S - Symptomatic; NA - Non applicable; CI - Confidence interval.

microtubule associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9orf72*). Pathophysiological processes induced by these mutations may differ and some FTD subtypes have been associated with damage to the white matter (WM). This damage is visible as hyperintense signal on T2-weighted magnetic resonance (MR) imaging. The Genetic FTD Initiative (GENFI) is a longitudinal cohort study aimed at furthering understanding of disease in individuals with these three mutations. **Methods:** T1 and T2-weighted MR sequences were acquired for 180 subjects within the GENFI cohort, divided into 76 non-carriers, 61 presymptomatic mutation carriers (25 *GRN*, 8 *MAPT* and 28 *C9orf72*) and 43 symptomatic carriers (7 *GRN*, 13 *MAPT* and 23 *C9orf72*). WM hyperintensities (WMH) were automatically segmented using an algorithm based on outlier modelling in a multivariate Gaussian mixture model. Location in the WM was coded according to 1) a relative distance between ventricles and the cortex, divided into four equidistant layers (1st layer periventricular, 4th layer juxtacortical), and 2) to the closest cortical lobe. WMH in the basal ganglia were also investigated. Infratentorial regions were excluded from the analysis. Log-transformed WMH volumes were adjusted for age, gender, total intracranial volume, scanner type and years before expected onset. **Results:** Symptomatic *GRN* carriers had significantly more WMH than all other groups, but no differences could be detected between other subgroups (table 1). Symptomatic *GRN* carriers appeared to have a larger volume of WMH in the frontal and occipital regions compared with other symptomatic groups and presymptomatic *GRN* cases. Differences were most noticeable in periventricular layers, with higher WMH volumes in *GRN* cases compared with other groups. **Conclusions:** WMH patterns differ across FTD genetic subtypes, with symptomatic *GRN* carriers displaying particularly predominant fronto-occipital periventricular WMH. Future research should explore the pathophysiological mechanisms of WMH within genetic FTD.

IC-03-05 NON-FLUENT PRIMARY PROGRESSIVE APHASIA: PRION-LIKE BEHAVIOR OF MISFOLDED PROTEINS IN THE SYNTACTIC NETWORK

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Background: Animal studies and the brain atrophy pattern of neurodegenerative dementias suggest that misfolded proteins may propagate in a manner similar to infectious prions, spreading through brain networks. However, this propagation has not been demonstrated *in vivo* in humans. Alzheimer's disease affects the resting network, which is too complex to study tau propagation. In contrast, non-fluent primary progressive aphasia (nfPPA) affects the simpler syntactic network, with two major nodes, Broca's area and the temporal syntactic area, connected by the arcuate fasciculus. Damage in nfPPA begins in Broca's area. This study aimed to determine whether tau deposition in nfPPA follows a network pattern. **Methods:** Seven nfPPA patients, all PET amyloid-negative, and eight healthy controls had ^{18}F-AV-1451 PET. The SUV ratio over the cerebellar gray matter was calculated for t = 80–100 min. The two groups were compared using SPM. MRI tractography was performed in the nfPPA group. Additionally, in a different group of 35 healthy subjects, we determined normal network functional connectivity with BOLD MRI using the voxels with greatest ^{18}F-AV-1451 uptake in the nfPPA group as seed. **Results:** nfPPA patients had impaired language production and increased ^{18}F-AV-1451 uptake in two major clusters ($p < 0.05$ FWE corrected): the larger in Broca's area and the smaller in the syntactic comprehension area of the left temporal lobe, which was also the area most heavily connected to Broca's area in the MRI connectivity analysis in healthy subjects. Furthermore, MR tractography revealed abnormal thinning, most pronounced anteriorly, of the left arcuate fasciculus, connecting the frontal and temporal nodes of the language network. **Conclusions:** Increased ^{18}F-AV-14510 signal in nfPPA most likely reflects binding to either abnormal tau or a form of TDP-43; aggregates of either protein have a beta-pleated structure. Binding was greatest in Broca's area, where degeneration begins in nfPPA, and, to a lesser extent, in the posterior node of the syntactic network. The arcuate fasciculus was thinned in the left hemisphere suggesting that it is the pathway traveled by misfolded proteins associated with neuronal and axonal degeneration. Our findings provide *in vivo* evidence that, in neurodegenerative dementia, misfolded proteins propagate in a prion-like manner.