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Regional tract-specific white matter hyperintensities are associated with patterns to aging-related brain atrophy via vascular risk factors, but also independently

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Abstract

Introduction: We sought to investigate associations of regional white matter hyperintensities (WMHs) within white matter (WM) tracts with cardiovascular risk and brain aging-related atrophy throughout adulthood in the general population, leveraging state of the art pattern analysis methods.
Methods: We analyzed a large sample (n = 2367) from the Study of Health in Pomerania, Germany (range 20–90 years). WMHs were automatically segmented on T1-weighted and fluid-attenuated inversion recovery magnetic resonance images, and WMH volumes were calculated in WM regions defined using the John Hopkins University WM tractography atlas. Regions with the highest average WMH volume were selected. We calculated a subject-specific index, Spatial Pattern of Alteration for Recognition of Brain Aging, to measure age-related atrophy patterns. The Framingham cardiovascular disease risk score summarized the individual cardiovascular risk profile. We used structural equation models, independently for each region, using Spatial Pattern of Alteration for Recognition of Brain Aging as a dependent variable, age as an independent variable, and cardiovascular disease risk score and regional WMH volumes as mediators.
Results: Selected 12 WM regions included 75% of the total WMH burden in average. Structural equation models showed that the age effect on Spatial Pattern of Alteration for Recognition of Brain Aging was mediated by WMHs to a different extent in the superior frontal WM, anterior corona radiata, inferior frontal WM, superior corona radiata, superior longitudinal fasciculus, middle temporal WM, posterior corona radiata, superior parietal WM, splenium of corpus callosum, posterior thalamic radiation, and middle occipital WM (variance explained between 2.8% and 10.3%, $P < .0001$ Bonferroni corrected), but not in precentral WM.
Conclusions: Our results indicate that WMHs, in most WM tracts, 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 WMHs (such as controlling vascular risk factors or microglia depletion) could delay brain aging.

Keywords: White matter hyperintensities; Alzheimer disease; Brain aging; Cardiovascular disease

The authors declare no competing interests

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1. Introduction

Alzheimer's disease accounts for most dementia cases in the general population, followed by vascular dementia. Both dementia types are associated with age and vascular risk factors, which may, in turn, increase the accrual of cerebral white matter hyperintensities (WMHs). WMHs are usually defined by regions of high signal intensity on T2-weighted magnetic resonance (MR) images. WMHs are more prevalent in elderly individuals and are believed to be the result of axonal loss and demyelination that can be triggered by aging, ischemic small vessel disease, and/or neurodegeneration [1–3].

The associations between vascular risk factors and both cerebrovascular pathology and brain aging are well documented [4–6]. Although vascular risk factors could lead to brain aging and cerebrovascular pathology, the resulting overlap remains less quantified in the general population. MR imaging provides a non-invasive way to measure evidence of cerebrovascular disease by quantifying WMH volume so that one can study these complex associations. However, studies reporting the association of specific WMH locations with brain aging and dementia remain scarce [7,8]. In most analyses, WMHs are quantified using a single measure of total burden, or using relatively coarse anatomical parcellations [9], and this might lead to losing sensitivity to location-specific associations of WMHs. Importantly, increasing evidence is pointing to the role of fiber tract-specific WMH burden in neurodegenerative diseases [10,11], the prevalence of which substantially increases with age.

We sought to investigate associations of regional WMHs with cardiovascular risk and brain atrophy patterns related to brain aging throughout adulthood in the general population. We measured regional WMHs from structural MR images, by automatically segmenting and calculating WMH volumes within white matter (WM) tract regions defined on the John Hopkins University WM tractography atlas. We quantified imaging patterns related to aging using a machine learning–based summary index, Spatial Pattern of Alteration for Recognition of Brain Aging (SPARE-BA) [6]. We used structural equation models, independently for each region, for the final analysis.

2. Methods

2.1. Participants from Study of Health in Pomerania

We included in this study 2367 subjects from the Study of Health in Pomerania (SHIP), covering most of the adult life span (range 20–90 years, median = 53 years). SHIP is a population-based prospective cohort, was recruited from the German northern east region of Pomerania, and led by the Institute for Community Medicine at the Medical Faculty of the University of Greifswald [12]. The main focus of SHIP is the investigation of risk factors, preclinical diseases with highly innovative noninvasive methods. The SHIP study covers the human health with all related aspects involving collection and assessment of data. SHIP started at baseline with SHIP-0 between 1997 and 2001. From 2008 to 2013, the second follow-up examination SHIP-2 was carried out. Concurrent with SHIP-2, a new sample from the same area was drawn, and similar examinations were undertaken between 2008 and 2012 (SHIP-Trend). SHIP-2 and SHIP-Trend included whole-body magnetic resonance imaging (MRI) scans and neuroimaging components. The characteristics of this sample is described in Table 1 [1].

In SHIP, 3066 individuals completed both T1-weighted and fluid-attenuated inversion recovery (FLAIR) baseline brain scans. Expert radiologists have visually inspected head MRI scans for artifacts and clinical findings. We excluded in this study scans based on existence of following criteria: clinical stroke, multiple sclerosis, epilepsy, cerebral tumor, intracranial cyst or hydrocephalus (n = 150), and high level of motion artifacts (n = 98) as well as subjects without cognitive testing (n = 176). Further exclusion took place after quality control of the automatically skull-stripped data (n = 121) and the automated WMH segmentation (n = 154). The Ethics Committee of the Medical Faculty of the University of Greifswald approved SHIP.

2.2. Data assessment and laboratory work in SHIP

Clinical data were collected by a computer-assisted face-to-face interview. We divided smoking in three categories, specifically: current smoking, former smoking, and never smoked. Having completed the interview, participants underwent medical examinations, including the measurement of height and weight (continuous variable). Waist circumference was measured in centimeters (continuous variable). After a 5-minute resting period, blood pressure was measured three times on the right arm of seated subjects using a digital blood pressure monitor (HEM-705CP; Omron, Tokyo, Japan), with each reading being followed by a further resting period of 3 minutes. Cuffs were applied according to the circumference of the participant's arm. The mean of the second and third measurements (mm Hg) was used for the analyses (continuous variables). All subjects were informed to bring in their packing containers of all medication they had taken during the last 7 days, as well as their drug prescription sheets. Every compound was recorded. We used antihypertensive, antidiabetic, and lipid-lowering drugs, as indicators for cardiovascular disease (CVD) risk factors in the general population. High-density lipoprotein cholesterol concentrations were measured photometrically (Hitachi 704; Roche, Mannheim, Germany). Total cholesterol, low-density lipoprotein, and high-density lipoprotein were measured as dimensional scores.

2.3. Image acquisition

SHIP included whole-body MRI protocol [13]. The neurocranium module of SHIP included, among others,