Thesis

Peak Width of Skeletonized Mean Diffusivity (PSMD) and cognition in healthy adults

submitted by

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Graz, 27.02.2025 *Kirolos Gendy m.p.*

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Zusammenfassung

Fragestellung: Die „Peak Width of Skeletonized Mean Diffusivity“ (PSMD) hat sich als vielversprechender DTI-Marker zur Bewertung der Integrität der weißen Substanz erwiesen, deren Intaktheit in hohem Maße mit kognitiver Gesundheit assoziiert ist. Es gibt nur wenige Arbeiten, die Zusammenhänge zwischen PSMD und Kognition untersucht haben, insbesondere nur zwei longitudinale Studien. Das erste Ziel dieser Arbeit war es, bei kognitiv gesunden Erwachsenen Zusammenhänge zwischen PSMD und Kognition im Rahmen einer Querschnittstudie zu untersuchen. Das Hauptziel der Arbeit war es, longitudinal zu untersuchen, ob PSMD-Veränderungen mit kognitiven Veränderungen über die Zeit zusammenhängen. Darüber hinaus wurden Zusammenhänge zwischen PSMD, Alter, Geschlecht, vaskulären Risikofaktoren, Marklagerhyperintensitäten und Hirnvolumen untersucht.

Methodik: Insgesamt wurden 326 gesunde Erwachsene im Alter von 38-87 Jahren in die Querschnittstudie aufgenommen. MRT-basierte PSMD-Werte wurden zusammen mit Messungen des Gesamthirnvolumens und der Hyperintensitäten der weißen Substanz (WMH) berechnet. Die kognitive Leistung wurde in vier Bereichen bewertet: Gedächtnis, visuell-praktische Fähigkeiten, exekutive Funktionen und ein zusammengesetzter Score für globale Kognition. In einer Untergruppe von 61 TeilnehmerInnen mit vollständigen longitudinalen Daten wurden die Veränderungen der PSMD, des WMH-Volumens und der kognitiven Leistung im Längsschnitt untersucht.

Ergebnisse: In der Querschnittsanalyse mit 326 TeilnehmerInnen zeigte PSMD eine starke positive Korrelation mit dem Alter, wobei ein steilerer Anstieg bei TeilnehmerInnen im Alter von ≥ 60 Jahren beobachtet wurde. In dieser Altersgruppe wiesen Männer außerdem signifikant höhere PSMD-Werte als Frauen auf. Darüber hinaus war die PSMD positiv mit dem Volumen von Hyperintensitäten der weißen Substanz (WMH) assoziiert. In der Querschnittsanalyse waren höhere PSMD-Werte außerdem signifikant mit einer geringeren Leistung bei visuell-praktischen Fähigkeiten und exekutiven Funktionen assoziiert.

Die Längsschnittanalyse (n = 61) ergab ebenfalls eine Zunahme der PSMD im Laufe der Zeit. Die Zunahme der PSMD korrelierte positiv mit der Zunahme des WMH-Volumens. Eine Zunahme der PSMD im Laufe der Zeit korrelierte jedoch nicht mit Veränderungen in einem der untersuchten kognitiven Bereiche.

Fazit: Unsere Ergebnisse bestätigen, dass die PSMD-definierte Integrität der weißen Substanz mit höherem Alter und steigender Schädigung durch Marklagerhyperintensitäten

abnimmt. Assoziationen mit Kognition waren nur im Querschnitt, nicht aber im Längsschnitt nachweisbar. Dies kann durch die geringe Fallzahl unserer longitudinalen Daten bedingt sein und weitere Studien mit der gleichen Zielsetzung sollten größere Studienpopulationen und längere Intervalle zwischen den Erhebungen im Längsschnitt anstreben.

Abstract

Objective: The "Peak Width of Skeletonized Mean Diffusivity" (PSMD) has been shown to be a promising DTI marker to assess white matter integrity, which is highly associated with cognitive health. There are few papers that have investigated associations between PSMD and cognition, in particular only two longitudinal studies. The first aim of this work was to investigate associations between PSMD and cognition in cognitively healthy adults in a cross-sectional study. The main aim of the work was to longitudinally investigate whether PSMD changes are related to cognitive changes over time. In addition, associations between PSMD, age, gender, vascular risk factors, white matter hyperintensities, and brain volume were investigated.

Methods: A total of 326 healthy adults aged 38-87 years were included in the cross-sectional study. MRI-based PSMD values were calculated together with measurements of total brain volume and WMH volumes. Cognitive performance was assessed in four domains: Memory, visual-practical skills, executive functions, and a composite score for global cognition. In a subgroup of 61 participants with complete longitudinal data, longitudinal changes in PSMD, WMH volume, and cognitive performance were examined.

Results: In the cross-sectional analysis with 326 participants, PSMD showed a strong positive correlation with age, with a steeper increase observed in participants aged ≥ 60 years. In this age group, men also had significantly higher PSMD levels than women. In addition, PSMD was positively associated with the volume of WMH.

In the cross-sectional analysis, higher PSMD levels were also significantly associated with lower performance in visual-practical skills and executive functions.

The longitudinal analysis (n = 61) also revealed an increase in PSMD over time. The increase in PSMD correlated positively with the increase in WMH volume. However, an increase in PSMD over time did not correlate with changes in any of the cognitive domains analyzed.

Conclusion: Our results confirm that PSMD-defined white matter integrity decreases with age and increasing damage from WMH. Associations with cognition were only detectable cross-sectionally, but not longitudinally. This may be due to the small number of cases in our longitudinal data and further studies with the same objective should aim for larger study populations and longer follow-up times.

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Abbreviations and their meaning

ADNI-Cog13	Alzheimer Disease Assessment Scale-Cognitive
ADNI-Mem	Alzheimer's Disease Neuroimaging Initiative – memory
ANOVA	Analysis of Variance
ASPS	Austrian Stroke Prevention Study
ASPS-Fam	Austrian Stroke Prevention Family Study
BMI	Body mass index
CNS	Central nervous system
CSF	Cerebrospinal fluid
DBP	Diastolic blood pressure
DTI	Diffusor tensor imaging
DWI	Diffusion weighted imaging
FA	Fractional anisotropy
FLAIR	Fluid attenuated inversion recovery
HC	Healthy controls
ICH	Intracerebral hemorrhages
IQR	Interquartile ranges
LDL	Low-density lipoprotein
MD	Mean diffusivity
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MPRAGE	Magnetization Prepared Rapid Acquisition with Gradient Echoes
MRI	Magnetic resonance imaging
MTI	Magnetization transfer imaging
PSMD	Peak Width of Skeletonized Mean Diffusivity
RAM	Random access memory
SBP	Systolic blood pressure
SD	Standard deviation
STAC-r	revised Scaffolding Theory of Aging and Cognition
SVD	Small vessel disease
TBSS	Tract-Based Spatial Statistics
TBV	Total brain volume

TIV	Total intracranial volume
WMH	White matter hyperintensities

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1 Introduction

1.1 Structural brain aging

The typical aging process involves biological changes in the brain, which relate to age-related deterioration of cognitive abilities. Given that the brain serves as the foundation for cognitive processes, alterations in its structure over time have been linked to a reduction in cognitive abilities. Brain aging affects not only individuals who suffer from neurodegenerative diseases, such as Alzheimer's disease, but is a natural part of the aging process. This indicates that in individuals without cognitive impairment, neurodegenerative processes may occur and be discernible through magnetic resonance imaging (MRI) even before clinical manifestations emerge. The identification of structural alterations in the brain and their correlation with the deterioration of specific cognitive functions significantly contributes to the comprehension of brain aging and its consequences (1).

According to Lockhart et al. (1), aging accounts for about 50% of the total differences in cerebral brain volume. These changes become significantly more pronounced after the age of 50, whereas they remain relatively minor before this age. Numerous brain imaging studies have shown that aging is linked to specific changes in brain volume, varying by region. The frontal lobe is the area most affected by this aging process (1). In a cross-sectional study performed by DeCarli et al. (2) the frontal lobe showed a decline of approximately 12% across participants ranging from 30 to over 90 years old (2). In contrast, the changes in the volume of the occipital lobe are modest (1).

A quantitative MRI study conducted by Coffey et al. (3) explored the cognitive aspects of brain aging in humans, revealing a link between age-related changes in brain structure and a decline in attention, psychomotor speed, and visual delayed memory. The study involved elderly volunteers, aged 66 to 90, who were clinically normal and had a MMSE (“Mini Mental State Examination”) score of 24 or higher. This study, too, showed a strong relation between aging and changes in brain volume as well as aging and cognitive test performance: A higher age was associated with smaller cerebral hemisphere volume, larger volume of the lateral fissures, the lateral ventricles and the third ventricle. The performance on cognitive tests was also shown to be linked to the age of the participants (3).

In a 2003 published longitudinal MRI study (4), which included 92 non-demented participants (age 59-85) the rates and regional distribution of gray and white matter loss were examined. Every participant was included after evaluation of the past medical history. All

92 persons were free of diseases of the central nervous system (CNS), severe cardiovascular or pulmonary diseases and free of metastatic cancer. On a follow-up examination at year 5 all individuals were still free of dementia. Additionally, there was a sub-group of 24 very healthy adults. This term means that they were free of any medical condition or cognitive impairment at the year 5 follow-up. The authors performed MRI scans on every participant at a baseline, 2-year and 4-year follow-up. They found out that there were significant age changes in gray and white matter volumes. The annual rate for total brain tissue loss was observed at approximately 5.4 cm^3, meaning 0.5% per year. The rate of gray matter loss was calculated at approximately 2.4 cm^3, the white matter indicated a loss of 3.1 cm^3. On the contrary, the volume of the ventricles increased annually at a rate of 1.4 +/- 0.1 cm^3 per year. The rates of increase in ventricular volume were significantly higher for older people, than for younger. The study also found out, that the frontal and parietal lobes were significantly more affected by tissue loss than the occipital and temporal lobes. Rates of tissue loss could also be seen in the sub-group of the 24 very healthy adults, although on a slower rate (e.g., 3.7 cm^3 total brain tissue loss, 1.2 cm^3 increase of ventricle volume per year, respectively). This indicates that individuals who stay medically and cognitively healthy experience slower rates of brain atrophy (4).

Another study performed by Courchesne et al. (5) had 116 healthy volunteers aged 19 months to 80 years undergoing MRI scans to examine age-related change in intracranial space, whole brain, gray and white matter as well as cerebrospinal fluid (CSF) volumes. The authors observed an 25%-27% increase in total brain and intracranial volume between infancy and early adolescence (mean age 26 months to 14 years). After that, the total brain volume decreased, with the volumes of the oldest participants (age 71 to 80) being similar to the whole-brain volumes of young children. In the same study the authors saw that gray matter increased 13% in volume from early to later childhood (age 6 to 9). After early childhood, gray matter kept increasing, but more slowly until its volume reached a plateau in the fourth life decade. From there, gray matter volume again decreased by 13% in the oldest participants (5).

A newer longitudinal study published in 2022 performed by Bagarinao et al. (6) also examined age-related volumetric changes in the brain of 227 healthy older adults (age 50 to 80). All participants underwent MRI scans at a baseline and two follow-ups approximately one year apart. All patients were healthy and stayed medically and cognitively sane (MMSE 26 or above, no observable anomality in the brain, no white matter hyperintensities (WMH) that were grade 2 or 3 based on the Fazekas hyperintensity rating scale) (6). The authors

were able to show results very similar to those of Resnick et al. (4) in their 2003 published longitudinal study (4).

The individuals in this study showed an annual decline rate of 2,5 cm^3 for the gray matter and 2,6 cm^3 for the white matter. In this study, too, the frontal and parietal lobes showed faster rates of tissue loss than the temporal and occipital lobes. Conversely, some areas in the temporal and occipital lobe even seemed almost unaffected by tissue loss. The authors concluded that the areas, which mature later are prone to faster decline in later stages of life, whereas regions in the temporal and occipital lobe, that are known to develop much earlier, preserve themselves much better from tissue loss. This suggests that an optimal and early development of the frontal and parietal brain areas, that are crucial for higher-order cognitive functions, is essential for healthy brain aging (6).

Given that most individuals show similar gray matter tissue loss, it remains unclear, why some older people stay cognitively healthy while others suffer from severe cognitive dysfunction. There are two concepts trying to explain this discrepancy. First, the concept of brain reserve. This idea states that the accumulation of neural resources in early stages of life could mitigate the effect of gray matter tissue loss at a higher age. The frontal and parietal lobe, being responsible for more complex cognitive processes and integrating information from unimodal brain regions are known to mature later and therefore being amenable for developing neural reserve capacities (6). On the other hand, exactly these areas, that develop later and are therefore potentially more amenable to develop a neural reserve capacity, are those which decline first and more rapidly. This is known as the “retrogenesis hypothesis”. Supported by the finding, that the frontal lobe changes first and most, followed by the parietal lobe and even the temporal lobe showing areas that change up to 25% comparing age 45 and age 90 the assumption of an anterior-to-posterior gradient of age vulnerability has been made (7).

The other concept trying to explain the stated discrepancy is the idea of brain maintenance. In contrast to the frontal and parietal lobe, the occipital and temporal lobe are known to mature early and show a steadier gray matter tissue value in later life. The preservation of these regions through repair mechanisms could counteract tissue loss and cognitive malfunction later. However, one of the two concepts is supported by anatomical evidence (6).

Moreover, most brain areas and components do not show a linear trajectory in change over age. There seems to be an acceleration in volume alterations after the age of 50 to 55. This concerns the increase in CSF volume, the decrease of total brain volume and the decrease of

hippocampal volume for instance. In contrast to the white matter, the gray matter seems to follow a continuous, near linear change over time and begins to change later, too. Overall, it can be stated, that the process of brain tissue alteration experiences an acceleration with increasing age (7).

1.2 Aging and cognition

Normal cognitive aging is a process every human being is affected by, though, large differences exist. Some cognitive domains, like processing speed, memory or executive function begin to deteriorate in early adulthood, while other mental abilities like verbal or numeric abilities as well as general knowledge do not suffer from age-dependent decline. The inter-individual discrepancy of cognitive decline can be referred to several factors. Genetics, atherosclerotic disease, diet, lifestyle, and general health disorders are some of them. The decline of so called fluid mental abilities like processing speed or memory does not only impact the ability to lead a self-organized life but also leads to the decline of other cognitive domains (10). A central hypothesis about the influence of fluid mental – or cognitive – abilities on further cognitive decline in aging is built on information processing speed. When the speed with which cognitive tasks are executed slows down, this leads to a decline in cognitive abilities. There are two reasons for this: the limited time mechanism and the simultaneity mechanism. First, when speed is low, there is simply not enough time to execute special cognitive operations (limited time). Second, when processing speed slows down, products of early processing may be gone as soon as later processing has been carried out (9). This of course does not apply to every crystallized cognitive domain. Slowing processing speed is nowadays mainly accepted for its mediating effect on age-related memory and special ability. This is backed by longitudinal data from over 800 patients covering five measurements in a total of 16 years of follow-up time (10).

One pressing question is why some individuals suffer from severe cognitive deterioration in higher age while others seem to be affected to a much lesser degree. As mentioned above, brain reserve (that means the size of the brain or number of neurons), or cognitive reserve are responsible for discrepancies in cognitive abilities among older people.

One theoretical model trying to unite different environmental circumstances, brain structure and cognitive abilities is the revised Scaffolding Theory of Aging and Cognition (STAC-r) designed and revised by Reuter-Lorenz and Park (11). The theory is founded on structural and functional neuroimaging and tries to explain how adverse and compensatory neural

processes lead to different levels of cognitive function between different ages. The first concept of this theory was published in 2009 (12) and was later revised in 2014 to implement life-course factors that can either positively or negatively influence neural resources and therefore play a role in the development or change in brain structure, its function and related to that, cognitive abilities (13).

1.2.1 The STAC-r theory: an adaptive brain

Older adults are exposed to numerous "neural challenges" that are primarily structural changes such as cortical thinning, regional atrophy, loss of white matter integrity and dopamine depletion. Another category of "hazards" is summed up as "functional deterioration" meaning several functions that suffer from age-related decline. This category includes decreased medial temporal recruitment (related to memory), decreased specificity of ventral-visual and motor areas and dysregulation of the default mode network (13).
The latter describes brain areas that are usually deactivated during active task performance. In aging (as well as in dementia) those specific regions show a reduced resting metabolic activity, which hints at a possible relation between the malfunction of the regions of the default mode network (including large parts of the lateral parietal cortex, the medial parietal cortex and the medial frontal cortex) and difficulties with attention and focus as well as alterations in the mental health status in both, aging and dementia (14).
These two forms of negative influence, meaning "neural challenges" and "functional deterioration", have an impact on the alterations in cognitive abilities – alongside a beneficial process, termed as "compensatory scaffolding" (13).

1.2.1.1 "Compensatory scaffolding" – the heart of the STAC-r theory

The brain architecture does not only change negatively reaching advanced age. The stated term describes a form of positive neural plasticity that occurs in the aging process to maintain cognitive functions as well as possible. With advancing age, the brain seems to adapt to its challenges in the shape of an overactivation. This could be seen in tasks of memory as well as in executive and perceptual tasks. To stay able to perform, the brain activates additional prefrontal and parietal regions which are not activated during the same tasks in younger individuals. Furthermore, activities that normally trigger unilateral activation of the responsible brain region seem to initiate a bilateral activation for the same tasks. This means that the brain undergoes the aging process not only in a diminishing way but rather adapts

to be able to perform. The above stated negative influences of “neural challenges” and “cognitive deteriorations” even seem to stimulate the scaffolding to a certain extent. External influences in terms of learning new skills, formal cognitive training and even physical exercise are also stated to have a positive impact on positive plasticity (13). The work of Peterson et al. (15) was especially crucial for the STAC-r theory. They found out that a set of prefrontal regions was highly active during the early phase of acquiring a new skill. With steady repetition of the same task, it became more and more a habit and those brain areas that were initially very active, “turned off” during the execution of this skill. Instead, other skill-related regions were activated. The researchers suggest that the initial burst of prefrontal activity acts as a form of "scaffolding"—a temporary support system that helps build the structure of the new skill (13). Reuter-Lorenz and Lustig (16) additionally came to the conclusion, that skills that are more demanding in the beginning seem to activate even more areas responsible for executive functions, especially located in the prefrontal cortex. Thus, the brain possesses the ability to adjust to new and demanding skills. It has been suggested that similar mechanisms can be used by the brain to maintain cognition in aging (13).

1.2.2 Aging and memory

Memory can roughly be divided in retrospective and prospective memory (17). Retrospective memory describes the ability of retrieving previously acquired information. It can be further separated into a short- and long-term memory. The long-term memory, however, can be subdivided into an explicit (involving episodic and semantic memory) and an implicit memory. The episodic memory portrays the capability of recalling or recognizing events from the past. It can be tested by either recalling or recognizing a set of words for example (11). The episodic memory, especially the sub-aspect of recalling in contrast to recognition, is known to subsequently getting worse during aging (18), although staying rather consistent until the age of 60 according to longitudinal studies (19). The ability to recollect and use factual knowledge that has been obtained in the past is called semantic memory. Contrary to episodic memory, it seems to be rather resistant to the aging process and increases at least until age 55 (19). The implicit memory refers to the unconscious influence of previously acquired information on present performance and seems to be rather resistant to aging (11). The results of a longitudinal study performed by Fleischmann et al. (20) on cognitively healthy older individuals showed no performance loss in the domain of

implicit memory over a follow-up time of three years. Therefore, the authors state, that implicit memory remains rather unaffected by age-related detrimental processes even until late age (20).

The short-term memory, especially the working memory, can be understood as "random access memory" (RAM) if translated to computer language. It is needed for processing and updating information (11) and is strongly associated with fluid intelligence (21). A decline can be seen starting as soon as age 20, following a linear trend (22). The term of prospective memory describes the remembering of plans made prior and operating according to them in the presence or future. A real-life example would be taking daily medications as the prescription foresees it. In lab-testing, the prospective memory abilities seem to drastically decline with time. However, in real life the results of the lab-testing do not seem to apply as drastically, which could be due to higher motivation or flexibility that are higher in the normal every-day life than in lab-testing (11).

1.2.2.1 Changes in brain structure and memory

The episodic memory, as stated above, is known to be the most targeted by the aging process (11). Numerous MRI studies were able to depict a correlation between episodic memory performance and the volume of gray matter of medial temporal regions (23,24). Especially the hippocampus seems to have a big impact on this cognitive domain. Adults with higher baseline hippocampus volumes or such showing less hippocampal atrophy over time showed less decline in episodic memory abilities over a time span of 4 to 8 years (25,26). Mungas et al. (27) state that hippocampal volume is the primary determinant of memory decline in their longitudinal study (27). A higher baseline episodic memory performance is also associated with the cortical thickness of right hemispheric regions. (28) Furthermore, a steeper decline in whole brain volume and increase of the CSF, especially the lateral ventricles, also correlate with lower efficiency in episodic memory (11).

1.2.3 Aging and attention

Attention may be differentiated into three sub-aspects. There is the sustained attention which refers to the ability of staying aware and vigilant over a period of time and does not usually suffer much decline in later stages of life. The selective attention describes the skill to focus on task-relevant information while ignoring less important input. This aspect can be assessed with the Stroop Interference Test. A proband has to name colors of printed words while

ignoring that the letters read another color than the word is printed in. This aspect of attention is regarded to be much more sensitive to age. Its decline is connected to a diminished inhibitory control of the brain. Thus, distractibility increases. To be able to focus on two or more stimuli at once is called divided attention. Like with selective attention, a decline can be seen in higher age. Related to divided attention, the competence to switch between different tasks or skills suffers from aging, although the decline is stated to be related to the general decline of executive functioning and associations with white matter tracts located in the prefrontal cortex have been reported (29).

1.2.4 Aging and executive functioning

Executive functioning is constructed of a general component and several basic abilities including the suppression of predominant responses or switching between different tasks or ideas. It also covers the processing of information stored in the working memory domain (11). In general, it can be understood as a cognitive construct of high-order targeting as it manages self-regulation and goal-directed behavior as well as working out complex tasks with provided information. The "seat" of executive functioning can be linked to the prefrontal cortex, that is by itself connected to a various number of other brain regions. The issue with executive functioning in higher age seems to be that the ability to generate or use necessary strategies to carry out a specific task diminishes. The area of strategizing is the prefrontal cortex (29).

1.2.4.1 Changes in brain structure and executive functioning

Elderkin-Thompson et al. (30) found out that volumes of specific areas of the prefrontal cortex (e.g. gyrus rectus or anterior cingulate cortex) are directly connected to specific executive functions. They also state that declining executive functioning is not directly linked to higher age but rather to atrophy (30).

In a longitudinal MRI study with a follow-up time of 8 years Leong et al. (26) were able to link hippocampal atrophy and ventricular enlargement to a decline of executive functioning (26). Another longitudinal study was able to show an association between baseline volume of the hippocampus and decline of executive function over four years. The author states that individuals with lower baseline volume in that region experience a steeper decline in executive function (25).

1.2.5 Aging and processing speed

Processing speed is strongly associated with aging and slows down within a person's life span. Additionally, lower processing speed correlated with declines in other cognitive domains, like memory (31).

Some studies, like the one by Ritchie et al. (32), were able to show a correlation between the whole brain gray matter volume and processing speed. In a longitudinal study, a slower decline of processing speed was seen when there was less decline in the gray matter of the whole brain (32).

Like mentioned from Leong et al. (26) there is not really one brain area responsible for processing speed. Data suggests that the decline of processing speed could be connected to the loss of integrity of white matter with advancing age. Lower values of fractional anisotropy (FA), a measurement for the integrity of white matter, were associated with poorer processing speed (26). Similar findings were presented by Lövdén et al. (33) who observed a correlation between the decline of the microstructure of the corticospinal tract and slowing of processing speed over 2 years in healthy older adults. They stated that the steeper the decline of the white matter integrity the more the individual suffers from lack of processing speed (33).

1.3 Small vessel disease

Small vessel disease is counted as one of the leading causes for vascular cognitive impairment, a term that gathers all cerebrovascular pathologies leading to cognitive decline (34). Small vessel disease (SVD) itself is an umbrella term for numerous pathologies of cerebral vessels, reaching from small arteries and veins to capillaries (35). These pathologies include WMH, lacunar infarctions, microbleeds, perivascular spaces, microinfarcts and brain atrophy (36). The first three can be regarded as the hallmark pathologies of SVD (37). The appearance of these lesion does not always cause symptoms, or at least not immediately. However, the accumulation of many SVD-connected lesions are associated with cognitive impairment, dementia and even depression (36). In addition, SVD is responsible for about 25% of strokes (38), is further associated with stroke recurrence and a higher mortality in the aftermath of a stroke (39) and is the second frequent pathology behind developing dementia after Alzheimer's disease (40).

Timing and extent of clinical manifestation in general depend on the cause of the disease and the brain area involved (35).

The prevalence of SVD increases with age. At age 50, it affects around 5% of individuals. This percentage reaches almost 100% when looking at persons over the age of 90. Other risk factors are hypertension (which is the most important one), radiation exposure, cerebral amyloid angiopathy, vasculitis of immunological cause or certain infections. SVD-caused pathologies can be detected with brain imaging. Further advanced imaging techniques, like diffusion tensor imaging or perfusion MRI, can hint at pathologies way earlier, possibly paving the way to prevent progression before clinical symptoms appear. Due to the lack of understanding the exact pathology behind SVD, the current best treatment is the management of vascular risk factors, especially high blood pressure (38).

1.3.1 SVD-related pathologies in MRI over time

To be able to monitor the effectiveness of treatment options, it is important to understand how SVD-caused pathologies change over time. This can help to determine surrogate markers and endpoints for future treatment studies. A surrogate marker therefore has to show a visible progression over time so that treatment effects can be monitored in a rational time period. Further, the monitored changes need to be correlated to changes in the clinical condition of the individual. With advancing MRI techniques, studies show that the full impact of SVD-damage cannot be depicted by standard MRI. For example, diffusion tensor imaging (DTI) and Magnetization transfer imaging (MTI) are able to show brain damage related to white matter lesion on a microstructural level which refers much better to the clinical condition of the examined individual (37).

1.3.1.1 White matter hyperintensities

The most common pathology caused by SVD are WMH. Approximately over 90% of people aged 65 or above show WMH in varying severity. They can be further distinguished in punctate, early confluent and confluent lesions, with the latter two being those mainly progressing (37). Taylor et al. (41) stated an increase of nearly 27% in WMH over a two year period in elderly patients. They also reported that, in their study, higher age and diabetes mellitus were associated with a greater increase in WMH (41). Over the span of three years 74% of participants (523 subjects) in the longitudinal study of Gouw et al. (42) showed an increase of WMH at least in one brain area. The area most targeted is the subcortical white

matter, where the highest baseline and progression scores could be found (42). Unlike the one by Taylor et al. (41), this study states that the baseline level of WMH allows a prediction of the degree of their progression. So, the higher the baseline volume, the bigger the increase. Here also, diabetes was an associated risk factor for progression of lesions, as well as high blood glucose and stroke in the past medical history. Whereas high blood pressure was not found to be a risk factor (42). In the Austrian Stroke Prevention Study Schmidt et al. (43) included 296 volunteers aged 50 to 75 undergoing MRI scans at a baseline and two follow-ups (after three and six years). After the second follow-up 58 patients with no and 123 patients with only punctate white matter lesions showed low tendency for increase of lesion volume. Participants with early confluent or confluent lesions at baseline suffered increases of 2,7 cm^3 and 9,3 cm^3, respectively. The best predictive marker for progression appeared to be the level of baseline lesion load. Age and high blood pressure did not seem to have an impact on lesion progression (43), the latter was also stated by Maillard et al. (44), in whose study the annual rate of WMH progression was also not associated to hypertension (44).

1.3.1.2 Lacunar infarcts

Lacunar infarcts present the second most frequent entity of SVD-caused pathologies. In the general elder population they occur in 6 to 20% of individuals (37). In a study performed by Giroud et al. (45) the incidence and survival rates over two years of cerebrovascular events (intracerebral and subarachnoid hemorrhages, cortical infarcts, lacunes and TIA) were measured. The researchers had a very large sample of 140,000 participants, from whom 984 suffered their first stroke during the observation period. 16.7% of these strokes were attributed to lacunes. The annual incidence rate for lacunes per 100,000 was 30 (45). Duering et al. (46) studied the topographic distribution of incidental lacunes and found out that most of them (nearly 91.3%) developed at the edge of WMH. This states that tissue adjacent to WMH seem to be a predilection site for ischemia and lacune forming (46) supporting the assumption that WMH are not sharply delineated injuries but rather may represent areas of more widespread white matter changes (47).

1.3.1.3 Microbleeds

Microbleeds present themselves as hypointense lesions in T2* gradient echo or susceptibility-weighted magnetic resonance imaging (48). The prevalence of microbleeds continuously increases with age. They occur to 6.5% in total at an age of 45 to 50 with the

percentage increasing to 35.7% for people at age 80 or older (49). Poels et al. (50) performed a longitudinal study with 831 participants who received MRI scans at a baseline and 3 year follow-up. They found that the overall prevalence of microbleeds increased from 24.4% to 28.0% in that time. Approximately 10% of the individuals showed new microbleeds whereas only 6 participants showed a lower amount of microbleeds in the follow-up compared to the baseline scan (50).

Besides age, hypertension is strongly associated with the presence of microbleeds, especially in the basal ganglia and infratentorial region (51). Another strongly associated risk factor is excessively cigarette smoking (> 20 per day) (48). Individuals with lacunar infarcts and larger volumes of WMH seem to be more prone to develop new microbleeds. Additionally, individuals with microbleeds at a baseline level have a five-time higher risk of developing new ones in a follow-up time of three years (50). The presence of microbleeds also appears to be associated with the presence of intracerebral hemorrhages (ICH) (49). The degrees of microbleeds in the subcortical area or deep gray matter strongly correlated with the finding of intracerebral hemorrhage in the same areas (52). Chen et al. (53) additionally reported about a topographic relationship between microbleeds and ICH in basal ganglia and thalamus (53).

1.3.2 SVD-related brain changes and cognition

Greater burden of SVD-related brain changes is associated with general cognitive decline (54). Executive functioning, attention, processing speed and verbal fluency (35) as well as working memory are influenced (40). However, SVD-caused pathologies do not seem to be directly associated to decline in single cognitive skills but rather to diminishing cognition in general, which can be seen with advanced aging. This supports the understanding of SVD being a diffuse disease that affects the whole brain by disrupting connections between brain regions that are important for our normal cognitive function (54). This disconnection is based on the loss of white matter integrity even in normal aging and provides a structural explanation for diminishing of cognition over time (55).

The presence of SVD-caused WMH and lacunes has been especially emphasized to be predictive for cognitive decline. Both, WMH and lacunes – being different expressions of SVD, show a moderate association to each other and separately increase the risk for cognitive decline. The presence of SVD-related tissue damages even seems to enhance the pathologies causing dementia (56), especially in people around age 75 (57).

1.3.2.1 WMH and cognition

Cerebral WMH are associated with deterioration of cognitive abilities (58), although for a long time it was rather uncertain to which extent (59). A 2014 published meta-analysis from Kloppenborg et al. (60) examined 23 cross-sectional and 14 longitudinal studies on this subject and found a significant association between the presence of WMH and cognitive deficits for all investigated domains including memory, attention, executive function, and processing speed. Further, they managed to display an association between progression of WMH load and further worsening of cognitive abilities. This association was especially strong for attention and executive function (60). So, the amount of WMH volume matters and its progression contains clinical relevance in terms of cognitive performance (61). This is backed by a study that sub-divided its participants into 4 categories depending on the severity of WMH load. In all cognitive tests, subjects with higher WMH load exhibited impaired performance on cognitive tests and greater worsening of cognitive abilities (62). A newer longitudinal study from 2020 that investigated 818 participants with a total follow-up time of 7 years was able to verify and further strengthen these findings. In their study, Wang et al. (63) likewise state the correlation between WMH volume and worse cognitive functions. Longitudinally, individuals with high WMH load did worse on several cognitive tests like the MoCA (Montreal Cognitive Assessment Test), the MMSE, the ADNI-Mem (Alzheimer's Disease Neuroimaging Initiative – memory) and the ADAS-Cog13 (Alzheimer Disease Assessment Scale-Cognitive). Additionally, subjects with high WMH load showed the likelihood of developing dementia (62). Further, the location of the lesions seems to matter (64). Generally speaking, WMH can be distinguished into periventricular and deep lesions (65). Frontal lesions, nearby the frontal ventricles, seem to mainly affect executive function while lesions in the proximity of the posterior horns are related to memory diminishing. Deep white matter lesions, like such affecting the corticospinal tract, were associated with worse motor speed performance (64).

1.3.2.2 Lacunes and cognition

Lacunes were linked to cognitive dysfunction and dementia in patients who prior suffered a stroke – in dependence of their number and localization (34). Benisty et al. (66) saw that individuals with lacunar infarcts in the thalamus performed worse in the MMSE. They also showed declined abilities regarding speed and motor control as well as executive

functioning. The finding of lacunes in the putamen, however, showed association with poor memory performance (66). In a longitudinal study Jokinen et al. (67) performed MRI scans at a baseline and 3 year follow-up to test the influence of incident lacunes on cognition. The researchers found out that incidence of lacunes was associated with poorer performance on executive functions, (67) which is further supported by Mungas et al. (27) who made the same claim in their longitudinal study (27). Jokinen et al. (67) also found out that speed and motor control also showed a decline connected to lacunes. However, an association between lacunes and memory decline as well as lacunes and global cognitive function could not be found. Overall, lacunes should not be considered benign (67) and management of cerebrovascular risk factors such as high blood pressure, hypercholesteremia or diabetes should be optimized in order to preserve cognitive abilities (68).

1.3.2.3 Microbleeds, microinfarcts and cognition

Other than WMH and lacunes, which are widely accepted to have an influence on cognitive decline, the impact of microbleeds still remains unclear (69). The overall evidence however do suggest a clinical relevance on cognition (70) although the pathophysiology behind their influence on cognition is speculative (71). Li et al. (72) stated that cerebral microbleeds do have an impact on cognition, depending on their amount and location. Presence and progression of microbleeds were associated with diminishing of global cognitive functioning but also with memory decline and executive function. These categories declined in association with lobar microbleeds. As for memory, especially temporal lobe microbleeds seemed to matter (72) which further strengthens the outlook on the importance of temporal lobe sanity on memory preservation (11). The study of Li et al. (72), however, was performed on patients who suffer from Alzheimer disease (72). In a study that included healthy patients, patients with mild cognitive impairment and dementia, Hilal et al. (73) saw that an increased amount of cortical microinfarcts (73), which are present in patients with higher SVD burden (74), does predict an acceleration in overall cognitive decline. The association for microinfarct dependent worsening in memory and language skills over time was significant (73). Akoudad et al. (71) similarly report an association between high count of microbleeds (more than four) and cognitive decline in all domains. The authors further state that lobar microbleeds can be associated with diminishing of distinct cognitive skills. They too mention the association of multiple microbleeds in the temporal lobe and memory worsening. Deeper microbleeds (e.g., in the basal ganglia or internal capsule), however, seem to influence motor

function negatively. The presence of multiple microbleeds also increase the risk for developing dementia. In Alzheimer's disease 18-32% of the patients feature microbleeds, mainly in the cortico-subcortical area (71).

1.4 Diffusion-weighted MRI

To understand on which pathways information is integrated and exchanged between brain areas, more specific MRI tools need to be used. The "structural connectivity" between different gray matter regions in the brain is typically provided by white matter tracts. The structural connectivity of the brain needs to be examined by processing diffuson-weighted imaging (DWI) data (75).

For the understanding of DWI – and overall important for MRI – the definition of a voxel is important. Voxels are a geometric form, that can be understood as the 3D-counterpart to the two-dimensional pixels (76). So, like pixels, they refer to an element of an image. More specific, they refer to a volume element (75). Voxels can abstractly be presented as cubes. Rather than using the whole cube for image representation, the center point, or the corner points of each one represents the whole (76).

The core principle of DWI is that each voxel is imaged multiple times with each one of these images being sensitive to diffusion in the direction of a specific axis. For each voxel the combination of images then describes the preferred direction of diffusion ("flow") within it (75).

Diffusion tensor imaging (DTI) was first launched in 1994 by Basser et al. (77) as an improvement of DWI. DWI technique on a molecular level is based on the Brownian motion of water molecules. However, in tissue this principle does not fully apply, because the molecules are restricted in their movement by barriers, like cell membranes (describing an anisotropic diffusion). Thus, the usual pattern to describe how water molecules move randomly and freely – which would equal a Gaussian distribution – does not match how water molecules really move inside our body. Therefore, DTI was introduced. Both techniques use the characterization of diffusion direction of water molecules to picture the orientation and integrity of white matter tracts. While DWI uses one or more specific directions to describe diffusion, DTI normally uses from 12 to more than 100 directions, which provides a much more accurate depiction of diffusion direction of water molecules and thus also the direction and integrity of the axons. Using ellipsoids (mathematically: tensors of 3x3 matrices), DTI can display the movement of molecules in three dimensions

for every voxel. It provides a much more precise depiction of the different direction and "intensities" of the motion. Due to its accuracy and high sensitivity, DTI is thought of as promising way to evaluate white matter injuries and their progression in the course of cerebral small vessel disease (78). It can be stated that DTI is made to measure diffusion in anisotropic environments, as water cannot flow equally in all directions due to mechanic barriers. Fractional Anisotropy (FA) is therefore a highly important measurement derived from DTI. It ranges between 0 and 1. Higher values indicate a highly anisotropic diffusion which is typical for well-organized and normal white matter. As white matter gets damaged and loses substance, the water that is detected by DTI runs more fluently because there is less mechanic barrier. This results in lower FA values. Another important value is the Mean Diffusivity (MD). It represents the average diffusion magnitude in a voxel and refers to how freely water molecules can move in tissue. Normally higher MD values are found in CSF, where water can move freely while a lower MD is found in dense cellular structures, like intact gray or white matter. So, MD and FA behave inversely when it comes to white matter integrity (79).

1.4.1 DTI and aging

As mentioned above, DTI can be very useful to evaluate the integrity of white matter and assess its injuries over time (78). Now, it is known that like grey matter, white matter exhibits various changes in the healthy aging process (80). Histological post-mortem studies refer about a loss of myelin substance and a decreased number of myelinated fibers (81). Some volumetric neuroimaging studies even suggest that white matter – in some areas – suffers more atrophy than gray matter (82,83). A prominent example is the prefrontal area. Here, in late aging, individuals show disproportionally more white than gray matter loss (84).
Salat et al. (80) cross-sectionally examined 38 adult participants through DTI-MRI and measured their regional FA values. Their results show a dominant age-related decline of prefrontal white matter and thus, lower FA values (80). Prefrontal FA is reduced in older adults when compared to younger individuals (85). A steeper decline can also be seen in the posterior limb of the internal capsule and the genu of the corpus callosum. The temporal and posterior white matter, as well as the parietal, appeared to be relatively well-preserved (80,86). The latter finding aligns with those of longitudinal voxel-based studies suggesting that occipital regions preserve themselves quite well from age-related white matter loss (87). Although age-related white matter alterations, measured by decreasing FA, can be detected

globally, some regions, like the prefrontal area, show an acceleration in tissue loss (80,86). A correlation between decrease of prefrontal white matter FA and volume can be described for individuals over 40 years old (85). A noticeable loss of myelinated fibers can be found in key brain regions like the corpus callosum or the precentral gyrus. Interestingly, the smaller connecting fibers in the front part of the corpus callosum, which develop later in life, seem to wear down earlier with age. This early degeneration might help explain some of the common declines in frontal brain functions that occur with advanced age (86).

1.4.2 DTI and cognition

The connection between brain function and structure is widely agreed on. When it comes to associate specific brain regions to specific cognitive tasks, however, some difficulties occur. Cognitive tasks mostly involve a network of brain structures rather than a single region (88). Numerous studies have shown that DTI is able to detect brain regions of cognitive domains by correlating performance on cognition tests to DTI parameters, like FA for instance (89,90).

In a study conducted by Sasson et al. (88) 52 healthy participants ranging from age 25 to 82 underwent a standardized battery of cognitive tests and DTI scanning. The authors used voxel-based analysis of both, gray and white matter, to associate micro-structural correlations with performance on processing speed, memory and executive functioning and were able to show that correlations between cognitive performance and DTI indices were region-specific. The findings well-aligned with the known areas that are important for the respective cognitive domain (88).

Processing speed is referred to correlate with DTI parameters of the cingulum, the corona radiata, the parietal white matter and the thalamus, while memory performance showed a strong link to temporal and frontal gray and white matter, including the parahippocampal area. The authors suggest that differences in cognitive performance and brain structure, as measured by diffusion tensor imaging, may help link tissue microstructure to cognitive ability and support other methods of mapping brain function (88).

Masalchi et al. (91) investigated the correlation between global cognitive performance, which they assessed through the MoCA test, and DTI measurements (among them, FA and MD) of white matter tracts in patients with small vessel disease and mild cognitive impairment using Tract Based Spatial Statistics (TBSS). In their study, MoCA scores significantly correlated with MD and FA values (negatively with MD values, positively with

FA values) of the white matter tracts of the hemispheres and the corpus callosum as well as with the inter-thalamic tracts. Thus, they state that global cognitive performance, represented by the MoCA score, is correlated to microstructural damage of white matter tracts that can be measured through DTI parameters (91).

Another study that searched for correlations between cognitive performance and integrity of white matter tracts (again, depicted by MD and FA values) was conducted by Reginold et al. (92). In their study, worse score on the Stroop test was associated with a decrease in FA of the corpus callosum and thalamic tracts (92). When healthy elderly people (61 to 86 years) were investigated, it seems that loss of cognitive performance correlates more with deterioration of white matter than gray matter. Especially white matter underlying association cortices seems to be targeted. Ziegler et al. (93) found region specific correlations between cognitive performance and white matter integrity. These correlations did not apply, however, for gray matter or cortical thickness. Episodic memory, for instance, was related to the integrity of the white matter of the temporal lobe (93). The authors state that worsening of some cognitive abilities may occur while aging through loss of integrity in the white matter, that builds the connection between the responsible neural networks (93–95).

1.4.3 Analysis of the brain structural network using DTI

Through DTI, the analysis of a structural network of the brain can be achieved (78). A network is a mathematical representation of a complex system through nodes and connections between these nodes that are called links. When applied to the brain, certain brain regions are depicted as nodes. White matter tracts represent the anatomical links that physically connect the nodes with each other (96).

To display the white matter fiber bundles that form the tracts, diffusion tensor tractography (DTT), a sub-technique of DTI, is used. Brain structural network analysis mostly uses graph theory to assess damage to connectivity and effects of disconnection on cognitive performance (78).

1.5 White matter integrity, brain structural network and cognition

We can use DTI to get information about the condition of the white matter tracts and their damage. This gives us an insight on the integrity of the brain structural network, and thus, probably on cognitive processes and their decline (78).

To assess the relationship between the brain structural network and cognitive decline in healthy aging and the mediating effect of WMH, Wiseman et al. (97) analyzed MRI scans of 558 individuals and generated tractographies between 85 segmented brain regions. They found out that worsening in visuospatial reasoning and information processing speed were associated to loosening of structural network. Processing speed showed the strongest association. A higher volume of WMH was partly responsible for the decline of information processing speed between the examined brain regions. However, memory seemed unrelated to white matter structure integrity (97). Similar findings have been stated by Vergoossen et al. (98) when they examined if WMH and cognitive decline are associated and further, if their association is mediated by structural connectivity. Here too, a larger WMH volume was associated with cognitive slowing. Additionally, WMH load was higher in the tracts that are important for information processing speed. This association was partly mediated by local structural network integrity (98).

It also seems to matter, where the WMH are located. The association between global cognitive decline – information processing speed in particular – and periventricular WMH is especially strong when compared to subcortical WMH (58). This finding is important because periventricular WMH are found in areas with a high density of long white matter tracts. These tracts connect different regions of the cortex and play a key role in supporting cognitive function. Vergoossen et al. (98) further state, however, that WMH are focal lesions. They apparently do not affect the structural brain network globally, but rather locally. So, the mediation effects between WMH and cognitive decline are induced by local network efficiency disruptions. The authors state that an increase of approximately 1.69 mL of WMH volume is equivalent to ten years of network aging (98).

A study performed on individuals with more severe SVD-caused damage reports that a higher amount of WMH is associated with lower local as well as global network strength. They stated that SVD-caused damage across different brain regions cumulates and leads to cognitive impairment through weakening the overall global network structure of the brain. The weakened global network structure, in turn, is associated with lower cognitive performance (99).

High burden of WMH causes brain network deficits in elderly, even healthy, individuals. It is still unclear if and how local damages affect the overall global structure. In a study done by Liu et al. (100) a higher tract-specific WMH-value was associated with worse diffusion characteristics in the same tracts. This did not only affect the diffusion in the area immediately suffering from the WM-injury and its penumbra but seemed to affect the

diffusion even in remote areas of affected tracts. The higher MD values of distal tracts suggest that WMH cause an overall, thus global, destruction of microstructure of white matter tracts. These higher MD values of certain tracts directly correlated to worse cognitive performance in the areas of executive functioning, which is a complex mechanism which involves many brain regions and is depending on their inter-connection. The authors stated that a higher burden of WMH could have a disruptive influence on the tract in its entirety, thus lead to worse diffusion and therefore lead to damages in the global connectivity between brain regions (100).

In a recently performed longitudinal study, in which 270 individuals' cognition was evaluated and linked to DTI measurements, the authors similarly concluded, that SVD most certainly affects cognition by disrupting white matter connections. They saw that declines in the strength of peripheral connections were linked to reductions in overall cognition, psychomotor speed, and executive functions. In the same study the association between a high SVD burden and cognitive decline, or even the development of dementia, were mediated by decrease of global network efficiency and peripheral connection strength (101). Another study reported that the degree of reduction in global network efficiency predicted cognitive decline and development of dementia over a 5-year follow-up period. The authors hypothesized that the rate of change in network global efficiency could be an useful marker to predict risk of progression to dementia (102).

In a study exploring the link between cognitive performance and brain structure in patients with small vessel disease (SVD) and vascular mild cognitive impairment, researchers used the MoCA test to evaluate overall cognitive health (103). The MoCA assesses essential skills like attention, executive function, and psychomotor speed (107). The findings revealed that lower MoCA scores – reflecting poorer cognitive function – were correlated to lower levels of FA and negatively correlated to higher levels of MD in white matter. As higher MD values and lower FA values depict worse diffusion and therefore show deterioration in white matter tracts, this suggests that as white matter integrity declines, so does cognitive health (103,104).

1.6 Peak Width of Skeletonized Mean Diffusivity

The standard parameters to examine white matter integrity are the Fractional Anisotropy (FA) that capture alteration in the directionality of tissue and the Mean Diffusivity (MD) that allows to determine the magnitude of diffusion. Both parameters, however, suffer from time-

consuming, complex data post-processing. The peak width of skeletonized mean diffusivity (PSMD, first established in 2016) is a new fully automatized marker that combines two DTI processing techniques: skeletonization and histogram analysis (105). PSMD was designed to quantify the white matter damage in patients with cerebral SVD and to elaborate on possible cognitive impairment due to the damage. Here, the strongest correlation exists between PSMD and processing speed (106,107). This is important, as reduction of processing speed is said to lead to worsening in various cognitive domains (108). A big benefit of PSMD is its simple usability. It allows a straighter forward measure of white matter integrity as it spares complicated data postprocessing in terms to remove the signal of cerebrospinal fluid from MD images (105).

The automatized calculation of PSMD includes following steps.

1. The data drawn from DTI is automatically processed. The result is a skeleton (as shown in A) of the white matter tracts that is generated using the TBSS procedure as it realizes the alignment between white matter fiber bundles. The skeleton, then, compounds of thin central lines that represent the major white matter tracts (78,105).
2. After generating the skeleton, the MD images are projected on it (105).
3. After the projection of the MD images, the PSMD is calculated as the difference between the 95^{th} and 5^{th} percentiles and depicted as histogram (105).

When compared to other MD sub-parameters, PSMD values showed the strongest association to processing speed scores in the study of its establisher (105).

1.6.1 PSMD and Aging

As of now, there is only one study (109) that focused directly on the age-related change in PSMD value. Beaudet et al. (109) performed this cross-sectional multi-cohort study on 20,000 participants ranging between approximately 18 and 92 years of age. The participants were sub-divided in age-groups in steps of ten. Then, they valued PSMD and other DTI-derived parameters for each participant. They state, that PSMD constantly increased from the individuals in post-adolescence to the very old of age 88 and above. In contrast, other DTI-derived markers seemed to stay rather stable until later age. PSMD first increased slowly until age 60, then rose more sharply. The value of PSMD tripled between the 58- to 68-year group and the 78- to 98-year group. As PSMD is the only parameter that seems to

change throughout the entire adulthood, the authors state that it could make for a valuable marker of white matter aging (109).

1.6.2 PSMD and cognition

PSMD has been consistently associated with cognitive performance, especially in patients with a high burden of white matter lesions. On the other hand, association between PSMD and cognition appears to be rather weak in patients with a mild load of white matter hyperintensities (105,110).

A study by Deary et al. (111) performed on 731 older adults, with a mean aged of 73 explored how PSMD relates to different domains of cognition, like processing speed, visuospatial skills, memory, and overall cognitive ability. The findings showed that higher PSMD was linked to worse processing speed, weaker visuospatial skills, and lower general cognitive performance. PSMD stood out as a strong predictor for visuospatial abilities and overall cognition. However, other variables like white matter volume, gray matter volume or atrophy also showed independent associations to cognitive domains, just like PSMD (111).

A study by Lam et al. (112) examined 801 stroke- and dementia-free individuals at baseline and at a three-year follow-up. The findings showed that PSMD was negatively associated with processing speed at baseline and, over time, also with both processing speed and memory. The same study further highlighted that the association between vascular risk factors and cognition at baseline (hypertension and processing speed, diabetes and processing speed, smoking and processing speed, smoking, and memory) is mainly mediated by DTI markers, like PSMD. Among these, PSMD demonstrated the strongest mediation effect for age-related cognitive changes, particularly in processing speed and memory, as assessed by the MoCA test. This underscores the role of vascular factors in normal cognitive aging, largely due to their impact on brain white matter integrity, as reflected by DTI. A notable advantage of PSMD compared to other DTI markers, however, is its efficiency, as it avoids tedious postprocessing steps, for instance the removal of CSF artifacts out of MD pictures (112).

Wei et al. (113) investigated 111 individuals with WMH and 50 healthy controls (HC). They further sub-divided the participants into three categories: HC, WMH with normal cognitive function, and WMH with cognitive impairment. There were no significant age differences among the groups. They found that the average PSMD value was highest in the WMH group with cognitive impairment, followed by the WM group with normal cognition, and lowest

in the HC group. Cognitive performance was evaluated using the MoCA test, considered by Pasi et al. (114) to be more effective for patients with SVD than the MMSE. While no strong link between PSMD and cognition was seen in the HC group, there was a clear correlation between higher PSMD values and poorer cognitive performance in the WML groups, both with and without cognitive impairment, with the correlation being stronger for the patients with cognitive impairment. The research focused on global cognition and executive function, noting that PSMD reflects the overall integrity of white matter across the brain but does not provide detailed information on specific microstructural changes of every single white matter tract. The study suggests that PSMD could be a useful marker for tracking disease progression and therefore might play an important role in future therapeutic trials (113).

The review of Zanon Zotin et al. (106) found that PSMD correlated with various cognitive outcomes. PSMD correlated in previous studies with global cognitive ability (111,115), visuospatial functioning (111), memory (111,112,116), and executive functioning (107,113). To date, only two studies analyzed the longitudinal change of PSMD value and if there is an associated longitudinal change in any cognitive domain (105,116). Baykara et al. (105) longitudinally analyzed 58 participants over 18 months. The data showed a significant change for PSMD value and WMH volume. However, processing speed scores did not seem to change in line with that (105). The other study performed by McCreary et al. (116) showed similar results. After a follow-up time of 1.1 years the 68 participants showed significant increase of PSMD values (approximately 10% increase over one year). But again, there was no association between an increasing PSMD value and lower performance in cognitive domains (here: psychomotor speed) (116).

2 Methods

2.1 Participants

The participants were drawn from the Austrian Stroke Prevention Family Study (ASPS-Fam). The ASPS-Fam is a prospective, single-center, community-based study. The aim of the study is to investigate the cerebral effects of vascular risk factors in the normally aging population in Graz, Austria (117). The ASPS-Fam is the extended version of the 1991 initiated Austrian Stroke Prevention Study (ASPS) (118,119). Between 2006 and 2013, the participants from the ASPS study and their first-degree relatives were invited to join the ASPS-Fam study cohort. The ASPS-Fam study contains a total of 381 participants from 169 families. Participants were eligible to be included if their past medical history excluded

stroke and dementia. Further, all participants needed to have normal neurological examination (117).

2.2 Data Acquisition

MRI Data: MRI was conducted using a 3T whole-body scanner (TimTrio; Siemens Healthcare, Erlangen, Germany) equipped with a 12-channel head coil. The conventional MRI protocol included an axial FLAIR sequence (TR=10000ms, TE=69ms, inversion time=2500ms, number of slices = 40, slice thickness = 3 mm, in-plane resolution=0.86mm×0.86mm) and high-resolution T1 weighted 3d sequences with magnetization preparation (MPRAGE) and whole brain coverage (TR=1900ms, TE=2.19ms, inversion time = 900 ms, flip angle = 9°, isotropic resolution of 1 mm).
DWI was obtained using either 6 or 12 directions. The imaging was performed under following settings: b-values (0,1000), TR=6700ms, TE=95ms, voxel size = 1.8 x 1.8 x 2.5/3 mm3, gradients: 38 mT/m – 170 mT/m/s (117).

MRI measurements included total brain volume (TBV), total WMH volume, and peak skeletonized mean diffusivity (PSMD). Total brain and WMH volumes were standardized by total intracranial volume (TIV). TBV and TIV were calculated using the FreeSurfer software (120).
WMH were recorded on FLAIR images. Lesions were outlined using a custom written IDL program (Exelis Visual Information Solutions, USA). Lesion areas were segmented by combined region growing and local thresholding following manual selection. The total lesion volume (cubic millimeter) was calculated using the program FSLMATHS (121) by multiplying the lesion area with the slice thickness (117). WMH volume was log-transformed to correct for skewness.

Pre-processing of diffusion data: The pre-processing of raw diffusion-weighted image data was performed using the eddy correct software from “FDT”, part of FMRIB’s Diffusion Toolbox in FSL (122).

PSMD protocol: PSMD is a publicly available fully automatized DTI marker. Its processing contains tensor fitting, skeletonizing the DTI data, applying a custom mask and conducting a histogram analysis (122). The process is built on three primary stages:

1. In the first processing stage the skeletonization of the white matter tracts took place by using TBSS and the FMRIB 1-mm FA template at a value of 0.2. MD images were projected on the computed skeleton by using the FA-derived projection parameters. The MD skeletons were then masked with a more conservative standard skeleton at a FA value of 0.3 to minimize interference through CSF (122).
2. To further minimize contamination, a mask was applied to exclude brain regions prone to CSF. Structures that are adjacent to the ventricles were omitted from the process (122).
3. In the last of three processing stages a histogram based on the MD values of the voxels in the skeleton was generated. PSMD is defined as the difference between the 5^{th} and 95^{th} percentiles of the histogram distribution (122).

Cognitive Data: Cognitive performance was assessed across four domains: memory, visuopractical skills, executive function, and a score for global cognition.

The cognitive tests that were used to examine the respective domain have been widely used in German-speaking countries and were performed in a standardized sequence under consistent laboratory conditions. To assess the intermediate memory recall and learning ability, participants underwent the "Bäumler's Lern- und Gedächtnistest" (LGT-3) which is a challenging paper-and-pencil test that consists of six sub-tests. Three sub-tests (word and digit association tasks, and story recall) evaluated verbal memory, while two others (trail and design recall) examined visuospatial memory. The total learning and memory performance score derives from the scores of these sub-tests and an image recognition paradigm. Executive functions were examined using the Wisconsin Card Sorting Test, part B of the Trail Making Test, and digit span backwards from the Wechsler Adult Intelligence Scale – Revised (117). Global cognition was determined using age-standardized test scores through a principal component analysis (122). To reduce floor and ceiling artifacts and other sources of measurement error, summary measures of cognitive function were applied for the analysis rather than the results of individual tests. Summary measures of the specific cognitive domains were formed. These summary measures were calculated by converting individual test scores to z-scores within the group and by computing the average of the scores in each cognitive domain (117).

2.3 Statistical Analyses

Descriptive Statistics: Means and standard deviations (SDs) were calculated for normally distributed continuous variables, while medians and interquartile ranges (IQRs) were used for skewed variables. Categorical variables were summarized as counts and percentages.

Cross-Sectional Analyses: Linear regression models were used to assess associations between PSMD and predictors including age, sex, vascular risk factors (SBP, DBP, BMI, HbA1c, LDL), and MRI metrics (log-transformed WMH, standardized brain volume). Regression coefficients (β), standard errors, and p-values were reported.
For age, both linear and quadratic models were tested to account for potential non-linear relationships. Model fit was evaluated using adjusted R^2 and ANOVA comparisons.

Age Group Analyses: Due to a bimodal age distribution, analyses were repeated in participants aged < 60 years and ≥ 60 years. Separate regression models were fitted for each subgroup.

Residualized Analyses: To evaluate relationships between PSMD and cognitive performance, residualized plots were generated. Cognitive scores were adjusted for age, sex, education, and log-transformed WMH volume. Similarly, PSMD was residualized to account for covariates before plotting relationships.

2.4 Longitudinal Analyses

Participants were included if they had complete data on diffusion MRI, white matter hyperintensity (WMH) volume, and cognitive performance at baseline and follow-up assessments (61 participants). PSMD (peak skeletonized mean diffusivity) was used as a measure of white matter microstructure. WMH volumes were normalized to intracranial volume (TIV) and log-transformed due to skewness. Cognitive performance was assessed across four domains: memory, visuopractical skills, executive function, and global cognition.
To examine changes in PSMD over time, a linear mixed-effects model was used, with PSMD as the dependent variable. Time (baseline vs. follow-up) was included as a fixed effect, along with baseline age and sex as covariates. Participant-specific random intercepts accounted for

repeated measures. Model estimates were used to quantify the effects of time, baseline age, and sex on PSMD.

Changes in PSMD and WMH volume over time were calculated as the differences between follow-up and baseline values. WMH differences were log-transformed to account for skewness. Pearson correlation was used to assess the relationship between changes in PSMD and WMH volume. A series of linear regression models were fitted, with PSMD change as the dependent variable and log-transformed WMH change as the primary predictor, adjusting for baseline age and sex. Scatter plots were created to visualize the relationships. Changes in cognitive performance were computed as the differences between follow-up and baseline z-scores for memory, visuopractical skills, executive function, and global cognition. Pearson correlation analyses were conducted to examine the associations between changes in PSMD and each cognitive domain. Scatter plots were generated to visualize the relationships. All analyses were conducted in R (version 4.2.0).

3 Results

3.1 Cohort description

The study cohort comprised 326 participants aged 38 to 87 years (mean age = 65.53 years, SD = 11.09). The sample included 42.64% males (n = 139) and 57.36% females (n = 187). Education levels were categorized into four groups: 17.18% of participants had completion of Primary Education (n = 56), 42.02% had completion of apprenticeship (n = 137), 23.01% had high school leaving examination (n = 75), and 17.79% had a university degree 4 (n = 58).

Descriptive statistics were calculated for systolic blood pressure (mean = 137.52 mmHg, SD = 21.17, range = 68.4–200), body mass index (BMI; mean = 26.53, SD = 4.68, range = 16.16–43.58), HbA1c (mean = 5.69, SD = 0.63, range = 3.5–8.9), and low-density lipoprotein cholesterol (LDL; mean = 117.99 mg/dL, SD = 32.75, range = 44–207). These variables were assessed to characterize vascular and metabolic health within the cohort.

Descriptive statistics were calculated for total brain volume (mean = 1092700.88 mm^3, SD = 112830.45, range = 859071–1438321), total WMH volume (median = 4081.09 mm^3, IQR = 6250.7), and PSMD (mean = 0.000301, SD = $5.2x10^{-5}$, range = 0.00019453–0.000460261).

3.2 Results of cross-sectional analysis

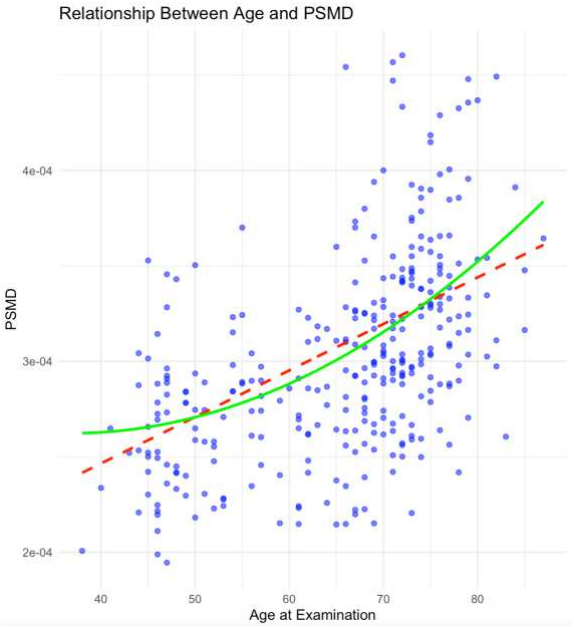

Figure 1. Relationship between PSMD and age using linear and quadratic models.

Scatterplot illustrating the relationship between PSMD and age with linear (red line) and quadratic (green line) regression fits, adjusted for sex. The quadratic model demonstrates a statistically significant U-shaped trajectory.

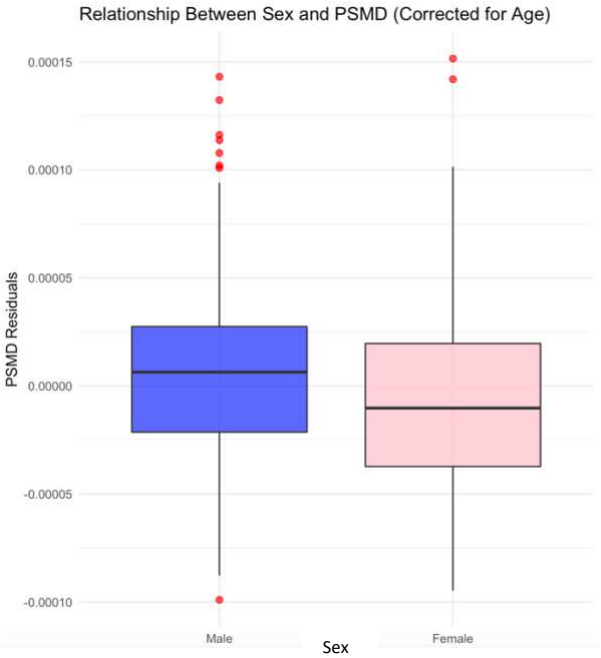

Figure 2. Relationship between PSMD and sex.

Boxplot showing the relationship between PSMD and sex, adjusted for age.

Linear regression revealed a significant positive association between age and PSMD ($\beta=2.436\times10^{-6}$, $p<2\times10^{-16}$) indicating that PSMD increases with age (**Figure 1**). Sex was also a significant predictor, with females showing lower PSMD values compared to males, as can be seen in **Figure 2** ($\beta=-1.253\times10^{-5}$, p=0.0129). To explore potential non-linear relationships, a quadratic regression model was tested, which included a quadratic term for age. The quadratic term was significant ($\beta=9.859\times10^{-5}$, p=0.0283), suggesting a non-linear relationship between age and PSMD. The quadratic model demonstrated a better fit (R^2 = 0.2864) compared to the linear model (R^2=0.2756), as supported by ANOVA (p=0.0283). These findings indicate that the relationship between age and PSMD is predominantly positive but exhibits a subtle curvature.

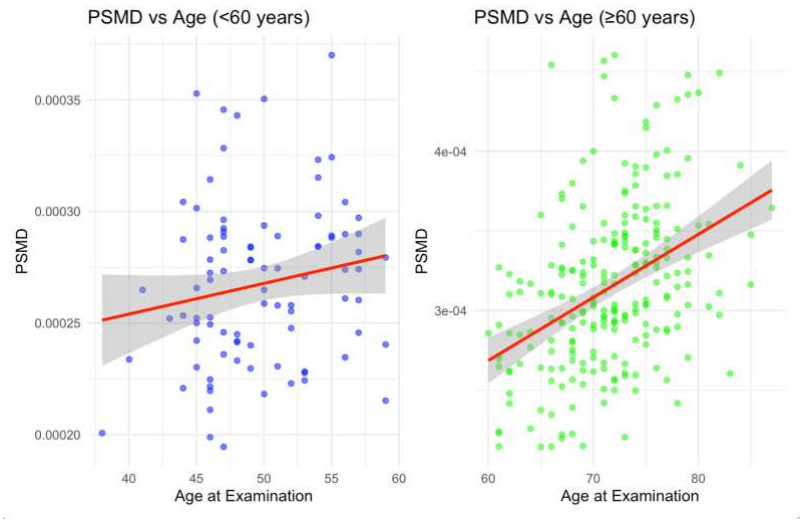

Figure 3. Relationship between PSMD and age in separate age groups.

Scatterplots showing the relationship between PSMD and age for participants aged <60 years (left panel) and ≥60 years (right panel). Axes are scaled to emphasize the data distribution within each age group.

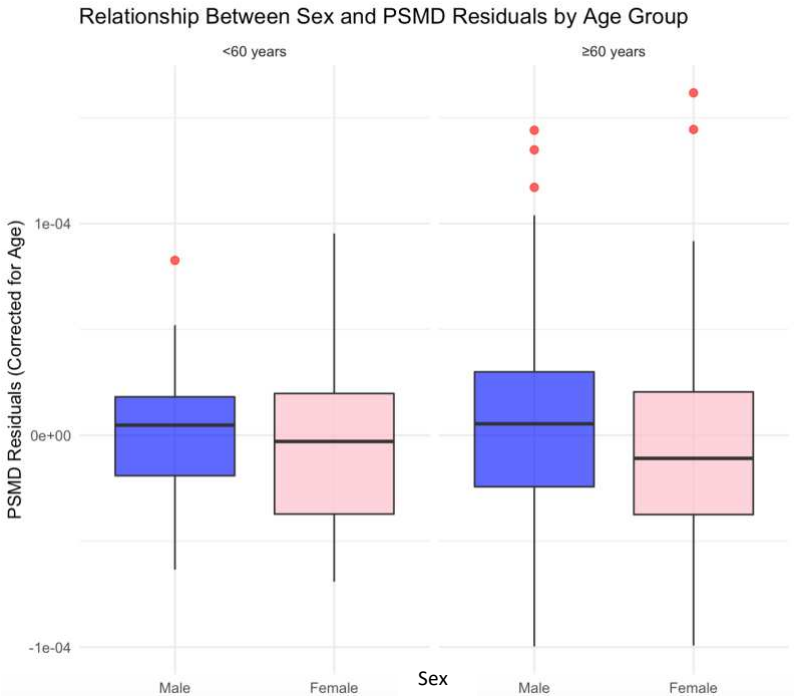

Figure 4. Relationship between PSMD and sex in separate age groups.

Boxplots showing the relationship between PSMD and sex for participants aged <60 years (left panel) and ≥60 years (right panel). Residualized PSMD values are plotted to account for adjustments for age.

Because of the bimodal age distribution in our cohort, we decided to conduct analyses separately for participants < 60 years of age and ≥ 60.

In participants aged <60 years, neither age ($\beta=1.413\times10^{-6}$, p=0.0931) nor sex ($\beta=-2.619\times10^{-6}$, p=0.7364) were significantly associated with PSMD, as depicted in **Figure 3**. In contrast, **Figure 4** shows that in participants aged ≥ 60 years, age was significantly associated with higher PSMD ($\beta=3.813\times10^{-6}$, $p=2.87\times10^{-10}$), while males had significantly higher PSMD than females ($\beta=-1.380\times10^{-5}$, p=0.0284).

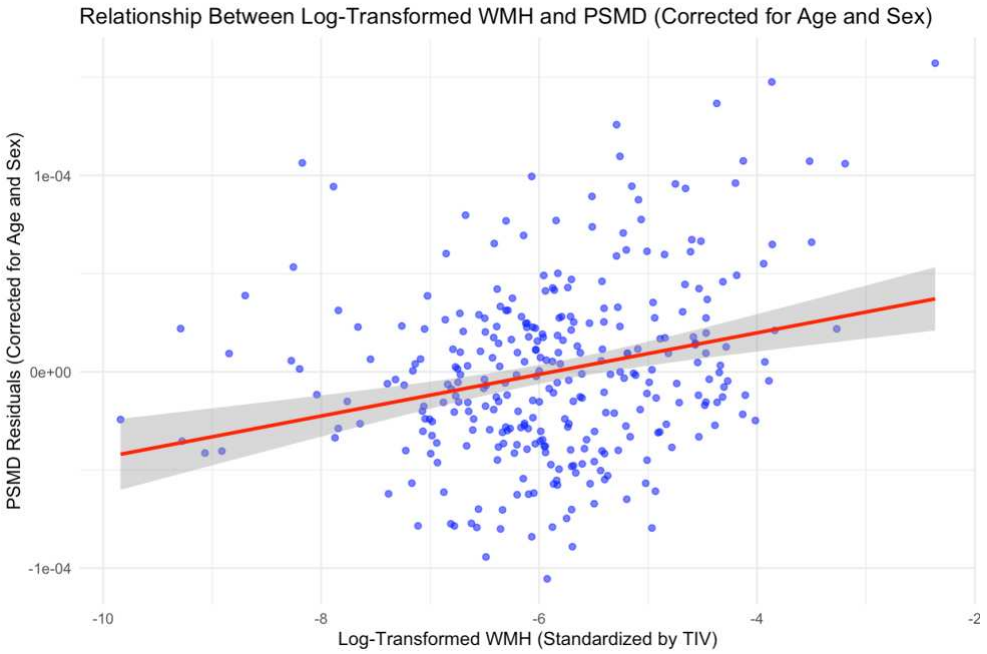

Figure 5. Relationship between PSMD and log-transformed WMH volume.

Scatterplot showing the relationship between PSMD and log-transformed WMH volume in the total cohort, adjusted for age and sex.

When log-transformed WMH volumes (standardized by intracranial volume) were analyzed as predictors, a significant positive association with PSMD was observed ($\beta=1.385\times10^{-5}$, $p=9.11\times10^{-8}$), indicating that higher WMH volumes are linked to increased PSMD (**Figure 5**). Age also remained a significant predictor of PSMD in this model ($\beta=1.754\times10^{-6}$, $p=1.82\times10^{-11}$), confirming that the relationship between PSMD and age is independent of WMH volumes. In contrast, when PSMD was analyzed as a predictor of brain volume (standardized by intracranial volume), no significant association was found ($\beta=5.3915$, $p=0.886$).

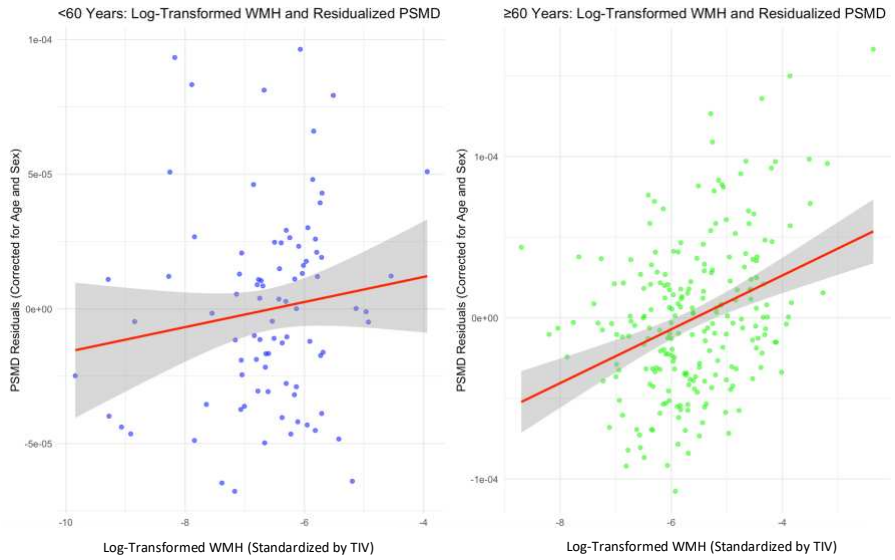

Figure 6. Relationship between PSMD and log-transformed WMH volume.

Scatterplots for participants aged <60 years (left panel) and ≥60 years (right panel), with regression lines adjusted for age and sex.

When analyzing the relationship between log-transformed WMH (corrected for intracranial volume) and PSMD, **Figure 6** shows that no significant association was observed in participants aged <60 years ($\beta=5.728\times10^{-6}$, p=0.164). In contrast, a strong positive association was found in participants aged ≥60 years ($\beta=1.787\times10^{-5}$, $p=2.15\times10^{-8}$), even after adjusting for age and sex. This highlights the independent contribution of WMH to PSMD in older participants.

In participants aged <60 years, higher PSMD was significantly associated with lower brain volume (standardized by intracranial volume; $\beta=-164.1$, p=0.0397), independent of sex. However, this relationship was not observed in participants aged ≥60 years ($\beta=56.02$, p=0.198).

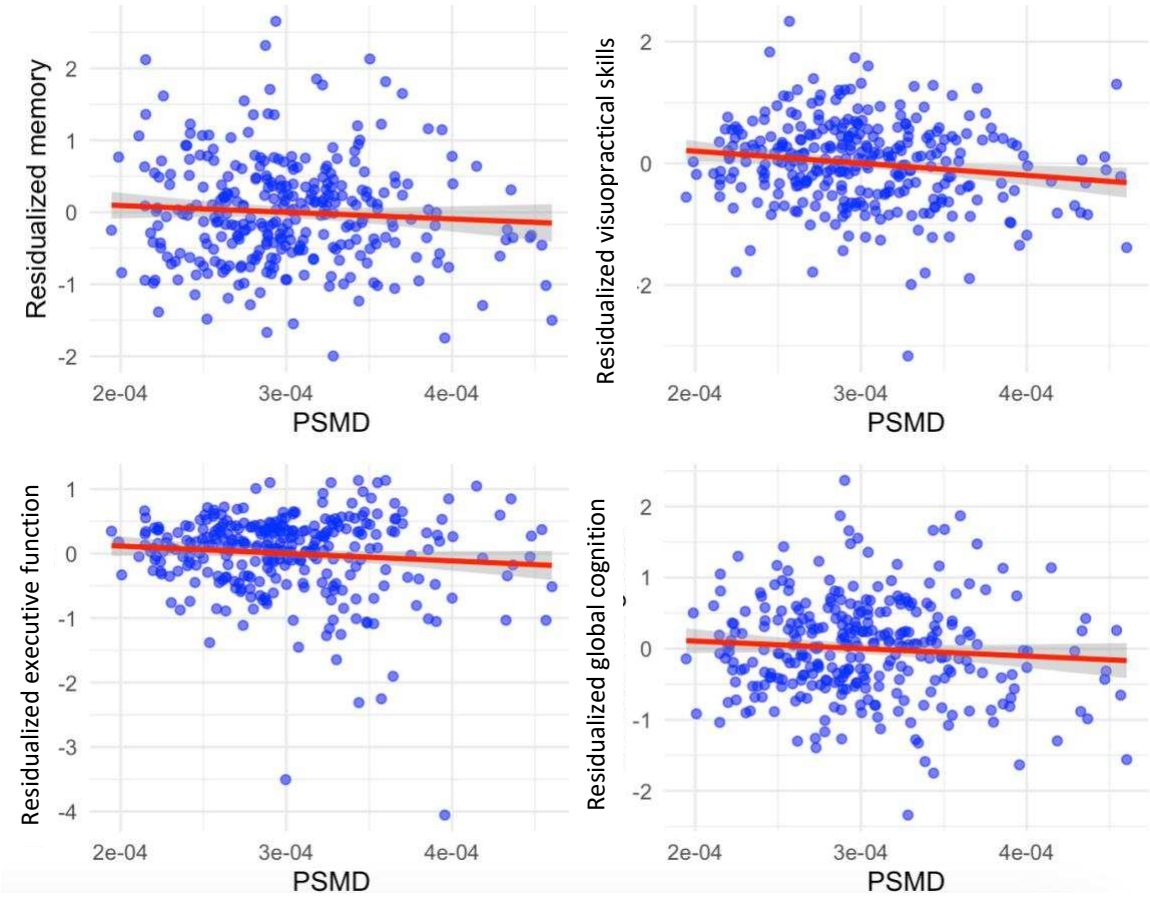

Figure 7. Relationships between PSMD and cognitive domains in the total cohort.

Scatterplots of residualized memory, visuopractical skills, executive function, and global cognition scores against PSMD, adjusted for age, sex, education, and log-transformed WMH volume. Regression lines are shown for each relationship.

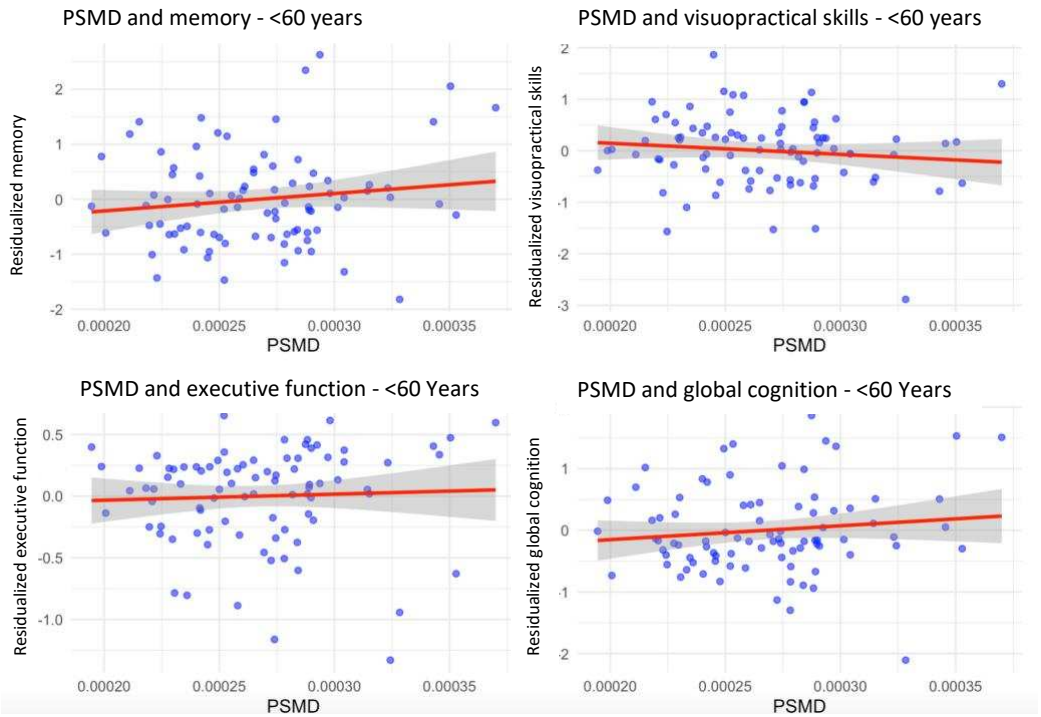

Figure 8. Relationships between PSMD and cognitive domains in participants < 60 years

Scatterplots of residualized memory, visuopractical skills, executive function, and global cognition scores against PSMD for participants aged <60 years. Regression lines are adjusted for age, sex, education, and log-transformed WMH volume.

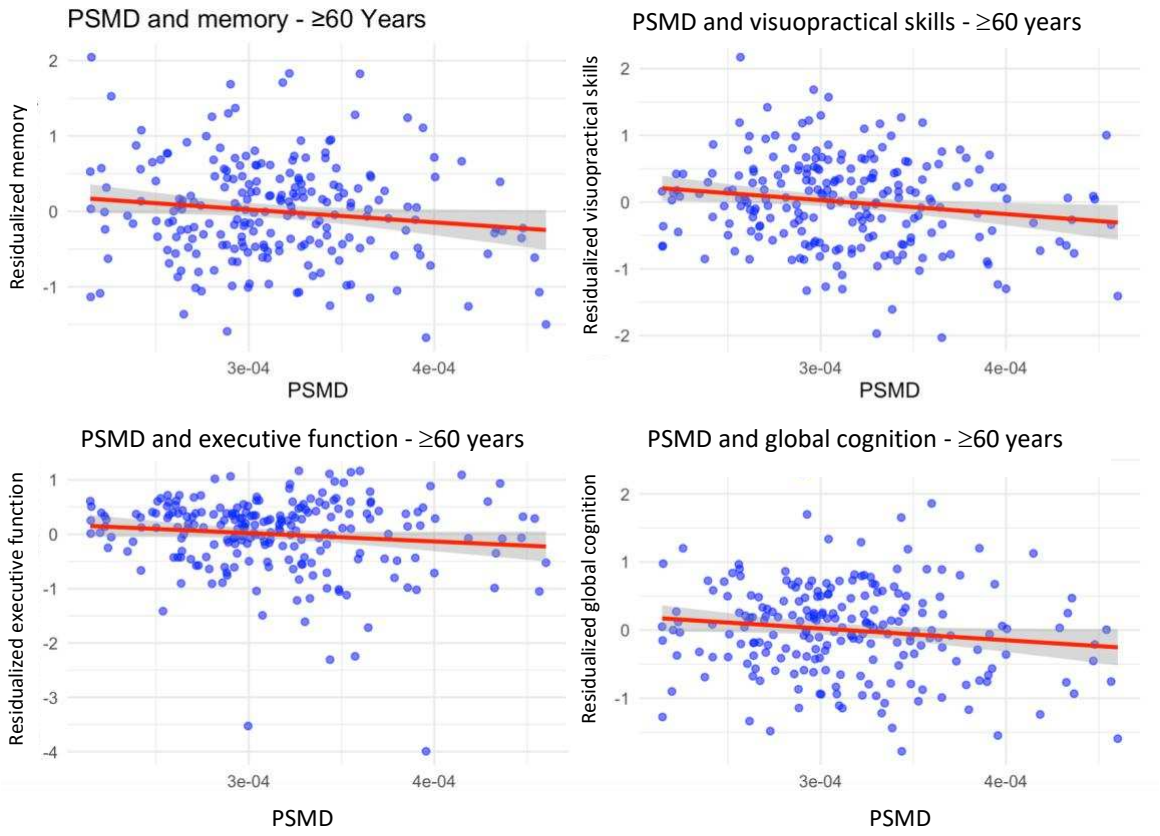

Figure 9. Relationships between PSMD and cognitive domains in participants ≥ 60 years

Scatterplots of residualized memory, visuopractical skills, executive function, and global cognition scores against PSMD for participants aged ≥60 years. Regression lines are adjusted for age, sex, education, and log-transformed WMH volume.

In the whole cohort (**Figure 7**), higher PSMD was significantly associated with poorer performance in visuopractical skills (β=−3004.38, p=0.001) and executive function (β=−1750.38, p=0.039). Associations with memory (β=−1414.00, p=0.152) and global cognition (β=−1599.12, p=0.086) did not reach statistical significance, though trends were observed. **Figure 8** demonstrates that in participants aged <60 years, no significant relationships were found between PSMD and any cognitive variable. Among participants aged 60 years or older (**Figure 9**), PSMD was significantly associated with all cognitive domains after correcting for age, sex, education, and log-transformed WMH volume. Higher PSMD values were associated with lower memory scores (β = -2374.23, p = 0.0219), visuopractical skills scores (β = -2920.17, p = 0.0042), executive function scores (β = -2166.22, p = 0.0456), and global cognition scores (β = -2425.63, p = 0.0199).

3.3 Results of longitudinal analysis

The longitudinal dataset included 61 participants with a mean age at baseline of 62.92 years (SD = 8.19), ranging from 44.17 to 77.79 years. The sample comprised 34 males (55.74%) and 27 females (44.26%). The mean follow-up time was 5.58 years (SD = 1.02), with a range of 3.98 to 7.36 years.

Educational attainment among participants was distributed as follows: 14.75% (n = 9) had completed elementary school, 32.79% (n = 20) had vocational school education, 32.79% (n = 20) had a high school diploma, and 19.67% (n = 12) had obtained a university degree.

The mean brain volume at baseline was 1,117,432 mm^3, ranging from 876,765 mm^3 to 1,438,321 mm^3. White matter hyperintensity (WMH) volume at baseline had a median of 3,834.056 mm^3, with an IQR of 4,466.599 mm^3.

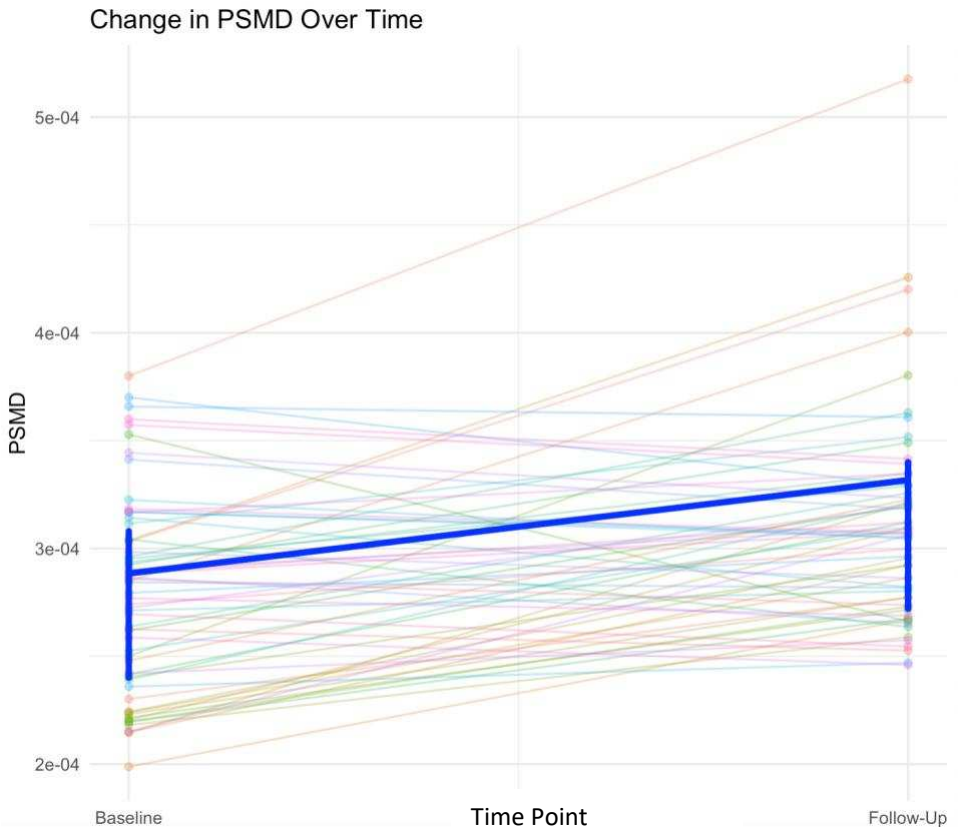

Figure 10. Change in PSMD over time.

The linear mixed-effects model showed a significant increase in PSMD from baseline to follow-up. The thick blue line represents the model-predicted trajectory of PSMD over time, adjusted for baseline age and sex. Individual trajectories are shown as faint lines to illustrate variability across participants.

The linear mixed-effects model (**Figure 10**) revealed a significant increase in PSMD over time, with an estimated change of 0.00003196 per time point (baseline to follow-up) ($t = 5.16$, $p < 0.001$). Baseline age was also significantly associated with PSMD, with an estimated increase of 0.00000193 per year of age ($t = 3.90$, $p < 0.001$). Sex did not have a significant effect on PSMD ($t = -0.43$, $p = 0.67$).

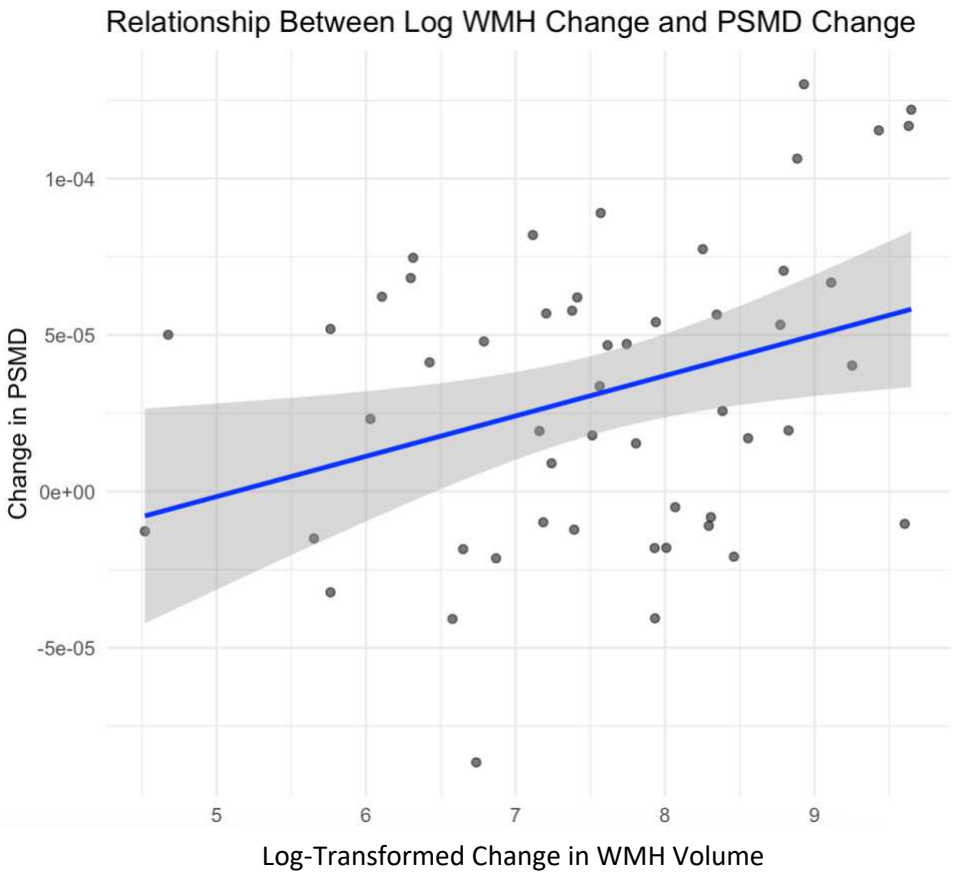

Figure 11. Relationship between changes in PSMD and log-transformed changes in WMH volume.

As shown in **Figure 11**, there is a significant positive correlation between the change in log-transformed WMH volume and the change in PSMD ($r=0.33$, $p=0.016$). A linear regression model without adjustment for covariates showed that an increase in WMH volume was significantly associated with an increase in PSMD ($\beta=1.29\times10^{-5}$, $p=0.016$). Adding baseline age as a covariate did not substantially alter this association ($\beta=1.33\times10^{-5}$, $p=0.028$), and baseline age was not significantly related to PSMD change ($p=0.87$). Similarly, including sex as an additional covariate resulted in no significant contribution from sex ($p=0.20$) or baseline age ($p=0.99$), while the association between WMH and PSMD changes remained significant ($\beta=1.48\times10^{-5}$, $p=0.017$).

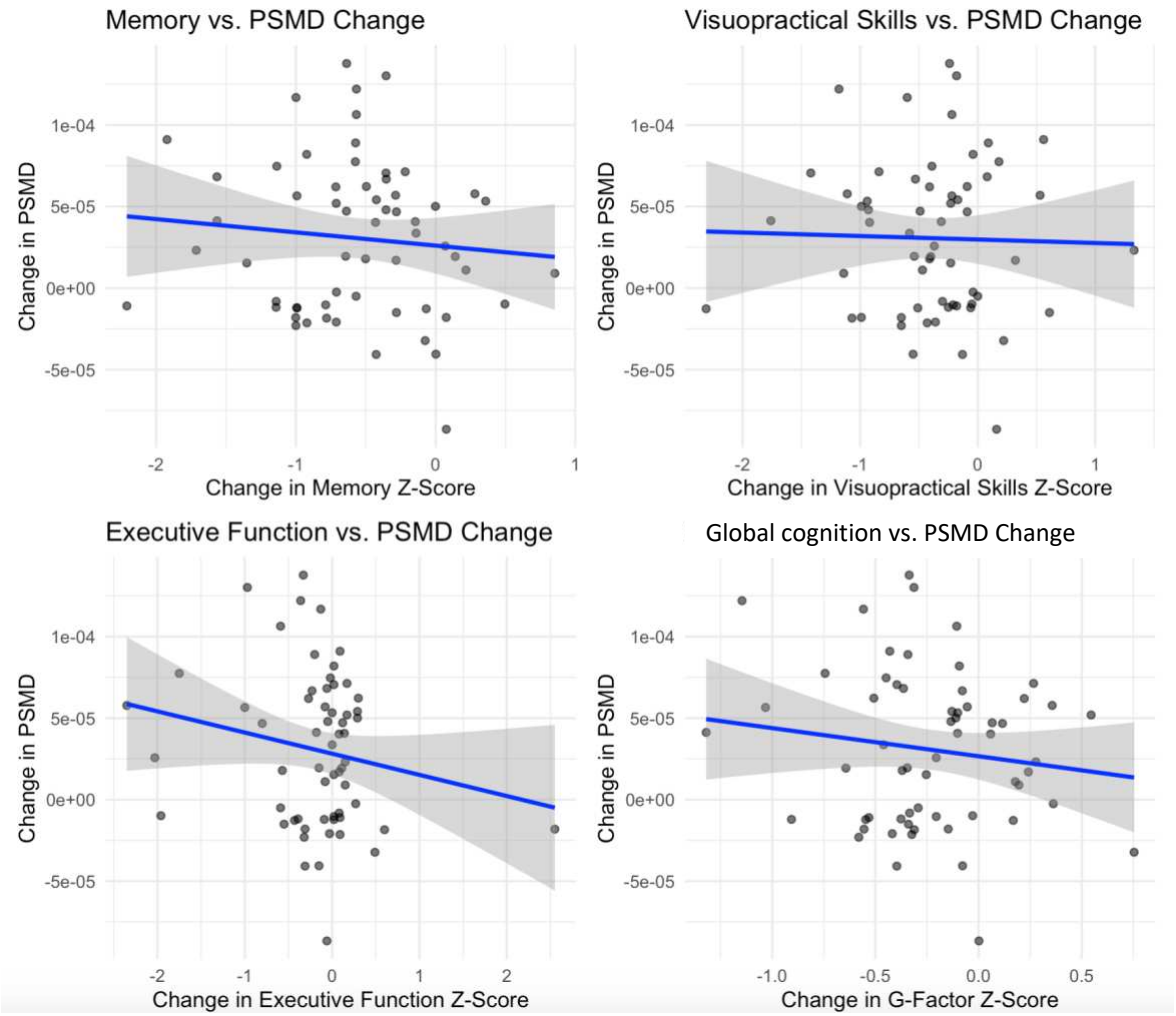

Figure 12. Scatterplots showing the relationship between changes in PSMD and changes in cognitive domains over time: Memory, Visuopractical Skills, Executive Function, and global cognition (G-Factor).

Correlation analysis revealed no significant associations between changes in PSMD and changes in cognitive domains over time (**Figure 12**). The correlation between PSMD change and memory change was weak and non-significant ($r = -0.10$, $p = 0.447$), as was the correlation with visuopractical skills ($r = -0.03$, $p = 0.844$). Similarly, changes in PSMD were not significantly correlated with changes in executive function ($r = -0.19$, $p = 0.156$) or global cognition ($r = -0.14$, $p = 0.284$). These findings indicate that increases in PSMD over time were not associated with changes in cognitive performance across any of the assessed domains.

4 Discussion

The aim of this study was to explore whether an increase in PSMD over time correlated with cognitive decline in healthy adults. Our initial hypothesis was that higher PSMD values would be associated with cognitive decline. While cross-sectional analysis did reveal significant relationships between PSMD and various cognitive functions, the longitudinal analysis, the focus of this study, showed no correlation between higher PSMD values and declining cognitive abilities over time.

4.1 PSMD, age and sex

Previously, the large cross-sectional study performed by Beaudet et al. (109) was the only one to examine the relationship between age and PSMD values. Our study was able to reproduce very similar results despite including significantly less probands. As stated above, Beaudet et al. (109) found that PSMD is the only DTI-derived marker that is constantly increasing with higher age. They further state a slow increase before the age of 60. The increase accelerates past the age of 60 and even triples between the 58- to 68-year old's and the 78- to 98-year old's (109). Our cross-sectional analysis showed very similar results. Overall, our linear regression revealed a significant positive association between age and PSMD indicating that PSMD increases with age. In participants aged < 60 years, our study showed that age was not significantly associated with PSMD. In contrast, in participants aged ≥ 60 years, age was significantly associated with higher PSMD. We were able to reproduce similar results with considerably fewer participants, which confirms that PSMD is a sensitive marker for white matter aging and its integrity. In contrast to other DTI metrics (like FA or MD), PSMD seems to be the one that shows a constant increase over time (109). Not only age but also sex seems to influence PSMD values. Here again, our findings align with those of the large multi-center study of Beaudet et al. (109), which strengthens the observation that men show significantly higher PSMD values than women. This effect applies for the age group ≥ 60 years old.

4.2 PSMD, WMH and cognition

As for the relationship between PSMD and WMH volumes, we were able to show a significant positive association, which indicates that higher WMH values are linked to higher PSMD values. This aligns with previous studies (115,123) that came to similar conclusions

and stated that PSMD is a sensitive marker for vascular derived white matter damage, especially for WMH, which it originally was established for (106). Nowadays it is known and widely accepted that WMH contribute negatively to the individual's cognitive abilities (61). As PSMD shows to be linked to WMH load, it might be of value as a surrogate marker for a person's cognitive abilities through mapping the integrity of their white matter.

Cross-sectionally, we have been able to reproduce (105,111) that PSMD was associated to lower cognitive scores. Overall, a poorer performance in visuopractical skills and executive function was associated with higher PSMD values. In participants below the age of 60 there was no significant association. In participants aged 60 and above, PSMD was associated with all tested cognitive domains (memory, visuopractical skills, executive function, global cognition).

The longitudinal analysis strengthened the findings of a positive association of PSMD with age and PSMD with WMH volume, respectively. Nonetheless, the main subject of this study was to investigate, if higher PSMD values can be associated to cognitive decline in healthy adults. The correlation analysis revealed no significant correlation between increase in PSMD and decline in any of the examined cognitive domains.

Our study was the third to evaluate the longitudinal relationship between PSMD and cognitive abilities. Baykara et al. (105) analyzed 58 participants over 18 months whereas McCreary et al. (116) examined 68 individuals with a follow-up time of roughly one year. Neither study was able to reveal a longitudinal correlation between PSMD and cognition. Ours included, all three studies have rather small sample sizes (58, 61 and 68 participants) which can be the limiting factor if, indeed, there wa a correlation between increasing PSMD values and declining cognitive abilities.

While PSMD may highlight differences in cognitive ability between individuals (showing an association when analyzed cross-sectionally), it might not be a sensitive marker for tracking cognitive decline longitudinally. Rather than directly reflecting cognition, PSMD could instead indicate a general structural vulnerability of the white matter.

4.3 Strengths and weaknesses

This study has several strengths that contribute to its validity. First, it is based on the well-defined ASPS-Fam participants. This ensures a homogeneous sample of healthy adults by excluding individuals with stroke and dementia, reducing potential confounders.
The use of high-resolution 3T MRI ensures precise measuring of the acquired imaging variables. Additionally, cognition was examined across multiple domains and by using well-established and standardized assessments, which minimizes measurement bias.
The study uses a robust statistical approach, that contains the use of linear and quadratic regression models, mixed-effects modeling and residualized analyses.
By splitting the cohort in two age groups (< 60 and ≥ 60 years), the study provides a clearer insight about how PSMD relates to age differences. Through including a longitudinal analysis, the study uses the gold standard of assessing age-related changes. It is only the third study to examine the longitudinal relationship between age, cognition and PSMD.
Despite these strengths, following limitations should be mentioned. One of the main limitations is the small longitudinal sample size (61 individuals), which reduces the statistical power to detect associations between PSMD changes and cognitive decline. Additionally, this is a single-center study which may limit the generalizability of the findings on a broader population. The lack of significant findings regarding cognitive decline over time may be due to a still too short follow-up time.

4.4 Conclusion and outlook

This study provides valuable information about the relationship between white matter microstructure, healthy aging, and cognitive performance. Utilizing high-resolution 3T MRI imaging and a well-characterized cohort from the ASPS-Fam study, the findings confirm that PSMD increases with age and is associated with greater WMH volume, particularly in individuals aged 60 years and older. However, despite significant cross-sectional associations between PSMD and cognitive function, the longitudinal analysis did not show a clear correlation between increase in PSMD over time and cognitive decline.
Future studies investigating whether PSMD and cognition over time are correlated, should aim for a higher number of participants and a reasonable follow-up time, probably exceeding 5 years. Although PSMD, to this date, does not seem to be a promising marker for longitudinal cognitive decline, we can firmly say that it is a very strong indicator of white

matter integrity, as individuals with higher load of WMH have higher PSMD values, making it probably a good tool, as Wei et al. (113) state, for assessing white matter integrity loss over time. Therefore, PSMD could still be used as a marker in clinical trials regarding patients who suffer from small vessel disease, or more precisely, from white matter hyperintensities. It also can be used to further study the effect of aging on our brain, because of the reproducible and consistent change over time.

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