# WHITE MATTER HYPERINTENSITIES AND PHYSICAL ACTIVITY IN PEOPLE AT RISK OF ALZHEIMER'S DISEASE


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**Purpose:** Alzheimer's Disease (AD) is the most common cause of dementia and there is no disease modifying treatment yet. During the last decade, research has focussed not only on optimizing treatment, but also on investigating modifiable risk factors with the aim to slow down the neurodegenerative progression in people at increased risk of developing AD. These risk factors include unhealthy diet, cerebrovascular risk factors (VRFs) (e.g. diabetes, heart disease, hypertension, obesity, smoking, etc.), and lack of physical and cognitive activity. Potential biomarkers and techniques for detecting AD pathology include measurement of total tau protein (t-tau) and Aβ42 in cerebrospinal fluid as well as neuroimaging (MRI, PET). White matter lesions or hyperintensities (WMHs), which characterize cerebrovascular disease (CVD) on MR images, are considered to be associated with an increased risk of AD. However, the impact of physical activity (PA) on cognitive function and CVD remains under-researched. In this work, we analyse WMHs of T2-FLAIR MR images and hippocampal volumes of older adults with subjective memory complaints (SMC) or mild cognitive impairment (MCI) and examine their association with different PA assessments.

**Methods:** Baseline MR images were acquired of 89 eligible participants (61 SMC, 28 MCI, 49 women, 40 men, mean age: 72.93 ± 5.93, min. age: 61) out of a total number of 108 older adults (Protocol: 3D FLAIR sequence, voxel size = 0.5x0.5x1mm$^3$, TR=5300ms, TE=355ms, TI=1800ms, flip angle=120°, Siemens 3.0T Tim Trio). They are enrolled in the AIBL Active trial [1], a randomized controlled trial investigating the benefits of PA in participants with SMC and MCI who have CVD risk factors and are part of the AIBL study (Australian Imaging Biomarkers and Lifestyle) [2]. Different steps were used for image processing:
**1)** All the images were reoriented to the MNI152 template, which is seen as the standard space, to match the position of the labels. **2)** We normalized the intensity of all images to a mean intensity = 100 of the 3D volume. **3)** To facilitate the segmentation of the WMHs, the brain extraction tool (BET) v2.1 [3] was used for skull removal and bias field and neck clean up in the MR images (Threshold: 0.3) **4)** Images were resampled to 160x512x128 slices. **5)** Manual segmentation: ROIs for the WMHs were drawn on the MR Images by one expert tracer. The traces were performed on the axial view and white matter lesions were considered as hyperintense if appearing bright on the FLAIR images (Fig.1). **6)** The total volume of the WMHs was calculated by adding the number of voxels of the lesions together and multiplying by the slice thickness. Steps 1)-3) were performed by using the freely available software tool FSL v5.0 [3] and steps 4)-6) with ITK-Snap (www.itksnap.org).
For further analysis, volumes were obtained with Freesurfer (FS) Image Analysis Suite v5.1.0 [4]. In FS, no manual intervention was done, the integrated whole brain segmentation and cortical parcellation have been used and the estimated structural volumes of hippocampus (left and right) were extracted from the statistical result files. The hippocampus is known to be a region which is affected in AD with volume loss and its MRI-based volumetric measurement has been proven as a potential biomarker.
Level of PA was measured using the CHAMPS (community healthy activities model program for seniors) questionnaire [5]. This questionnaire, designed for older adults, collects information on various low-, moderate-, high- and very high-intensity physical activities undertaken during a typical week in the last four weeks, including their frequency and duration. The 6-minute Walk Test was used to assess cardiovascular endurance. Participants walked up and down a 20 metre corridor as fast as possible for six minutes. Heart rate was measured each minute using a heart rate monitor and the distance walked in six minutes was recorded.

| | WMHs volume | HC volume | AERA | ALERA |
|---|---|---|---|---|
| SMC (n=61) | 0.00472 (±0.01062) | 0.00532 (±0.00066) | 751.97 (±307.05) | 487.38 (±205.33) |
| MCI (n=28) | 0.00366 (±0.00438) | 0.00515 (±00070) | 782.14 (±345.80) | 489.11 (±235.91) |

**Table 1:** Mean and std. dev. in the SMC and MCI subgroup: total white matter hyperintensities (WMHs, column 1) and hippocampal (HC, column 2) volume, both with ICV correction, all exercise-related activities (AERA, column 3) and all low-intensity exercise-related activities (ALERA, column 4), both measured in mins./week

| | WMHs volume | HC volume | AERA | ALERA |
|---|---|---|---|---|
| WMHs volume | | r=-0.031 (p=0.812) | r=-0.322 (p=0.011) | r=-0.332 (p=0.009) |
| HC volume | r=0.041 (p=0.836) | | r=-0.195 (p=0.132) | r=-0.105 (p=0.419) |
| AERA | r=0.026 (p=0.895) | r=-0.109 (p=0.582) | | r=0.716 (p<0.001) |
| ALERA | r=0.092 (p=0.643) | r=0.116 (p=0.557) | r=0.663 (p<0.001) | |

**Table 2:** Spearman correlation coefficients for different subgroups: SMC (highlighted orange, upper right half of the table) and MCI (highlighted blue, lower left half of the table)

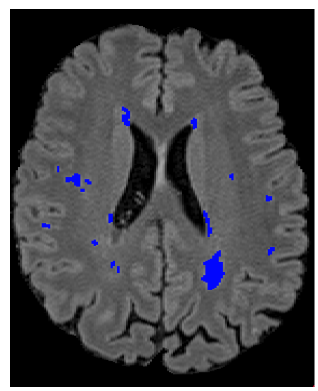

**Fig 1:** One axial slice of a 66-year old, male participant with a medium amount of WMHs (blue ROIs)

**Results:** Statistical analysis was performed using SPSS 21.0 (SPSS, Chicago, IL). We normalized all structural volumes (hippocampus and WMHs) to the total estimated intracranial volume (ICV) and calculated Spearman correlations to compare the PA measures with the MRI related data. As shown in Table 1, there were no significant differences in the measurements of volumes and PA between the SMC and MCI subgroup. However, in the total data set (n=89), we found a significant correlation between WMHs volume and all exercise-related activities at baseline (r=-0.210, p<0.05, data not shown). Table 2 shows the Spearman correlations across the two volumetric measurements and two PA assessments. In the SMC subgroup (n=61), both, all exercise-related activities (AERA, r=-0.332, p=0.011) as well as all low-intensity exercise-related activities (ALERA, r=-0.332, p=0.009) have been significantly correlated with WMHs volume. However, this finding could not be replicated for the MCI group (n=28). Furthermore, both AERA and ALERA were highly correlated (p<0.001) in both subgroups, which is not surprising given they are both measures of individual PA levels.

**Discussion:** Previous literature has already shown an increase of hippocampal size through exercise in healthy older adults longitudinally [6]. We used T2-FLAIR MR images and the community healthy activities model program for seniors (CHAMPS) [5] in a cohort of 89 people with SMC and MCI to analyse the association between WMHs, HC volumes and PA assessments. The normalized total WMHs volume was associated with exercise-related activities in the total group as well as in the people with SMC, but not in the MCI group. The lack of effect in the MCI group may be related to statistical underpowering due to the smaller number of MCI (n=28) vs. SMC (n=61). HC volumes were not associated with PA levels in the subgroups.

**Conclusion:** Physical activity may play a role in reducing the risk of CVD and confer a protective effect against AD. WMHs provide a measure of cardiovascular health of the brain and may be influenced by physical activity. Longitudinal studies on SMC or MCI patients undertaking a physical activity program may provide new evidence about the protective effect of PA in patients at increased risk of AD.


**References:** [1] Cyarto et al., BMC Psychiatry 2012; 12:167, [2] Ellis et al., Alzheimers Dement 2010;6:291-6, [3] Jenkinson et al., NeuroImage 2012; 62:782-90, [4] Fischl et al., Neuron 2002; 33:341-355, [5] Stewart et al., MSSE 2001; 33(7): 1126-1141, [6] Erickson et al., PNAS 2011; 108(7):3017-3022