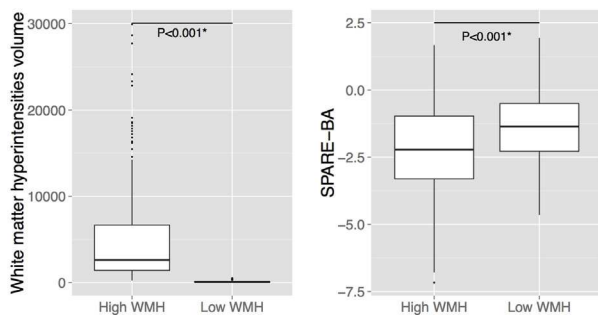*Biomedical Image Computing and Analytics / University of Pennsylvania, Philadelphia, PA, USA;* [2]*Institute for Community Medicine / University of Greifswald, Greifswald, Germany;* [3]*Department of Psychiatry / University of Greifswald, Greifswald, Germany;* [4]*Institute on Aging / University of Pennsylvania, Philadelphia, PA, USA;* [5]*Department of Neurology / University of Greifswald, Greifswald, Germany;* [6]*Department of Radiology / University of Greifswald, Greifswald, Germany;* [7]*German Center for Neurodegenerative Diseases (DZNE), Greifswald, Germany.*
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Background: Previous studies have shown associations between white matter hyperintensities (WMH) and increased risk of dementia, which might be affected from common factors such as vascular risk and age. We sought to investigate the association of WMH burden and cardiovascular risk with brain atrophy patterns related to brain aging (BA) and to Alzheimer disease (AD), in the general population, leveraging state of the art pattern analysis methods. **Methods:** We quantified WMH burden through automated segmentation in a large population-based sample (n=2,367) covering a wide age (range 20-90 years, median=53 years), from the Study of Health in Pomerania, Germany. Using machine learning methods, we calculated two indices summarizing brain atrophy: i) the SPARE-BA index to quantify age-related brain atrophy, and ii) the SPARE-AD index, previously developed to capture AD-like atrophy patterns. Framingham cardiovascular disease risk score (CVD-RS) was used to summarize individual risk profile. We used two linear regression models, in which WMH and CVD-RS were independent variables, and SPARE-AD and SPARE-BA scores were dependent variables respectively, after adjusting for age, gender and education level. **Results:** BA was associated with atrophy in regions such as the frontal lobe, putamen amygdala and insula. BA patterns of atrophy were overlapping to some extend with, but notably deviating from, AD-like patterns of atrophy. WMH were associated with gray matter atrophy in regions such as anterior temporal, frontal lobe and hippocampus. Linear regression models showed that higher WMH burden was significantly associated with SPARE-BA, as well as with SPARE-AD scores (P<0.0001 for both). CVD-RS was significantly associated with SPARE-BA score (P<0.0001), but not with SPARE-AD score (P=0.087). We found that high and low WMH burden groups in age older than 60 years, defined as subjects with age-adjusted WMH volume above 70th percentile and below 30[th]percentile respectively, displayed brain age differences that would correspond in average to 4.6 years of additional aging. **Conclusions:** Our results

Table 1
Linear regression model with WMH volume, and CVD-RS as independent variables and SPARE-BA as dependent variable. Results are adjusted for age, gender and education.

Factor			
	SPARE-BA SHIP participants n=2,367		
	Estimate	S.E.	P-value (factor)
White matter hyperintensities volume[0]	-0.052[$]	0.005	<0.0001*
Framingham cardiovascular disease risk score	-0.029[&]	0.006	<0.0001*
	$R^2 = 0.69$		

* Significance at level P < 0.05, S.E: Standard Error.
° Values in mm^3 are transformed using cubic root function.
$ A lesion volume increase of 1mm leads to 3.5 months of additional brain aging approximately (transformed WMH volume range was [0-30.3], standard deviation=4.6, median=4.7).
& A 1 unit increase of CVD-RS leads to 1.9 months of brain aging atrophy approximately (CVD-RS range was [-5,27], standard deviation=6.4, median=ll).

Table 2
Linear regression model with WMH volume, and CVD-RS as independent variables and SPARE-AD as dependent variable. Results are adjusted for age, gender and education.

Factor			
	SPARE-AD SHIP participants n=2,367		
	Estimate	S.E.	P-value (factor)
White matter hyperintensities volume°, mm	0.039	0.004	**< 0.0001***
Framingham cardiovascular disease risk score, arbitrary units	-0.008	0.005	0.087
	$R^2 = 0.194$		

* Significance at level P < 0.05, S.E: Standard Error, ° Values are transformed using cubic root function.

revealed that WMH and cardiovascular risk are additive factors that might accelerate the brain aging process. WMH are also associated with AD-like atrophy patterns in the general population. Preventive strategies against WMH and cardiovascular risk could help to delay brain aging.

Boxplots of WMH volumes (left) and SPARE-BA values (right) for high and low WMH burden groups in age older than 60. The groups were defined as subjects with age-adjusted WMH volume above 70th percentile and below 30th percentile respectively. The difference in average SPARE-BA value between the two groups was 0.8 (P<0.001), corresponding to 4.6 years of additional brain aging.
* Significant difference at P<0.05

Figure 1.

O2-03-04 **BASELINE NORMAL APPEARING WHITE MATTER STRUCTURAL INTEGRITY AND CEREBRAL BLOOD FLOW CAN PREDICT WHITE MATTER HYPERINTENSITY EXPANSION OVER TIME: A VOXEL-WISE ANALYSIS**

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Background: White matter hyperintensity (WMH) penumbra is the normal appearing white matter (NAWM) surrounding WMH that

demonstrates decreased structural integrity and perfusion, and is vulnerable to becoming injured white matter. Previous longitudinal work has shown that baseline cerebral blood flow (CBF), DTI-FA, and FLAIR intensity can predict WMH expansion over time. However, none of the previous studies identified which signal can best predict the growth of WMH and none performed voxel-wise analysis. The aim of this study was to identify the sensitivity of CBF, DTI and FLAIR signals in predicting WMH development. **Methods:** Fifty-two cognitively intact (CDR = 0) elderly volunteers (mean age 83.5 years old) underwent two scan visits with 3T MRI FLAIR, MPRAGE, PASL and DTI. The mean interscan interval was 16 months. For each individual dataset, baseline and follow-up WMH were aligned and subtracted from each other, creating a binary map containing 0s and 1s for persistent NAWM and new WMH voxels, respectively. We focused on the 5 mm area surrounding WMH where there was significant growth of WMHs. Baseline CBF map. DTI-FA, DTI-MD and FLAIR images were then registered to the binary map. Correlation analysis was performed between the binary map and CBF map, DTI and FLAIR images, individually. The predictive order was determined by comparing the group mean R^2 using paired t-test. **Results:** Increased FLAIR intensity had the strongest correlation with new WMH voxels, followed by increased DTI-MD, decreased DTI-FA and decreased CBF for both periventricular (PV) and deep WMH penumbras (p<0.001). Mean R^2, ordered from greatest to smallest associations, are 0.072, 0.014, 0.011, and 0.005 for PV WMHs, and are 0.025, 0.014, 0.004, and 0.001 for deep WMHs. **Conclusions:** Within the immediate WMH environment, baseline indicators of microstructural WM damage are more predictive of future WMH expansion than CBF. For future studies, investigating the contribution of CBF to future microstructural WM degeneration is needed.

O2-03-05   **CEREBROVASCULAR DISEASE, ALZHEIMER'S DISEASE BIOMARKERS AND LONGITUDINAL COGNITIVE DECLINE**

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Background: Cerebrovascular disease (CVD) is commonly seen to co-exist with Alzheimer's disease. Recent studies suggest that the two pathologies may mediate distinct, additive insults on cognitive performance. We examined the contribution of subclinical CVD (sCVD) and Aβ burden at baseline to risk for incident dementia over six years. **Methods:** 219 non-demented participants from the AIBL Study (169 normal cognition, 50 mild cognitive impairment) with 3-Tesla MRI and ^{11}C-PiB PET at baseline and clinical assessments over 18-monthly intervals over six years. Persons with a history of clinical stroke were excluded from AIBL. Participants were classified as Aβ+ if PiB Neocortical SUVR ≥1.5 and sCVD+ if MRI evidence of stroke or significant sCVD. Incident cognitive decline and dementia were determined from clinical panel consensus following neuropsychological test performance at each timepoint. Cox proportional hazard regression was performed including Aβ and sCVD, age, *APOE* ε4 status, gender and education as covariates, and cognitive decline, or dementia, as outcome variables. **Results:** 25% of participants were classified as having cognitive decline and 16% progressed to dementia. While both sCVD and Aβ were associated with incident dementia in univariate analyses, the interaction between sCVD and Aβ was not. Only the association with Aβ remained significant after adjustment for all covariates (Hazard ratio [for cognitive decline] 3.8, p < 0.001; [for dementia] HR = 7.4, p < 0.001). In participants with normal cognition at baseline, risk for incident dementia at six years was only significant in those with Aβ and sCVD at baseline (HR = 25.9, p = 0.004). **Conclusions:** In this non-demented cohort, Aβ more strongly predicts incident cognitive decline and dementia than subclinical CVD. Subclinical CVD lowered the threshold for incident dementia in those with Aβ, although sCVD alone was not sufficient to predict future dementia. These data have implications for clinical trials in preclinical and prodromal AD.

O2-03-06   **NEUROPATHOLOGIC CORRELATES OF WHITE MATTER HYPERINTENSITIES IN A COMMUNITY COHORT OF OLDER ADULTS**

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Background: White-matter hyperintensities (WMH) are commonly observed in the brain of older adults and have been associated with lower cognitive function, lower motor performance, and increased risk of dementia. A number of studies have combined brain MRI with measures of neuropathology to assess the neuropathologic correlates of WMH. However, these studies were characterized by one or more of the following limitations: long intervals between MRI and autopsy, focus on one or few pathologies, use of clinical cohorts, low numbers of participants. The purpose of this work was to examine the association between WMH and age-related neuropathologies using a study design that addresses the above shortcomings by combining ex-vivo MRI and pathology on a large community cohort of older adults. **Methods:** Cerebral hemispheres were obtained from 544 deceased participants of two longitudinal, epidemiologic clinical-pathologic cohort studies of aging. All hemispheres were imaged ex-vivo on a 3T MRI scanner, while immersed in 4% formaldehyde solution. Following imaging, all hemispheres underwent neuropathologic examination. One rater was trained by an expert to rate WMH on ex-vivo MRI, in periventricular and deep white matter separately, according to the original Fazekas scale. The maximum of the two ratings was used in analyses. Intra-class correlation was used to assess intra-rater reliability and agreement with the expert. Ordinal logistic regression was used to test the association of WMH rating with beta-amyloid, PHF-tau tangles, Lewy bodies, TDP-43, hippocampal sclerosis, gross infarcts, microscopic infarcts, atherosclerosis, arteriolar sclerosis, and cerebral amyloid angiopathy, controlling for age at death, sex, education, and postmortem interval to fixation. **Results:** Intra-rater agreement was strong (ICC=0.75, 95% C.I. 0.69-0.79, F=6.8, p<10^{-4}) and agreement