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Doaa G. Ali, Student Dr. Gregory A. Jicha, Major Professor Dr. Clair Clark, Director of Graduate Studies

Title

Assessment Of The Interplay Between Regional β-Amyloid Burden And White Matter Hyperintensities On Cognition And Default Mode Network In Clinically Normal Older Participants.

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Medicine at the University of Kentucky

By

Doaa G. Ali Lexington, Kentucky Director: Dr. Gregory A. Jicha, Professor of Neurology Lexington, Kentucky 2023

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ABSTRACT OF DISSERTATION

Assessment Of The Interplay Between Regional β-Amyloid Burden And White

Matter Hyperintensities On Cognition And Default Mode Network In Clinically Normal

Older Participants.

Objective: Alzheimer's disease (AD) and subcortical vascular dementia are considered the most common pathologic contributors to dementia in the aging population. Both frequently coexist in over 80% of community dwelling adults with dementia. The neuropathological development of AD arguably begins with β -amyloid (A β) deposition in the brain. This series of studies aims to test the hypothesis that early focal regional amyloid deposition in the brain is associated with cognitive performance in specific cognitive domain scores in preclinical AD (pAD) (study1). Since mixed dementia is widely recognized as the norm rather than the exception, the second study aimed to explore the relation between regional and global A β and WMH with core cognitive function (executive function (EF) and memory) scores in cognitively normal (CN) older adults (study2). Finally, the relationship between WMH and A β is strongly determined by the spatial distribution of the two pathologies, so the third study aimed to quantify A β in Default mode network (DMN) regions to examine whether cerebral small vessels disease (SVD) disruption of connectivity affects A β deposition in disconnected DMN regions (study3).

Method: Global and regional Standard Uptake Value ratios (SUVr) from A β -PET, WMH volumes from MRI FLAIR images, and cognitive test scores were analyzed across a sample of CN participants. Linear regression models adjusted for age, sex and education used to assess the relationships between regional SUVr and cognitive test scores across 99 CN from Sanders Brown Center on Aging (study1). Moderation, and mediation modeling were used to define the interplay between global, regional A β and WMHs measures in relation to EF and memory composite scores outcomes at baseline and after approximately 2 years across a sample of 714 CN from the Alzheimer's Disease Neuroimaging Initiative ADNI (study2). The association of WMH volume in anatomically defined white matter tracts of atlas-based fiber tract with A β SUVr specifically in connected cortical regions within DMN was tested across sample of 74 CN from ADNI3.

Results: EF performance was associated with increased regional SUVr in the precuneus and posterior cingulate regions only (p<0.05). The moderation regression analysis showed additive effects of A β and WMH over baseline memory and EF scores (p =0.401 and 0.061 respectively) and synergistic effects over follow-up EF (p < 0.05). Through mediation analysis, the data from study 2 showed that WMH affects, mediated by global and regional amyloid burden, are responsible for baseline cognitive performance deficits in memory and EF. Finally, the regression analysis from study 3 demonstrated that increased WMH volumes in superior longitudinal fasciculus (SLF) was associated with increased regional SUVr in inferior parietal lobule (IPL) (p<0.05).

Conclusion: While the prevailing view in the field suggests that memory performance is the earliest clinical hallmark of AD, the present data demonstrate that changes in EF, mediated by A β deposition in the precuneus and posterior cingulate may precede memory decline in pAD. After adding the second key driver of cognitive decline in CN, the finding suggested that WMH dependent changes in baseline cognitive performance are related to direct effect of WMH and an indirect effect through both global and regional A β burden. Further studies are needed to show the longitudinal influences of WMH on A β distributions in participants with mixed dementia.

KEYWORDS Regional standardized uptake value ratio (SUVr); Cognition; Preclinical Alzheimer's disease; White Matter Hyperintensities (WMH); neuroimaging; Default mode network.

Doaa G. Ali

(Name of Student)

[01/21/2023]

Date

Assessment Of The Interplay Between Regional β-Amyloid Burden And White Matter Hyperintensities On Cognition And Default Mode Network In Clinically Normal Older Participants.

> By Doaa G. Ali

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Director of Dissertation

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[01/21/2023]

Date

DEDICATION

To my sole inspiration and my soul mate. "My husband" The one who always believed in me. To my loving mother and father. To my daughter and son.

ACKNOWLEDGMENTS

If I am to take a glimpse to thank those whom I owe, neither the words nor the few lines will help me. Thanks to our entire participant who gave their time and effort to participate in the studies of this project and help the science to go forward without their participations none of these experiments could be happened.

Thanks to my mentor Dr. Gregory Jicha, who guided me on every step of this path and taught me how to think like a scientist. Dr. Jicha pushed me outside my comfort zone to pursue my interest and achieve my dreams. He creates such an inclusive work environment and finds the strength in every member of his team. He has dedicated countless hours to helping me become a better scientific communicator through careful review and critique of my work. I am grateful to the opportunity I had to learn from him.

I also would like to thank the members of my graduate committee; each of them has been invaluable in this process. I would like to thank Dr. Brian Gold who opened his lab doors to me to interact and learn from his team. A special thanks to Dr. Riham El-Khouli, who guides me in the track of PET analysis. She provided to me generous help and sincere advice that enlightened my mind forever. I would like to thank Dr. Donna Wilcock and Dr. Yang Jiang. Each of them has been invaluable to me. They pushed me to learn and obtain extensive knowledge in this process. Thanks for Dr. Ann Stowe for putting her experience and science to serve as external examiner in the committee.

There were no words will help me to thank Dr. Erin Abner who I learnt from. She gave too much of her times and efforts to review the statistical models and explain many statistical terms that were hard to understand before finishing my statistical course. Especial thanks to Dr. Ahmed Baharni for the time and effort he spent on training me in MRI analysis.

Sander Brown center on aging has been my home at UK for the last three plus years. I am grateful to have had the opportunity to interact and learn from so many great people there including the clinical coordinator and the imaging team.

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Finally, I would like to thank my family for their support. To my amazing husband, Dr. Moamen Gabr, thank you for providing unconditional support and for always pushing me to do my best. To my parents who I owe most of my success to them.

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CHAPTER 1. INTRODUCTION

1.1 Alzheimer's disease (AD) and Vascular cognitive impairment and dementia (VCID)

Alzheimer's disease (AD) is the most common neurodegenerative cause of dementia. The pathological hallmarks of AD include but are not limited to extracellular amyloid plaques containing abnormal aggregates of amyloid-beta (A β) protein, intracellular neuronal fibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, synaptic loss, neuronal death, mitochondrial dysfunction, oxidative stress, metabolic dysregulation, and neuroinflammation. A β occurs many years before the overt detection of cognitive decline (representing the research construct of preclinical Alzheimer's disease (pAD)).[1, 2]. It is challenging to detect early A β burden in pAD as it is often low or focal at this stage of disease [3]. A β deposition develops over time in discrete regions of the brain in a temporally progressive manner [4], from temporobasal and frontomedial areas, to the remaining associative neocortex, to primary sensory-motor cortex, the medial temporal lobe, and finally the striatum [5]. Global A β burden assessment in pAD is likely suboptimal and may miss the earliest signs of A β pathology without consideration of the temporal progression of regional A β deposition [3].

Vascular cognitive impairment and dementia (VCID) is the second most common cause of dementia after AD corresponding to about 20 % of cases, it received high attention as a modifiable factor for dementia [6-8]. VCID is characterized by cerebral hemodynamic alteration and the underlying mechanisms include large and small vessel diseases and decrease cerebral blood flow [9]. Pathological and neuroimaging studies have pinpointed brain parenchymal lesions that are associated with VCID [8]. The underlying neuropathological lesions help classify VCID into three major categories caused by: strategic infarcts, multiple small (lacunar) and or larger vessel infarcts, and subcortical small vessel ischemic disease, which is considered the most common cause of VCID [10]. Advances in multimodal biomarkers like neuroimaging, cerebrospinal fluid (CSF), and blood biochemical analysis contribute to stratifying risk, prognosis, and in the development of treatment plans for VCID patients [11, 12]. Neuroimaging modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are used to determine the extent and the location of vascular injury and provide structure and function information [9, 13].

Diagnosis of dementia relies on a wide range of neuroimaging modalities [14]. MRI is the key neuroimaging modality in VCID [15] and is used to analyze the morphological alterations

that occur in both white and grey matter. Different acquisition sequences can be used to identify the structural and even biologic processes contributing to VCID. Structural T1 identifies area of encephalomalacia from ischemic injury, T2 and fluid-attenuated inversion recovery (FLAIR) imaging identifies area of injury that have not yet progressed to overt encephalomalacia [16], diffusion tensor imaging (DTI) identifies abnormalities in white matter tracts of the brain affected by ischemia, susceptibility-weighted imaging detects areas of active and or prior hemorrhage, arterial spin labeling can detect brain perfusion deficits [17], and spectroscopy can detect biochemical changes associated with regional brain injury and inflammation [18]. The inclusion of quantitative metrics for research applications, is slowly being incorporated into clinical care paradigms, but primarily serves as a toll for research discoveries. Quantitative MRI analysis uses both automated and semi-automated techniques afforded by specialized hardware and software, but while revealing, is also associated with extensive post-acquisition processing, which currently limits its widespread use in clinical practice [19].

1.2 Beta-amyloid (Aβ) protein deposition and Positron Emission Tomography (PET) scans

Brain $A\beta$ deposition can be measured using different radiotracers, including 18Fflorbetapir PET. $A\beta$ -PET scans enable quantitative evaluation of regional $A\beta$ elevations in pAD, unlike CSF, which can measure summative brain changes in $A\Box$, but cannot provide regional information. The standard quantification technique for $A\beta$ -PET imaging is comparing regional uptake to a reference region. The selection of target and reference regions directly affects the sensitivity of Standardized Uptake Value Ratio (SUVr) quantification. Neuroimaging studies examining the use of different reference regions in analyzing amyloid burden have shown that whole cerebellum, and cerebellar gray matter but not pons nor white matter, are appropriate reference regions in both AD and subcortical vascular dementia [20, 21] As such, the cerebellum is considered a gold standard reference region for $A\Box$ burden analyses [22-25]. Not only because it met the assumptions of a standard reference region like having the same tissue characteristics as the target tissue, and showing longitudinal stability [26, 27], but also because autopsies studies had shown low levels of amyloid plaques in this brain region [22, 23].

The integration of PET into our brain imaging toolkit affords an opportunity to improve early and differential diagnosis of many neurodegenerative diseases, through its ability to detect molecular signatures depending on the tracer used [28]. Co-registration of brain PET and MRI data allows for precisely identifying anatomical structures and lesions by providing accurate parcellation of the brain's gray (GM) and white matter (WM) [29]. Automated quantification of PET and MRI images requires using a series of registrations: first rigid registration between the PET scan and a corresponding T1-weighted MRI scan, then nonlinear registration between the corresponding T1-weighted MRI and a common template space, finally the regions of interest defined in the common template space are then backward-propagated to the subject scans [30]. Many tools could be applied for PET-MRI registration (e.g., tools in FSL, FreeSurfer, ANTs), but *spm_coreg* is most popular for amyloid PET studies [20, 31-34]. Several methods for amyloid PET quantification without MRI co=registration are in active clinical and research use [35-38]. This method of quantification poses many difficulties in interpretation of the data derived due to a lack of anatomic information related to the low resolution of PET imaging, partial volume effects [39-41], and the variability in intensity distribution across brain regions. CT scans are typically performed in the setting of PET to deal with many of the issues, but are suboptimal when using images outside of the structural T1 images, such as those needed to examine VCID and PET in combination. As such, co-registration with MRI is ideal for regional quantification of PET abnormalities that enhance clinical research.

1.3 The impact of $A\beta$ on cognition in clinically normal participants

It is challenging to determine the clinically significant cognitive change in pAD, and results often differ across studies [42-55]. The expression of symptoms may differ dramatically among participants with pAD, and the extent and distribution of amyloid pathology in the brain needs to be considered when analyzing the impact of early preclinical A changes. One recent study has been shown that slight deterioration in cognitive function occurred with subthreshold levels of global A β in cognitively normal participants [56]. Other studies of this type are scarce in the field. The quantitative evaluation of regional A β deposition and its relation to cognitive decline in pAD has not been fully described in the literature and relatively few studies have explored the association between specific cognitive functions and early preclinical A β deposition in discrete brain regions

1.4 The relation between cerebral SVD, $A\beta$, and cognition

A β deposition in the brain and its effect on cognitive decline should not be studied in isolation, but in the context of coexisting pathology. Autopsy studies have shown that brain A β frequently co-occurs with cerebral small vessel disease (SVD) suggesting an intreplay of these pathologic insults [57-60]. SVD refers to a varied group of diseases that affect the cerebral small

arteries and microvessels [61, 62]. Features of SVD seen on neuroimaging include recent subcortical infarcts, white matter hyperintensities (WMH), lacunes, prominent perivascular spaces, and cerebral microbleeds, frequently associated with cerebral atrophy [63].

Understanding the biological and pathological changes of white matter (WM) that occur in SVD is critical for identifying accurate outcome measures in future studies and clinical trials [64]. The pathological change of WM starts with chronic hypoxia, which leads to axonal loss, demyelination, increased inflammatory infiltrate, and gliosis [65]. These changes are detected as hyperintense signals on FLAIR MRI images [13]. WM damage is not always limited to the initially visible lesions (WMH) in FLAIR scan; there are subtle changes that occur in the normalappearing white matter like decreased myelin and/or axonal density leading to microstructural WM disruption [66]. Through DTI, microstructural WM disruption could be assessed in vivo by measuring the rate and direction of diffusion of water molecules trapped in neural tissue [67]. FLAIR and DTI seem to be appropriate predictors of white matter injury. FLAIR studies may fail to capture the true degree and extent of white matter injury but are easy to interpret in clinical practice [64]. Semi-automated and automated quantification techniques of WMH volumes vary across studies and research sites [68-72]. Generally, all of them use the same basic concepts regardless the difference in software and algorithms, which include: 1) image registration, 2) nonbrain tissue stripping, 3) intensity estimation and thresholding, and 4) manual editing (as deemed necessary) [70].

Irrespective of the relationships that may exist between A β and SVD, it is clear that cooccurrence of A β and WMH [73] increases the risk of dementia, suggesting an additive or even a possible synergistic effect [74, 75]. Previous studies evaluating the relationship between brain A β , WMH, and cognition have shown conflicting results [60]. Most of them have demonstrated an independent and additive effect of brain A β and WMH [59, 76-78] while; few studies had shown interaction effect between brain A β and higher WMH volumes on specific cognitive domains [79-81]. Studying the effect of A β and WMH on cognition without emphasizing the importance of lesion location may lead to a premature dismissal of hypotheses assessing the functional interactions between these two major pathologies.

1.5 The association between Cerebral SVD to AD

Despite the findings from the recent studies supporting the significant role of WMH in cortical A β accumulation and AD development [82-88], the "amyloid cascade hypothesis" [89] still drives ongoing basic and clinical research discoveries and has dominated the field in regards to clinical trials in AD [90, 91]. This may be because the underlying mechanistic linking of WMH to AD pathology is still unclear, and it is also not fully understood if WMH are merely additive to AD pathology or whether WMH may actually initiate or accelerate AD pathology. The pathology underlying individual cases of AD are likely quite varied based on the regional distribution of A β deposition, and may additionally be influenced by pre-existing and or accumulating WMH pathology [92]. The pathological interaction between WMH and AD pathology within discrete white matter tracts and connected cortical regions has not been closely investigated but deserves in depth investigation.

WM alterations (including overt WMH and microstructural WM disruption) have been largely identified in specific subcortical neuroanatomic regions that are connected with often distant cortical regions harboring the greatest amount of AD pathology [92-94]. The association between regional distribution of WMHs and global A β has been studied initially in a few crosssectional studies, that have suggested a greater posterior involvement of WMH in AD [92, 95-99]. Of interest, the tracts with the remarkable WM microstructure alternation (the main cingulum bundle, and the superior longitudinal fasciculi) are anatomically connected to the brain regions that are affected with A β pathology at the earliest stages of disease within the Default Mode Network (DMN) [100-102].

1.6 Chapters organization: this thesis consists of 5 chapters that are organized as fellow

Chapter 1 presents an introduction to basic concepts necessary to understand the brain change in the pAD stage and its diagnosis, which based on biomarker positivity. Also in this chapter is an introduction to explain the effect of WMH on A β and the effect of the two primary drivers of preclinical dementia on cognition.

Chapter 2 present a study that aims to test the hypothesis that early focal regional amyloid deposition in the brain is associated with cognitive performance in specific cognitive domain scores in pAD. Global and regional standardized uptake value ratios (SUVr) from 18f-florbetapir PET/CT scanning were determined across a sample of 99 clinically normal

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participants with Montreal Cognitive Assessment (MoCA) scores ≥ 23 . Relationships between regional SUVr and cognitive test scores were analyzed using linear regression models adjusted for age, sex and education. Participants were divided into two groups based on SUVr in the posterior cingulate and precuneus gyri (SUVR ≥ 1.17). Between group differences in cognitive test scores were analyzed using ANCOVA models. Executive function performance was associated with increased regional SUVr in the precuneus and posterior cingulate regions only. We also found no significant associations between memory and A β -PET SUVr in any regions of the brain. We conclude that increased A β deposition in the precuneus and posterior cingulate (the earliest brain regions affected with A β pathology) is associated with changes in executive function that may precede memory decline in pAD.

Chapter 3 aims to explore the relation between regional and global A β and WMH with cognitive performance in cognitively normal (CN) older adults at baseline, and further examine the relation between baseline WMH and regional A β deposition in relation to future cognitive performance. Moderation, and mediation modeling were used to define the interplay between global, regional A β and WMHs measures in relation to cognitive (memory and EF) composite score outcomes at baseline and after approximately 2 years across a sample of 714 clinically-normal (Mini-Mental State Examination (MMSE) ≥ 26), aged participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI2). The moderation regression analysis showed additive effects of A β burden and WMH over baseline cognitive performance and synergistic effects over longitudinal EF only. Through mediation analysis, we demonstrated that the influence of WMHs over baseline cognitive performance independently while WMH volumes exert effects on baseline cognitive performance directly and through influences on A β accumulation.

Chapter 4 aims to test the hypothesis that cerebral SVD is associated with increase A β distribution within areas of the brain disconnected by the cerebral SVD that lie within the DMN hit hardest and earliest in the pathogenesis of AD in even cognitively normal older adults. We explored the association of WMH volumes in major fiber tracts from DMN regions using Johns Hopkins University International Consortium for Brain Mapping probabilistic fiber tract atlas (JHU-ICBM-tracts) with A β -PET SUVr in cortical DMN regions across a sample of 72 clinically-normal MMSE \geq 26, aged participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI3). The regression analysis demonstrated that increased WMH volumes in

superior longitudinal fasciculus (SLF) was associated with increased regional SUVr in inferior parietal lobule (IPL) (p<0.05). The findings suggest that the relation between A β and SVD in influencing executive function in pAD is partially driven directly by WMH and is additionally contributed to by WMH injury that accelerates A β deposition ultimately leading to the deficits in executive function seen in pAD.

Chapter 5 presents a summary of this dissertation and points out future perspectives. This thesis includes a diverse set of work and experiments with a primary focus on the importance of using regional amyloid quantification rather than using global measure of A β . Another main objective of this thesis is exploring how regional A β and WMH interact on a biological level.

CHAPTER 2. Amyloid-PET levels in the Precuneus and Posterior Cingulate Cortices are Associated with Executive Function Scores in Preclinical Alzheimer's Disease Prior to Overt Global Amyloid Positivity

2.1 Introduction

Dementia is a major and increasing global health challenge with 40–50 million people currently living with dementia worldwide [103]. Alzheimer's disease (AD) is the most common cause of dementia corresponding to about 60% of cases [104]. The neuropathological development of AD arguably begins with β-amyloid (Aβ) deposition in the brain, which occurs many years before the appearance of cognitive decline (preclinical Alzheimer's disease (pAD)) [1, 2], and has been identified as a risk factor for subsequent dementia [105, 106]. The diagnosis of pAD is based on biomarker positivity using diagnostic tests such as amyloid tracer-based positron emission tomography (Aβ-PET) and cerebral spinal fluid (CSF) measures of Aβ [107].

It is challenging to detect clinically significant cognitive change in pAD, and results have been variable across studies [42-49, 51-55]. Although A β deposition is a gradual process [108] that develops over time in discrete regions of the brain in a temporally progressive manner [4], the majority of published studies have focused on global rather than regional measures of A β positivity. One recent study, however, demonstrated that patients with early focal $A\beta$ deposition had clinical features that differed from persons with more diffuse global A β deposition, suggesting that further study is needed [109]. Another recent study has shown that preclinical $A\beta$ accumulation in the precuneus, medial orbitofrontal, and posterior cingulate cortices can be detected in participants prior to the development of abnormal CSF Aβ42 or global Aβ PET scan positivity [102, 110]. Limitations of recent studies on regional quantification of amyloid pathology also include a primary focus on memory domain impairment rather than examining a broader array of cognitive domain involvement [111-113]. Additionally, previous studies examining relationships between regional A β deposition and different domains of cognition have largely focused on comparing cognitively normal participants to mild cognitively impaired or AD patients, but notably did not include pAD participants [114-116]. As early identification of pAD is an important goal for the field, an accurate and thorough understanding of the cognitive and brain changes accompanying this stage of disease is critical [117].

The main objective of this study was to test the hypothesis that early focal regional amyloid deposition in the brain is associated with preclinical cognitive decline in specific cognitive domains (memory & executive function) in elderly cognitively intact persons (pAD).

2.2 Methods

2.2.1 Study design and participants

This cross-sectional study included review of the neuroimaging and clinical data from participants who underwent F-florbetapir PET/CT scanning between 2015 and 2020 at the Sanders Brown Center on Aging. This study was approved by the University of Kentucky (UK) Institutional Review Board (IRB), and a signed IRB consent was obtained from each subject prior to participation.

Inclusion criteria included the availability of:

- Complete demographic information (age, sex, and years of education)
- Neurocognitive function that covered major cognitive functions [103], the Montreal Cognitive Assessment (MoCA) [104], The Trail Making Test (TMT), and California Verbal Learning Test -II (CVLT-II) [105],
- Cognitively intact participants with a MoCA score ≥23 to exclude participants with mild cognitive impairment (MCI) or dementia, as described previously [106].

2.2.2 Acquisition of Flobetapir PET/CT

For each scan, the participant received a single intravenous administration of approximately 370 MBq (10 mCi) of florbetapir F 18 (fast intravenous push). The injection of the imaging agent was followed by a saline flush. After an uptake period of 50 min, participants were positioned in a head stabilization unit designed for PET/CT scanners. All PET/CT scans were performed on a Siemens Biograph TruePoint 6-slice (Siemens Healthcare, Erlangen, Germany). Low resolution CT images of the head will be acquired (120 kVp, FOV 50 cm, pitch 0.55, 0.5 s

rotation time, slice thickness 4 mm, care dose). PET images of the brain were then collected for a 20-min, 3D emission scan. The emission images are reconstructed using 256×256 matrix and all-pass filter.

All F-florbetapir PET/CT images were analyzed using dedicated viewing software (Syngo.via[®]; Siemens) [107]. Siemens *Syngo.VIA* Amyloid Plaque (Siemens Medical Solutions Inc., Malvern, PA, USA) software package was used for neurological evaluations of PET/CT. Quantitative parametric analysis was performed with Database Comparison software (Siemens Medical Solutions, Inc.) that automatically identifies regions of interest (ROIs) based on the analysis method used by Fleisher [108]. The regions (frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus) were selected based on the analysis described by Fleisher and Clark in the use of florbetapir-PET in β -amyloid imaging analysis [108, 109]. Since the occipital region is significantly affected more than any other region in cerebral amyloid angiopathy, we exclude this region from the analysis [110, 111]. The mean uptake of ROIs was calculated. Standardized uptake value (SUV) is a semi quantitative measure of the intensity of radiotracer activity at each voxel [112]. The mean SUV of each region is normalized to the mean SUV of the cerebellum (SUVr) (SUVr = SUV target/SUV reference) [113].

A threshold of SUVrs greater than or equal to 1.17 was used to reflect pathological levels of amyloid associated with MCI and AD [108, 114, 115]. We choose to focus on the mean score of posterior cingulate and precuneus gyri SUVrs as these regions are among the earliest brain regions of amyloid deposition [25, 116-118]. The participants were divided into two groups (pAD and control group) based on SUVr in the posterior cingulate and precuneus gyri (SUVr≥1.17).

2.2.3 Neuropsychological cognitive test

We examined cognitive test scores that assess major cognitive functions, including global cognition with the MoCA [104], processing speed, attention and executive function with TMT [119], and memory function with the CVLT-II [105]. The MoCA is a brief test of cognitive function that assesses visuospatial, naming, attention, language, abstraction, delayed recall and orientation. Total score is generated by summing scores across all of these domains [120]. TMT is a neuropsychological test of visual attention and task switching. In Part A, participants were asked to link numbered points randomly distributed on a sheet of paper in ascending order according to numbers. In Part B, the participants were asked to link numbers and letters

alternately. The time of each test performance was measured, the number of errors were counted, and the difference in times: B-A was calculated [121]. CVLT-II is a widely used measure of verbal episodic learning and memory. A list of 16 items organized into four semantic categories are presented to the subject over five immediate recall trials, free and category cued recall is tested after short and longer (20-min) intervals. We chose to focus on the CVLT-II learning component of the test, which is the sum of the five immediate recall trials, as well as free delayed recall scores.

2.2.4 Statistical analysis

Statistical analyses were performed in IBM SPSS Statistics v28. Significance was set at P < .05, with Bonferroni correction based on the number of cognitive tests as a dependent variable.

In the first analysis, we used ANCOVA to evaluate whether the means of score of cognitive tests are equal across different levels of posterior cingulate and precuneus SUVr, while statistically controlling for the covariates (age, sex, and education). We tested the homogeneity to make sure the values of covariates did not vary and equal over all the two groups using ANOVA. Differences in performance on the neuropsychological cognitive tests between pAD and controlled group were tested using one-way ANCOVA after adjustment for covariates. The difference in the scores of cognitive function tests across different level of global SUVr were assessed using ANCOVA again.

In the second analysis, linear regression adjusted for age, sex and education was used to explore the relationship between regional SUVr (independent variables) and the cognitive function scores (dependent variable). Due to high co-linearity between regional SUVr measures regressions were initially run separately for each region. This process was repeated for each cognitive test (TMT B, TMT B-A, MoCA, and CVLT (learning score, short free delay recall, and long free delay recall)). Relationships between regional SUVr from multiple regression from the prior step and MoCA domain scores were analyzed using linear regression models adjusted for age, sex, and education.

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2.3 Results

The demographic, clinical and imaging characteristics of the sample are provided in table 2.1. Briefly, the sample included 68 women and 31 men with a mean age of 74.2 ± 6.3 years, education 16.7 ± 2.6 years. Posterior cingulate and precuneus SUVrs ranged from 0.85 to 2.43 in this study cohort.

2.3.1 The differences of the demographic and cognitive measures, between the preclinical and control group

Dividing the cohort into two groups based on SUVr of posterior cingulate and precuneus SUVr > 1.17, allowed an analysis of 45 participants in the pAD group and 54 participants in the control group. Between-group differences on demographic variables were not significant, including sex at birth, where a chi-square test showed non-significant between group differences (p value = 0.83; data not shown in Table 1). Cognitive and imaging measures that clearly defined the groups as distinct are presented in Table 2.1

	pAD		Control		
	Mean	SD	Mean	SD	р
Age	75.08	7.01	73.46	5.6	0.203
Education	16.8	2.93	16.57	2.39	0.69
MoCA	26.2	1.85	27	1.83	0.036*
TMT A	34.51	11.73	33.6	10.91	0.92
TMT B	92.07	38.41	73.36	27.6	0.011*
TMT B-A	57.56	31.62	39.75	21.3	0.002**
CVLT-II Total Learning	47	11.67	47.83	10.89	0.7
CVLT-II Short-Delay Free	9.91	4.25	11.3	3.57	0.089
CVLT-II Long-Delay Free	9.98	3.99	11.39	3.53	0.072

Table 2.1The differences of the demographic and cognitive measures, between the preclinical and control group

No significant between group differences on demographic variables were seen between pAD (n=45) and control groups (n=54). Significant between group differences were seen for MoCA, TMT B, and TMT B-A scores. Abbreviations: SD: standard deviation; SUVr: Standardized Uptake Value ratio; AD: 'Alzheimer's Disease; MoCA: Montreal Cognitive Assessment; TMT: Trail Making Test; CVLT: California Verbal Learning Test –II. *0.05 level significance Figure 2.1 differences of the demographic and cognitive measures, between the preclinical and control group



Comparison of cognitive measure scores Trail Making Test (TMT) part B-A, and The Montreal Cognitive Assessment (MoCA) among preclinical group and control group based on SUVr of posterior cingulate and precuneus SUVr > 1.17 after adjusted for age, education, and sex. Figure A shows the difference in the scores of TMT part B-A between the groups. Box and whisker plots of the MoCA score (Figure B) show medians, lower to upper quartile, and lines extending from minimum to maximum values

2.3.2 The association between regional A β -PET SUVr and cognitive test scores

In the second set of analyses (shown in Table 2.2), linear regression analysis was used with each region (A β -PET SUVr of independent frontal, parietal, temporal, anterior cingulate, posterior cingulate, and precuneus cortical regions) used as independent variables and cognitive test scores as a dependent variable to explore associations of amyloid deposition in regions of the brain with MoCA, TMT, and CVLT. Age, sex, and education were entered as covariates in the analysis. The adjusted linear regression analyses demonstrated that increased regional SUVr in the precuneus and posterior cingulate regions only were associated with reduced global MoCA score and TMT B-A scores (shown in figure 2.2) (p<0.05).

Table 2.2 Testing the independent effect of regional A β SUVr burden on cognitive function test scores

Cognitive Function test	Dogional SUVn	Coeff. β (p-	Adjusted R
Cognitive Function test	Regional SU VI	value)	square
MoCA	Frontal SUVr	-1.01(.172)	.052
	Parietal SUVr	-1.141(.176)	.052
	Temporal SUVr	-1.244(.157)	0.054
	PCC & precuneus SUVr	-1.612(.023)	0.086
	Anterior cingulate SUVr	-0.479(0.434)	0.039
	Frontal SUVr	-1.92(0.671)	0.028
	Parietal SUVr	1.31(0.799)	0.027
TMT part A	Temporal SUVr	-1.49(0.781)	0.027
	PCC. & precuneus SUVr	0.804(0.854)	0.027
	Anterior cingulate SUVr	-0.26(0.944)	0.026
	Frontal SUVr	11.231(0.401)	0.093
TMT part B	Parietal SUVr	16.833(0.268)	0.098
1	Temporal SUVr	9.57(0.547)	0.089
	PCC & precuneus SUVr	20.971(0.102)	0.112
	Anterior cingulate SUVr	9.25(0.401)	0.093

Table 2.2 continued

TMT (B-A)	Frontal SUVr	13.15(0.228)	0.108
	Parietal SUVr	15.526(0.210)	0.109
	Temporal SUVr	11.066(0.393)	0.100
	PCC & precuneus SUVr	20.17(0.04)	0.130
	Anterior cingulate SUVr	9.507(0.290)	0.104
	Frontal SUVr	-1.38 (0.772)	0.105
	Parietal SUVr	1.83(0.736)	0.106
CVLT (learning score)	Temporal SUVr	0.07(0.991)	0.105
	PCC & precuneus SUVr	-2.59(0.6)	0.107
	Anterior cingulate SUVr	0.17(0.965)	0.105
	Frontal SUVr	-0.66(0.692)	0.124
	Parietal SUVr	-0.57(0.764)	0.123
CVLT (short free delay	Temporal SUVr	-1.44(0.484)	0.127
recall)	PCC & precuneus SUVr	-1.63(0.343)	0.131
	Anterior cingulate SUVr	-0.06(0.965)	0.123
CVLT (long free delay	Frontal SUVr	-1.70(0.273)	0.180
recall)	Parietal SUVr	-1.75(0.320)	0.178

Table 2.2 continued

	Temporal SUVr	-2.73(0.155)	0.188
CVLT (long free delay			
	PCC & precuneus SUVr	-2.35(0.143)	0.189
recall)			
	Anterior cingulate SUVr	-0.91(0.470)	0.174

Coeff. β : coefficient β , SUVr: Standardized Uptake Value ratio; MoCA: Montreal Cognitive Assessment; TMT: Trail Making Test; CVLT: California Verbal Learning Test –II; PCC: posterior cingulate cortex. (All coefficient β values are adjusted for the covariates age, sex and education. Adjusted R square is the proportion of variance in the cognitive function scores that was explained by the model discounted for age, sex, education and regional SUVr).

Figure 2.2 Scatterplot between the mean score of posterior cingulate cortex and precuneus SUVr with cognitive function scores (MoCA and TMT B-A)



The scatterplots show the fitted regression line of the posterior cingulate cortex (PCC) and precuneus SUVrs as independent variables and cognitive function test scores (MoCA global score, and TMT part B completion time- TMT part A completion time) as the dependent variable. Figure A: Removing the visually obvious outlier (The mean SUVr of PCC and precuneus = 2.43 (p =0.048)) did not alter the statistical significant correlation between MoCA global score and the mean SUVr of PCC and precuneus.

2.4 Discussion

The main finding of this study is that regional amyloid deposition in the precuneus and posterior cingulate are associated with early preclinical decline in executive function in pAD, irrespective of global SUVr. Prior studies that have focused on regional amyloid deposition in the brain have shown that regional amyloid deposition in posterior cingulate gyri and precuneus are associated with global cognition [122, 123] and lower preclinical memory scores; however, analyses of A β influences on non-memory cognitive domains were not assessed [123-125]. Such studies with an *a priori* focus on memory domain impairment rather than exploring a broader array of cognitive domain relationships introduces a bias that limits our full understanding of the impact of early preclinical A β deposition.

While the majority of observational studies and clinical trials for pAD have defined populations on the basis of global SUVr cut-offs, the present data suggests that such criteria may be selecting for a later pathological stage of disease, perhaps mediated by cognitive reserve mechanisms. As the field moves towards earlier diagnosis and intervention, considering the development of modified biomarker criteria that takes into account the wealth of data accumulated in the area of pAD just makes sense. Such attempts to date, include lowering global A β SUVr cut-off scores for the diagnosis of pAD [126-128], that have enabled an even earlier examination of pAD. Our data suggests we can go even earlier by focusing on regional A β -PET SUVr levels in the precuneus and posterior cingulate rather than on global SUVr data that has already been adjusted to its threshold. While concerns about using such an approach might include a possibility of simply detecting incidental cerebral amyloidosis that may never progress, the present data demonstrating early preclinical cognitive test score associations argue against such a possibility, demonstrating that such early regional A β deposition is clinically meaningful. Moreover, accumulation of amyloid in precuneus had shown to be predictive of future global amyloid deposition in the brain [123].

In this context, the present data demonstrate that changes in executive function may be the earliest signs of pAD. Consistent with our findings, Snitz et al. reported that nonmemory domains, primarily executive functions is changed 7 to 9 years prior to neuroimaging change in A β -positive clinically normal participants comparing to A β -negative participants [50]. A more recent study using random forest machine learning analysis to rank the AD biomarkers in prediction of clinical dementia status in AD [129] found that A β deposition in precuneus, temporal and frontal as well as tau levels are highly correlated with cognitive function in

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cognitively normal participants and are predictors for early preclinical impairments in executive and memory function. This same study also demonstrated that increased tau burden is associated with lower memory but not executive function scores in clinically normal older individuals. Our data is aligned with these previous results suggesting that early change in executive function in pAD may be explained by preclinical A β deposition in precuneus and posterior cingulate gyri. Both posterior cingulate gyri and precuneus are part of default mode network, which is involved in attention and executive function [130].

It is also possible that the lower executive function performance associated with early preclinical A β deposition in the precuneus and posterior cingulate seen in the present study may not be dependent on neuroanatomic involvement of these regions but rather may be associated with more global changes in brain function and or pathology that lie below the level of A β -PET detection. As such, it is possible that early A β deposition in the precuneus and posterior cingulate is related to a more widespread production of early synaptotoxic soluble oligomeric A β species affecting regions such as the dorsolateral prefrontal cortex that is more widely recognized as a neuroanatomic substrate for executive dysfunction [131]. Interstitial fluid accumulation of such soluble oligomeric A β species may be well below the threshold of A β -PET detection. Alternatively, early tau abnormalities, inflammatory, or oxidative stress related mechanisms are just a few of the concomitant mechanisms that could be at play but remain below the level of detection in brain regions responsible for early executive dysfunction in pAD [132]. Much further work is needed before we fully understand the still enigmatic state of pAD.

Cognitive screening instruments such as MoCA are widely used to detect cognitive decline as one transitions from pAD to mild cognitive impairment or dementia due to AD [43], but are relatively insensitive for tracking cognitive decline in pAD. Our data, however, using adjusted linear multiple regression, demonstrates that increased A β deposition in the precuneus and posterior cingulate (the earliest brain regions affected with A β pathology[3, 102]) are associated with decreased global cognitive performance MoCA, further supporting at least one prior study in the literature [133]. The relationship of MoCA scores with A β deposition in the precuneus and posterior cingulate seen in the present study appeared to be driven by language domain subscores in individuals with pAD (data not shown). This result conceptually is in accordance with prior findings from a much smaller study (n =11 AD and 15 healthy control) that found a significant relationship between greater florbetapir F18 precuneus SUVr and poorer verbal fluency in AD [134].

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The main limitations of our study include the relatively small sample size, and an absence of tau measures in the analysis. Another main limitation of the study is unavailability of APOE in the analysis, despite its well-recognized influence on amyloid deposition in cognitively healthy individuals. Another limitation of this study is the use of a highly educated, predominantly white sample that limits the generalizability of the results to underrepresented groups. Despite this limitation it should be noted that the participants represented a well-characterized cohort that has undergone comprehensive longitudinal medical and neuropsychological exams. The strengths of our work include a focus on early regions of the brain affected by $A\beta$ pathology and their relation to domain-specific cognitive test performance in pAD, prior to development of global $A\beta$ positivity.

While the prevailing view in the field suggests that memory performance is the earliest clinical hallmark of AD, the present data demonstrate that changes in executive function, mediated by $A\beta$ deposition in the precuneus and posterior cingulate may precede memory decline in pAD. Ongoing and future efforts at developing more sensitive tests for preclinical executive function deficits may serve as the most sensitive, low cost, non-invasive clinical biomarkers of preclinical AD. Further studies are needed to show the longitudinal clinical and cognitive outcome of this early preclinical amyloid change, and for a complete understanding of the temporal progression of domain specific cognitive change in relation to regional progression of amyloid deposition in the brain.

CHAPTER 3. AMYLOID-PET AND WHITE MATTER HYPERINTENSITIES HAVE INDEPENDENT EFFECTS ON BASELINE COGNITIVE FUNCTION AND SYNERGISTIC EFFECTS ON LONGITUDINAL EXECUTIVE FUNCTION

3.1 INTRODUCTION

Alzheimer's disease (AD) and subcortical vascular dementia are considered the most common pathologic contributors to dementia in the aging population. Both frequently coexist in over 80% of community dwelling adults with dementia [135]. Cerebral small vessel disease (CSVD) has also been linked to the pathogenesis of AD and is largely responsible for the development of subcortical vascular dementia [61]. AD and CSVD share multiple risk factors [136], occurring concomitantly in over 50% of individuals with dementia [137], and there may be substantial overlap between these two conditions in terms of clinical, pathological and radiological findings. Co-occurrence of beta amyloid (A β) (a hallmark pathologic feature of AD) and white matter hyperintensities ((WMH), reflecting CSVD burden) increase the risk of dementia [74].

WMH and $A\beta$ are also key drivers of cognitive decline in healthy older adults, and both are considered biomarkers of preclinical dementia [77, 138]. Neuroimaging studies examining the combined impact of $A\beta$ burden and WMH on cognition have largely examined these variables independently rather than examining the potential interplay between these key pathologic hallmarks of dementia. Several studies have addressed this issue of interplay between $A\beta$ and WMH with often contradictory results [59, 76, 77, 80, 81, 138-141]. Notably, many of these studies focused on global measures of WMH and $A\beta$ without exploration of regional effects in relation to stage of disease. Studying the effect of $A\beta$ and WMH on cognition without emphasizing the importance of lesion location can miss the functional consequences of the two pathologies. Previous studies investigating the impact of regional distribution of WMH on (executive function) EF found that WMH in all cortical regions (frontal areas, occipital, parietal and temporal) are associated with deficits in EF scores [97, 142, 143], but regional quantification of $A\beta$ and its interaction with WMH volume has not been fully investigated in these prior studies.

Aβ deposition is hypothesized as being the initial step in the neuropathological development of AD and dementia [144], but findings from previous studies have also shown that WMH often occur prior to the presence of amyloid-β plaques in preclinical AD [145-147] supporting a retrograde degeneration hypothesis [148, 149]. Additionally, evidence from recent

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studies has suggested that the relationship between WMH and A β is strongly determined by the spatial distribution of the two pathologies [150]. The majority of published studies have emphasized the spatial heterogeneity of WMH [98, 151], but have left the potential heterogeneous influences of regional A β deposition relatively unexplored.

Since mixed dementia is widely recognized as the norm rather than the exception, in the present study we sought to explore the relation between regional and global A β and WMH with cognitive function (EF and memory) scores in cognitively normal (CN) older adults at baseline, and further examine the relation between WMH and regional A β deposition in relation to cognitive performance changes over time.

3.2 Methods

Data used in the preparation of this article were obtained from the summary data from Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

3.2.1 Participants:

Summary data from the Alzheimer's Disease Neuroimaging Initiative (ADNI 2) at http://adni.loni.usc.edu [152] were used in the present analyses. Only participants with a minimental state examination (MMSE) score greater than or equal to 26 at baseline meeting these inclusion criteria were included in the analysis: (1) Complete demographic information (i.e., age, sex, education) and ApoE genotype available; (2) Neurocognitive composite metrics for EF and memory at baseline and after approximately 2 years; (3) PET Florbetapir for focal and global Aβ quantification; and (4) T2 FLAIR scan acquisition with WMH volume quantification. Details of ADNI inclusion criteria, clinical procedures and methodology are available elsewhere [153, 154]. These criteria were developed to specifically investigate predisease and preclinical disease states that may lead to further cognitive impairment and dementia.

Participants with missing data required for the analyses were excluded. A total of 53 participants were excluded from the longitudinal analysis on the basis of missing data required for the analysis. Excluded participants did not differ significantly from these included in the analysis in regards to age, sex, education, ApoE, or baseline MMSE scores (data not shown).

3.2.2 Imaging analysis

3.2.2.1 White Matter Hyperintensity quantification method

WMH volumes were quantified using the 4-tissue segmentation method described previously [68]. Briefly, first step was co-registration of the FLAIR to the 3D T1 image inhomogeneity-corrected and non-linearly aligned to a minimal deformation template (MDT) using the T1 transformation and the FMRIB Software Library (FSL) toolbox[155, 156]. Modified Bayesian probability and structure prior probability maps were used to estimate WMH in the MDT. Binary WMH masks were then created using 3.5 SD threshold above the mean. The segmented WMH masks were then back-transformed into native space for tissue WMH volume calculation. An Expectation-Maximization (EM) algorithm was used for segmentation to isolate gray, white, and CSF measurements in template-space. Transforming these masks back to each image's native space produced rough estimate 3-tissue segmentations. Finally, WMHs were ultimately subtracted from segmented white matter volume and reported in cubic millimeters.

3.2.2.2 Calculation of Florbetapir cortical summary values.

Preprocessing of the AV-45 PET scans and computation of the global AV-45 PET values were done centrally by the ADNI core as described previously [157]. Briefly, each subject's florbetapir image was coregistered using SPM8 to that subject's MRI image that was closest in time to the florbetapir scan. Freesurfer processing was carried out to skull-strip, segment, and delineate cortical and subcortical regions in all MRI scans[158, 159]. Volume-weighted florbetapir means from a cortical summary region were extracted. A single binary cortical summary region composed of all the subregions was created to calculate the mean uptake across each region. We used the summary data of global and regional (frontal, parietal, and cingulate regions that have been most frequently associated with EF performance [51, 160-162]) SUVr determination was based on the whole cerebellum reference region. Details regarding regions of

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interest forming the subregions frontal, parietal and cingulate have been described previously [157].

3.2.3 Composite measures of executive function and memory: ADNI_EF and ADNI_Memory

The specific tests included in ADNI executive function (ADNI-EF) composite scores are Category Fluency (animal &vegetable naming), Trail Making Tests A and B, Digit Span backwards, Wechsler adult intelligence scale-revised (WAIS-R) Digit Symbol Substitution, and 5 Clock Drawing items (circle, symbol, numbers, hands, time). The memory composite (ADNI_Memory) included the Rey auditory verbal learning test (RAVLT), the cognitive component of the Alzheimer's disease assessment scale (ADAS-Cog), and Wechsler logical memory scale scores [163]. We used the ADNI-EF and ADNI-Memory scores corresponding to the baseline scan and EF and memory scores within one to three years from the baseline as follow-up scores.

3.2.4 Statistical analyses:

All statistical analyses were conducted using SPSS, version 26.0 (SPSS Inc., Chicago, IL, USA). Significance was set at P < .05, with Bonferroni correction based on the number of the analysis. We used multiple regression models including the interaction term and the main effects for A β and WMH to investigate the independent and combined associations of these pathologies with cognition (ADNI-EF and ADNI-Memory). WMH volume was logarithmically transformed due to the positive skewed distribution for the statistical analysis. Moderation analyses assessing the relationship between A β and WMH were fit to the data using the following equation:

 $\hat{\mathbf{Y}} = \mathbf{b}_0 + \mathbf{b}_1 \mathbf{W} \mathbf{M} \mathbf{H} + \mathbf{b}_2 \mathbf{A} \boldsymbol{\beta} + \mathbf{b}_3 \mathbf{W} \mathbf{M} \mathbf{H}^* \mathbf{A} \boldsymbol{\beta} + \mathbf{b} \mathbf{X},$

where \hat{Y} represents the mean and bX represents beta coefficients and adjustment covariates. Age (continuous values), sex (indicator variable), education (continuous values), ApoE (indicator variable), and total intracranial volumes (continuous values) were entered as covariates in all analyses. The models were built using Hayes' PROCESS macro for SPSS (model 1) [164]. Longitudinal analyses examined the association of the interaction between baseline A β burden and WMH with mean follow-up cognitive (ADNI-EF or ADNI-Memory) scores after controlling for baseline ADNI cognitive scores and time following the baseline scan acquisitions and cognitive testing. To consider the regional A β burden effects in addition to global A β burden and

WMHs on baseline and change in ADNI-EF and ADNI-Memory, moderated regressions were run for amyloid deposition (SUVr) in each of the *a priori* selected cortical regions (Frontal, cingulate and parietal), adjusting for age, sex, education, ApoE, and intracranial volumes.

Assuming that WMH is causally related to $A\beta$ deposition, which is in turn causally related to cognitive (ADNI-EF or ADNI-Memory) scores, mediation models were built to estimate the relationship between WMH (independent variable) and cognitive function (dependent variable) and $A\beta$ (mediator variable). This model was built using Hayes' PROCESS macro for SPSS (model 4) [164]. Significance was tested using 5000 bootstrap samples to calculate bias-corrected 95% confidence intervals. Indirect effects with bootstrapped 95% confidence intervals not crossing zero were considered significant. Age, sex, education, ApoE, and intracranial volumes were entered as covariates in the mediation regression models. Baseline ADNI composite scores and times between the two cognitive scores tests were added as covariates in the mediation regression models examining longitudinal cognitive score changes.

3.3 Results

The demographic, clinical and imaging characteristics of the included participants are provided in Table 3.1. Briefly, the sample included 326 women and 388 men with a mean age of 73.13 ± 7.4 years; participants were highly educated on average (16.3 ± 2.6 years).

Characteristic	Range	Mean (SD)	Sample size	
Age (years)	55-96	73.13 (7.41)	714	
Education (years)	10-20	16.31 (2.6)	714	
Global Aβ burden (SUVr)	0.84 - 2.01	1.19 (0.22)	714	
Frontal Aβ burden (SUVr)	0.83 -2.01	1.19 (0.23)	714	
Cingulate Aβ burden (SUVr)	0.89 - 2.36	1.29 (0.22)	714	
Parietal Aβ burden (SUVr)	0.87 - 2.08	1.20 (0.22)	714	
WMH volumes in cubic centimeters	0.07 - 61.02	6.94 (8.54)	714	
WMH volume (log-transformed)	-1.13 to 1.79	0.57 (0.52)	714	
Total intracranial volumes	1084.29 to 1861.82	411.88 (135.97)	714	
ADNI-EF (baseline)	-3.01 to 2.99	0.54 (0.94)	714	
ADNI-EF (follow-up)	-3.01 to 2.99	0.50 (1.06)	661	
ADNI-memory (baseline)	-2.8 to 3.14	0.56 (0.81)	714	
ADNI-memory (follow-up)	-2.62 to 3.06	0.52 (0.94)	661	
Time between test (years)	1 to 3	1.86 (0.49)	661	
APOE e4 allele N(%) copy1	2 to 4	58 (8.1)	714	
APOE e4 allele N(%) copy 2	3 to 4	300 (42.1)	714	
Sex male N (%)		388 (54.3)	714	

Table 3.1 Characteristics of participants

Key: Aβ, Beta Amyloid; WMH, White Matter Hyperintensities; ADNI-EF, Executive Function; SD, Standard Deviation; SUVr, Standardized Uptake Value Ratio.

3.3.1 Testing the interaction term and the main effect of global, and regional A β burden and WMHs with cognition

The moderation regression analysis detected a marginally statistically significant interaction effect between A β burden and WMH in relation to baseline EF (p-value=0.061), and a significant interaction term between the biomarkers in relation to longitudinal executive functions

with p-value= 0.036. Overall, when amyloid burden was higher, the association between log WMH and ADNI-EF was stronger. (+1SD above sample mean) (Figure 3.1A). Regarding memory composite scores, the models did not detect any statistically significant interaction effect between global A β burden and WMH in relation to baseline ADNI-memory scores or follow-up ADNI-memory scores (p-value 0.401 and 0.937 respectively).

The regional models examining the interaction between A β burden in discrete cortical regions and WMH volumes detected marginally significant interaction between frontal, parietal, and cingulate A β burden and WMHs in relation to baseline EF performance with p values (0.061, 0.059, and 0.071) respectively. In contrast, the models failed to detect even marginally significant interaction effects between regional A β burden and WMHs with baseline memory (p-values for interaction term were in frontal A β 0.360, parietal A β 0.353, and cingulate A β 0.411).

The moderation analysis detected a significant interaction effect of frontal and cingulate A β burden and WMH on longitudinal EF performance with p value 0.033 for frontal and 0.024 for cingulate (Figure 3.1B and 3.1C). The (regression) slopes illustrating the negative association of WMH volume with longitudinal executive function performance for 3 levels of regional A β burden and WMHs (-1, 0 and 1 SD using sample's mean) are shown in Figure 3.1. In contrast to the results for EF, the moderation regression analysis failed to detect a statistically significant interaction effect between regional A β burden and WMH in relation to follow-up ADNI-memory scores. Results regarding the moderation models between global and regional A β burden and WMH with baseline and follow-up cognitive (ADNI-EF and ADNI-Mem) scores are displayed in supplementary tables 3.2 and 3.3.

	Baseline		Longitudinal	
	EF		EF	
	Coefficient	P value	Coefficient	P value
Main effect of WMH	-0.198	0.003*	-0.073	0.177
Main effect of Global SUVr	-1.162	<0.001**	-0.708	<0.001**
Interaction WMH * Global SUVr	0.517	0.061	-0.482	0.029*
Main effect of WMH	-0.203	0.003*	-0.094	0.097
Main effect of Frontal SUVr	-1.104	<0.001**	-0.672	<0.001**
Interaction between WMH * Frontal SUVr	0.496	0.061	-0.452	0.033*
Main effect of WMH	-0.185	0.006*	-0.086	0.112
Main effect of Parietal SUVr	-1.126	<0.001**	-0.701	<0.001**
Interaction between WMH * parietal SUVr	0.505	0.059	-0382	0.052
Main effect of WMH	-0.217	0.015*	-0.098	0.144
Main effect of Cingulate SUVr	-0.801	<0.001**	-0.678	<0.001**
Interaction between WMH *cingulate SUVr	0.488	0.071	-0.455	0.024*

Table 3.2: The interaction between global and regional $A\beta$ burden and WMHs on cross-section and longitudinal performance in EF

Key: WMH, white matter hyperintensities; EF, Executive function; SUVr, standardized uptake value ratio; ** less than 0.001, * less than 0.05

	Baseline		Follow-up	
	ADNI-Memory score		ADNI-Memory score	
	Coeffici ent	P_value	coefficie nt	P_value
Main effect of WMH	-0.0753	0.202	-0.108	0.004
Main effect of Global SUVr	-1.257	<0.001**	-0.439	<0.001**
Interaction between WMH * Global SUVr	0.196	0.401	-0.012	0.937
Main effect of WMH	-0.078	0.170	-0.109	0.003*
Main effect of Frontal SUVr	-1.189	<0.001**	-0.491	<0.001**
Interaction between WMH * frontal SUVr	0.205	0.360	-0.051	0.917
Main effect of WMH	-0.063	0.291	-0.105	0.005*
Main effect of Parietal SUVr	-1.179	<0.0001**	-0.405	<0.001**
Interaction between WMH * parietal SUVr	0.209	0.353	0.021	0.887
Main effect of WMH	-0.079	0.119	-0.113	0.003*
Main effect of Cingulate SUVr	-1.015	<0.001**	-0.369	<0.001**
Interaction between WMH *cingulate SUVr	0.188	0.411	-0.007	0.923
Main effect of WMH	-0.083	0.14	-0.112	0.003*
Main effect of temporal SUVr	-1.366	<0.001**	-0.464	<0.001**
Interaction between WMH*Temporal SUVr	0.208	0.406	-0.026	0.873

Table 3.3 The interaction term and the main effect of global, and regional A β burden and WMHs with memory score:

Key: WMH, white matter hyperintensities; EF, Executive function; SUVr, standardized uptake value ratio; ** less than 0.001, * less than 0.05

Figure 3.1 Longitudinal EF performance at low (-1 SD), moderate (mean (0 SD), and high (1 SD) levels of baseline global and regional A β burden and WMH



The (regression) slopes representing WMH's negative associations with executive functions for high levels of regional A β burden (+1 SD using sample's mean). Figure 3.1A showed the interaction term of global A β burden and WMHs with Follow-up ADNI-EF scores. Overall, when amyloid burden was higher, the association between log WMH and ADNI-EF was stronger. (+1SD above sample mean). Figure 3.1B showed the interaction term of frontal A β burden and WMHs with Follow-up ADNI-EF scores. Figure 3.1C showed the interaction term of baseline cingulate A β burden and WMHs with Follow-up ADNI-EF scores. Figure 3.1D showed the interaction term of baseline parietal A β burden and WMHs with Follow-up ADNI-EF scores.

3.3.2 Testing the mediation effects of global and regional Aβ burden on WMH related cognitive performance

Mediation analyses were conducted to assess whether global and regional A β burden act as potential mediators of the relationship between WMH and cognitive performance. Path models of the mediation effect are presented in Figures 3.2, 3.3, 3.4 and 3.5. The path analysis revealed that global A β deposition mediates the relationship between WMH and baseline cognitive (EF and memory) scores (see figures 3.2A, 3.3A). The bootstrap confidence interval (CI) for the indirect effect demonstrated that the indirect effect of WMH on baseline EF performance (a× b = -0.045;

CI: -0.09, -0.01) and baseline memory scores (CI: -0.01, -0.006) through global A β burden were significant. Both Frontal and parietal A β SUVr mediated the effect of WMH on baseline EF and memory performance (see figure 3.2B, 3.2D, 3.3B, and 3.3D). In contrast, there was no significant mediation effect by cingulate A β SUVr for baseline cognitive performance (see figures 3.2C and 3.3C). The other model explored whether global and regional A β SUVr mediated the relationship between WMH and follow-up cognitive (EF and memory) scores after adding baseline cognitive scores and times since the initial cognitive test as the covariates. Results demonstrated that neither global A β SUVr nor regional A β SUVr mediates these associations as the CI for the indirect effect was crossing the zero and did not reach statistical significance (see figure 3.4 and 3.5). While our path analyses were conducted to assess whether global and regional A β burden act as potential mediators of the relationship between WMH and ADNI-memory scores, we tested its opposite direction, and no significant mediating effects were detected for baseline and follow-up ADNI-memory scores. (See supplementary figures 3.6 and 3.7)

Figure 3.2 Path models of the mediation effect of global and regional A β burden between WMH and baseline EF performance



such, path a is expressed the change in A β SUVr with one unit increase in WMH, whereas path b is expressed decrement of baseline EF associated with an increment of A β SUVr. Path c' the direct effect of WMH on EF and path c (total effect). The confidence intervals for the indirect mediation effects of WMH on baseline EF through frontal A β (a× b = -0.045; CI: -0.08, -0.005) and parietal A β (a× b = -0.058; -0.11, -0.02) were significant. (WMH, white matter hyperintensities; EF, Executive function; SUVr, standard uptake value ratio; A β , beta amyloid)

Figure 3.3 Path models of the mediation effect of global and regional $A\beta$ burden between WMH and baseline ADNI-memory scores



As such, path a is expressed the change in A β SUVr with one unit increase in WMH, whereas path b is expressed decrement of baseline ADNI-memory scores associated with an increment of A β SUVr. Path c' the direct effect of WMH on ADNI-memory scores and path c (total effect). The confidence intervals (CI) for the indirect mediation effects of WMH on baseline ADNI-memory scores through global (CI: -0.01, -0.006), frontal A β (CI: -0.11, -0.01), cingulate A β (CI: -0.07, 0.004), and parietal A β (CI: -0.11, -0.02). (WMH, white matter hyperintensities; SUVr, standard uptake value ratio; A β , beta amyloid; CI, confidence intervals).

Figure 3.4 Path models of the mediation effect of baseline global and regional A β burden on longitudinal EF performance



As such, path a is expressed one unit increase in WMH associated with increase of A β SUVr , whereas path b is expressed the change in longitudinal EF associated with an increment of A β SUVr. Path c' the direct effect of WMH on EF and path c (total effect). The confidence intervals (CI) for the indirect mediation effects of WMH on follow-up EF scores through global A β SUVr ((a× b = -0.015; CI :-0.045, 0.009), frontal A β (a× b = -0.012; CI: -0.041, 0.011), cingulate A β (a× b = -0.011; CI: -0.04, 0.014), and parietal A β (a× b = -0.021; CI: -0.05, 0.01). (WMH, white matter hyperintensities; EF, Executive function; SUVr, standard uptake value ratio; A β , beta amyloid; CI, confidence intervals)

Figure 3.5 Path models of the mediation effect of baseline global and regional $A\beta$ burden on longitudinal memory performance



As such, path a is expressed one unit increase in WMH associated with increase of A β SUVr, whereas path b is expressed the change in follow-up ADNI-memory scores associated with an increment of A β SUVr. Path c' the direct effect of WMH on follow-up ADNI-memory scores and path c (total effect). The confidence intervals (CI) for the indirect mediation effects of WMH on follow-up ADNI-memory scores through temporal A β (CI:-0.026, 0.06) cingulate A β (CI: -0.024, 0.05), parietal A β (CI: -0.035, 0.002), frontal A β (CI: -0.028, 0.04), and global A β (CI: -0.031, 0.002) were crossing zero. (WMH, white matter hyperintensities; SUVr, standard uptake value ratio; A β , beta amyloid; CI, confidence intervals).

Figure 3.6 path models of the mediation effect of WMH between global and regional $A\beta$ burden and baseline ADNI-memory scores



As such, path a is expressed the change in WMH volumes with one unit increase in $A\beta$ SUVr, whereas path b is expressed decrement of baseline ADNI-memory scores associated with an increment of WMH. Path c'

the direct effect of A β SUVr on ADNI-memory scores and path c (total effect). The confidence intervals (CI) for the indirect mediation effects of WMH on baseline ADNI-memory scores through global (CI: -0.043, 0.007), frontal A β (CI: -0.039, 0.05), cingulate A β (CI: -0.039, 0.04), and parietal A β (CI: -0.046, 0.012) were crossing zero indicating no significant mediating effects.

Figure 3.7 path models of the mediation effect of baseline WMH volumes on follow-up ADNI-memory performance



Figure 3.7d Figure 3.7e

As such, path (a) is expressed one unit increase in A β SUVr associated with increase of WMH volumes, whereas path (b) is expressed the change in follow-up ADNI-memory scores associated with an increase in WMH volumes. (Path c') the direct effect of A β SUVr on follow-up ADNI-memory scores and path c (total effect). The confidence intervals (CI) for the indirect mediation effects of WMH on follow-up ADNI-memory scores through temporal A β (CI:-0.04, 0.01) cingulate A β (CI: -0.036, 0.009), parietal A β (CI: -0.052, 0.0001), frontal A β (CI: -0.024, 0.006), and global A β (CI: -0.047, 0.04) were crossing zero indicating no significant mediating effects.

3.4 Discussion

The present results indicate that there is an independent effect of both $A\beta$ and WMH on cognitive performance at baseline and a synergistic interaction between these baseline biomarkers of pathology on longitudinal EF performance. This synergistic effect was not seen in longitudinal memory performance. The other main finding, demonstrated through mediation analysis, is that the extent of WMH dependent changes in baseline EF was mediated by both global and regional $A\beta$ burden. Thus, WMH accumulation appears to increase $A\beta$ deposition which in turn influences cognition longitudinally.

The present moderation analysis provides evidence of an additive effect of WMH and $A\beta$ in relation to baseline cognitive performance, which is consistent with the findings from other

cross-section biomarker studies [59, 76-78]. The present study extends the results from previous studies by analyzing the effect of baseline biomarkers of $A\beta$ and WMH on longitudinal cognitive performance. The data demonstrate that the combined effect of AB burden and WMH on longitudinal EF is greater than the sum of the two individual biomarker effects supporting a hypothesis of synergistic interactions between both A β and WMH. The synergistic effect between the baseline biomarkers of pathology on longitudinal EF performance was not seen in longitudinal memory performance. This finding may be related to the population studied as ADNI participants are largely well-educated and ADNI excludes participants with severe CSVD. One previous study showed that CN participants with low WMH volumes underwent low to no changes in memory performance, independent of amyloid burden [140]. Additionally, findings from another study have demonstrated that the association between WMH volumes and both EF and memory function were significant in demented participants but that the relationship between memory and WMH was not detected in CN participants, such as those included in the present study [165]. It is also possible that the synergistic effect seen in longitudinal EF performance but not memory performance may involve alterations in brain function and structure networks [166], WMH burden and/or A β deposition that were not included in the present analysis.

The present data further demonstrates that regional $A\beta$ burden in frontal, and cingulate regions, are most related to WMH effects on longitudinal EF change. These data suggests that this relation might be explained by WMH impacts on connectivity within the executive control, and default mode networks [166]. Indeed, the present findings support the hypothesis that executive function performance is dependent on both intact white matter pathway connectivity, as well as pathologic integrity of the cortical regions themselves [141, 167, 168] and that there is a synergistic interaction between baseline biomarkers of pathology on longitudinal cognitive functions that is dependent on frontal-subcortical circuitry in cognitive aging and pAD [81].

Studying the independent associations of WMH and $A\beta$ burden with baseline and longitudinal cognitive performance, the present data demonstrate that baseline EF performance is explained by both global amyloid burden and WMH, but that $A\beta$ burden was the only predictor of longitudinal EF performance and baseline memory performance (See supplementary tables 3.2 and 3.3). Consistent with our findings, one recent study from the University of California, Davis Alzheimer's Disease Research Center (UCD ADRC) diversity cohort found that WMH were related to baseline EF, but not longitudinal change in EF [140]. Conversely, the same group has argued that baseline WMH likely represents only a small percentage of the final WMH [169], suggesting that longitudinal EF performance may be most related to progression of WMH, rather than solely associated with baseline WMH. It is also possible that these findings are related to population studied, as ADNI excludes participants with severe vascular risk factors that may limit analysis of the full impact of WMH and other cerebrovascular injury in this cohort [76, 170]. It should also be pointed out that baseline WMH was one of the predictors for follow-up memory performance with $A\beta$ burden. These findings emphasize the important role of WMH as a risk factor for future memory decline even if it may not affect baseline memory performance at the stage of pAD [140, 171].

The present data clearly demonstrate that WMHs contribute to global and regional A β burden pathology, exerting an effect on baseline cognitive performance through multiple pathways. Consistent with our findings, a recently published study based on the C6 project in the Medical Imaging Trial Network of Canada (MITNEC-C6), which differs from ADNI in being a WMH enriched cohort [172] demonstrated that the relation between global WMH and cognition was mediated by global A β burden and cortical atrophy. The authors interpreted their results to suggest that A β burden appears to be aggravated in participants with WMH supporting a synergistic pathophysiological process. They further hypothesized that the relationship between WMH and A β burden may be related to impaired general cerebral perfusion [74, 173] or to vascular pathology affecting amyloid clearance pathways [139]. Another possible explanation presented by the authors focused on myelin damage [174], which has been shown to promote A β oligomerization, eventually contributing to amyloid deposition [175]. These potential mechanisms may help explain the topographic patterns of regional A β deposition in relation to WMH effects on critical brain networks seen in the present study. The hypothesis of a regional association between A β and WMH is supported by the present data

One major limitation of the present study is the possibility of selection bias as ADNI excludes participants with significant evidence for cerebrovascular disease, which may limit discoveries into the interactions between A β and WMH that may exist in more generalizable samples. Further studies examining the interaction between A β and WMH in participants with higher levels of CSVD including lacunes, small subcortical infarctions, microinfarcts, and microbleeds are needed to fully investigate the associations of A β with CSVD. Additionally, the sample of participants evaluated is relatively small for moderation analyses but was restricted by the availability of extant data. Longitudinal outcome analyses may also be limited by the relatively short follow-up period in the ADNI 2 participants studied. It is possible that a more

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extended follow-up period would help to clarify further the relationships between $A\beta$ and WMH across progressive stages of cognitive decline, including MCI and early dementia stages.

Strengths of the present study include the use of ADNI data allowing analysis in a large sample of relatively homogeneous CN participants that have been classified extensively for the presence of pAD and CSVD. An additional strength is the use of both mediation and moderation analyses in studying the relation between cognitive function and the effects of the two primary drivers of dementia in the population (A β and WMH) within discrete brain regions. While to what extent WMH affects A β burden and cognition remain unclear, the present data demonstrate that baseline A β burden and WMH volumes have both independent associations with EF and memory scores at baseline, as well as synergistic associations with longitudinal EF performance. The extent of WMH dependent changes in baseline cognitive performance was related to both the direct effect of WMH and an indirect effect moderated through global and regional A β burden. The biological relationships between regional A β and WMH responsible for this indirect effect need further investigation across a broader profile of the disease course of dementia.

CHAPTER 4. WHITE MATTER HYPERINTENSITIES INFLUENCE DISTAL CORTICAL B-AMYLOID ACCUMULATION IN DEFAULTS MODE NETWORK PATHWAYS

4.1 Introduction

Alzheimer's disease (AD) pathology can be influenced by modifying factors including age, APOE genotype and cerebral small vessel disease (SVD) among others [176, 177]. Despite findings from epidemiological and clinical-pathological studies supporting the relationship between SVD and AD [96, 147, 178-181], the mechanistic role of SVD in potentially contributing to the development and progression of AD pathology remains unclear [61]. To explore the effects of cerebral SVD on the development of AD, and vice-versa, studies that evaluate the pathological interplay between A β plaque deposition and White Matter (WM) alterations are needed. Findings from previous studies have demonstrated that WM alterations including white matter hyperintensities (WMH) often occur prior to the overt detection of amyloid- β deposition in preclinical AD (pAD) [145, 146, 182, 183]. Such findings support a hypothesis of retrograde degeneration, wherein axonal injury distal to the neuronal cell body, might upregulate amyloid production in connected cortical regions initiating and or accelerating the pathogenesis of AD.

Previous studies examining the relationship between WMH and AD pathology have shown that higher global WMH volume is associated with prefrontal and posterior cingulate A β deposition [184]. Increased global A β (measured in PET or CSF) has also been shown to be associated with posterior subcortical and periventricular WMH [97, 98, 185]. The main limitation of these studies involves the common use of global and or regional measures of WMH volume and A β deposition, rather than restricting the analyses to WMH in discrete fiber tracts and the upstream cortical regions where A β deposition occurs.

Recent studies on brain connectivity and functional neuroanatomy have enabled a better understanding of the potential mechanisms through which WM lesions may contribute to cognitive symptoms through disruption of the structurally connected cortical regions that represent the major networks of the brain [186, 187]. Moreover, WMH are associated with neuroinflammation that has been postulated to spread trans-axonally to interconnected cortical regions [188-190]. Among these networks, the default mode network (DMN) [191] plays a critical role in internally directed cognitive function. The DMN has been shown to exhibit not only functional disconnection, but also structural disruption associated with WM microstructural disconnection associated with CSF A β levels [66, 192] or by WMH that are associated with cortical A β accumulation [193]. However, the association between WMH volumes specifically within DMN tracts, in relation to A β deposition in interconnected DMN cortical regions, has not been closely investigated. We specifically chose to focus on the DMN rather than other brain networks since it is affected in both AD and SVD [96, 194-197], suggesting it may be a good candidate network to explore in order to inform further understanding of the potential biological association between two pathologies. The main objective of this study was to test the hypothesis that WMH associated with A β levels within areas of the DMN that are disconnected by SVD early in the pathogenesis of AD in cognitively normal older adults with early A β deposition pAD. We aimed to evaluate A β SUVr in the cortical regions containing the neuron cell bodies of the DMN in relation to downstream WMH in interconnected axon tracts in the DMN.

4.2 Methods

4.2.1 Participants

72 subjects with normal cognition (mini-mental state examination (MMSE) score greater than or equal to 26) were identified in the multicenter network Alzheimer's Disease Neuroimaging Initiative (ADNI) at http://adni.loni.usc.edu, recruitment phase 3 by the following criteria: Complete demographic information (i.e., age, sex, education) and ApoE genotype, available availability of an AV-45 PET scan (to assess levels of Aβ), three-dimensional (3D) T1weighted magnetic resonance imaging (MRI) scan (for spatial normalization and cortical parcellation), and 3D FLAIR scan (to assess WMH). Only subjects from ADNI 3 were included as previous ADNI cohorts did not include 3D FLAIR acquisitions required for precise WMH localization in DMN fiber tract pathways. Unfortunately, due to COVID interference with ADNI 3 recruitment and image acquisition, only a small cohort was available for the present analysis. Of note, we used all participants with available data at the time of this analysis. Details of ADNI inclusion criteria, clinical procedures and methodology are available elsewhere [153, 154]. A total of 8 participants were excluded from the analysis on the basis of missing data required for the analysis. Excluded participants did not differ from those included in the analysis in regards to age, sex, ApoE, or MMSE scores (data not shown).

4.2.2 Acquisition of florbetapir and MRI images

The MPRAGE sequence parameters included a Repetition time (TR) = 2300ms, Echo time (TE) = 2.26ms, inversion time (TI) = 900 ms, spatial resolution of $1 \times 1 \times 1$ mm³. The 3D FLAIR sequence included a TR = 4800 ms, TE = 119 ms, TI = 1650 ms, spatial resolution of $1.2 \times 1 \times 1$ -mm³ voxel resolution. AV-45 PET scans were acquired on a variety of different PET scanners (Siemens, GE and Philips) harmonized for ADNI data collection. AV-45 PET scans consisted of 4×300 -second frames measured 50 minutes after injection of 10 ± 1.0 mCi of ¹⁸F-Florbetapir AV-45

4.2.3 Florbetapir Amyloid PET processing and calculation of SUVr

Each participant's MPRAGE image was registered to the FLAIR images using FSL's linear registration tool (FLIRT) [198], then parcellated with FreeSurfer (v6.0) to derive cortical regions of interest for PET quantification.[158, 159] Pre-processed Florbetapir images were coregistered to the FreeSurfer-parcellated T1 image which was closest in time, using FreeSurfer's function *mri_coreg* as implemented in PETSurfer[199, 200]. Results were visually inspected to ensure correct co-registration. DMN regional amyloid burden was calculated using SUVr in the ADNI cortical summary region normalized by the whole cerebellum reference region.

4.2.4 Atlas-based fiber tract connecting DMN

We analyzed WMH volumes within major fiber tracts projecting from DMN regions using the Johns Hopkins University International Consortium for Brain Mapping probabilistic fiber tract atlas (JHU DTI-based white-matter atlases) [201]. The core DMN regions analyzed included the medial prefrontal cortex (MPFC), posterior cingulate (PCC), inferior parietal lobules (IPLs), and medial temporal lobe (MTL)[202]. The fiber tracts connecting the DMN cortical regions included the cingulum (CING) from PCC [203], cingulum–hippocampus tract (CING-Hippo) from MTL [203-205], superior longitudinal fasciculus (SLF) from IPL [206], and the inferior fronto-occipital fasciculus (IFOF) from MPFC [75, 100, 196, 207-211]. (Table 4.1)

DMN regions	JHU DTI-based white-matter atlases [201]	Freesurfer parcellation
MTL[203-205]	CING-Hippo	Entorhinal, Parahippocampal
MPFC[207, 208]	IFOF	Rostral Anterior cingulate, Caudal Anterior cingulate & Medial Orbitofrontal
PCC[203]	cingulum	Posterior cingulate
IPL[206]	SLF	Inferior Parietal

Table 4.1 A description of the atlas-based fiber tracts connecting cortical regions in the DMN

4.2.5 MRI analysis

4.2.5.1 WMH segmentation

3D FLAIR images were used to quantify WMH volume using semi-automated process that was developed in our lab as previously described [69, 70]. Briefly, 3D MPRAGE was coregistered to the FLAIR image using linear six parametric rigid body registration (FSL software library v5.0.8). The Brain Extraction Tool (BET), (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET), was used for non-brain tissue stripping of FLAIR images and to generate a binary brain mask. The binary brain mask was multiplied by the MPRAGE image to remove the non-brain tissue voxels. Statistical Parametric Mapping (SPM12) tool is operated based on MATLAB software (http://www.fil.ion.ucl.ac.uk/spm/), and was used for Multimodal segmentation to create separate native-space images representing gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using an in-house segmentation validated template created from 145 images of healthy older adults [72]. WM was modeled as two separate tissue classes to capture all WM intensities. The two WM segmentation images were summed and convert to a binary WM mask in the native space. The WM binary mask was multiplied by the FLAIR image to generate WM image that is mixed of normal appearing WM and WMH voxels. Gaussian fit was performed to the histogram of WM voxels was used to set the threshold for WMH as the mean plus 3 × SD, corresponding to a P value of .01. Manual editing was required to remove false positive and artifact voxels from the total WMH mask. The total volume of the WMH voxel was the sum of all WMH mask voxels [69, 70].

4.2.5.2 Tract-related WMH volume

Each participant's MPRAGE image was registered to their FLAIR image using FSL's linear registration tool (FLIRT) [198], then registered to the MNI152 T1 template using FSL's non-linear registration tool (FNIRT) with standard parameters to generate the transformation matrix. Using the inverse transformation matrix and inverse non-linear warping parameters, JHU-ICBM-tracts atlas in MNI152 space [201] was then registered back to each participant's native space, effectively aligning it with their FLAIR image in the native space. Total WMH volumes in each tract were calculated by multiplying the registered binary tract to the WMH mask to derive the WMH volume within each specific fiber tract (Figure 4.1).

Figure 4.1 Diagram of the tract-related WMH volume quantification protocol



4.2.6 Statistical analysis

Statistical analyses were conducted using SPSS, version 26.0 (SPSS, Inc.). Significance was set at P < .05. To validate the relationship between regional A β and WMH burden, we used regression analysis between SUVr within gray matter of DMN regions as the dependent variable and WMH volumes within fiber tracts as independent variables. The general linear model was adjusted for the covariates age, sex, ApoE and total intracranial volumes. WMH volume within each fiber tract was logarithmically transformed due to the positive skewed distribution for the statistical analysis. The regression analyses assessing the relationship between A β and WMH were fit to the data using the following equation:

PET SUVr gray matter of DMN = $b_0 + b_1$ WMH volume (log-transformed) in JHU DTIbased white-matter atlases + **bX**, where **bX** represents beta coefficients and adjustment covariates.

4.3 Results:

The demographic and imaging characteristics of the sample are provided in table 4.2. Briefly, the sample included 33 women and 31 men with a mean age of 75.7 ± 7.2 years.

	N	Mean (SD)
Age	72	74.96 (8.13)
MMSE score	72	28.39 (1.83)
IPL SUVr	59	1.52 (0.29)
MPF SUVr	59	1.46 (0.29)
MTL SUVr	40	1.3 (0.11)
PCC SUVr	67	1.55 (0.31)
Total intracranial volumes	72	1455.26 (132.46)
WMH volumes	69	4.43 (7.13)
Log WMH in SLF	55	1.12 (0.66)
Log WMH in IFOF	55	1.14 (0.65)
Log WMH in cingulum	25	0.92 (0.94)
Log WMH in cingulum hippocampus	25	0.95 (0.74)
APOE e4 allele N(%) copy1	71	7 (9.9%)
APOE e4 allele N(%) copy 2	71	26 (36.6%)
Sex male N (%)	72	37(49.3)

Table 4.2 Demographic, clinical, imaging, and genetic characteristics of the cohort studied

All the DMN SUVr values after excludes participants have SUVr less than 1.17 *Abbreviations: N: numbers; SD: standard deviation; SUVr: Standardized Uptake Value ratio; PCC: posterior cingulate; MPFC: medial prefrontal cortex ; IPL: inferior parietal lobules; MTL: medial temporal lobe; IFOF: inferior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus; WMH: white matter hyperintensities ; MMSE: Mini-Mental State Examination

4.3.1 Association between WMH volume IN JHU-ICBM-tracts atlas and Aβ burden in DMN regions:

For each fiber tract, the linear regression analyses were computed, with $A\beta$ within the tract's gray matter ROI as the dependent variable. The independent variable included WMH in each fiber tract, controlled for age, sex, ApoE and total intracranial volumes. The adjusted linear regression analyses demonstrated that increased WMH volumes in SLF was associated with

increased regional SUVr in IPL with p = 0.011 (Figure 4.2A). The analyses also detected marginally significant relation between MPF A β burdens with WMHs in IFOF (p value 0.074) (Figure 4.2B). In contrast, the regression models failed to detect significant relationships between the cingulum with PCC, or cingulum–hippocampus with MTL (p = 0.744 and 0.740 respectively) (Figures 4.2C and 4.2D) (Table 4.3).

DMN regions	WMH in JHU DTI-	Standardized	Р-	Adjusted R
	based white-matter	Beta Coefficient	value	square
	atlases			
PCC SUVr	Cingulum	0.059	0.744	0.04
MTL SUVr	Cingulum hippocampus	0.054	0.740	0.10
IPL SUVr	SLF	0.365	0.011	0.19
MPF SUVr	IFOF	0.262	0.074	0.09

Table 4.3 Independent effects of WMH IN JHU-ICBM-tracts atlas on DMN A β SUVr burden

The adjusted R square is the proportion of variance in regional SUVr that was explained by the model discounted for age, sex, APOE and WMH volumes in JHU-DTI- based white matter atlastracts). (All coefficient β values are adjusted for the covariates age, sex, APOE and ICV)

*Abbreviations: Aβ: amyloid β; SUVr: Standardized Uptake Value ratio; PCC: posterior cingulate; MPFC: medial prefrontal cortex; IPL: inferior parietal lobules; MTL: medial temporal lobe; IFOF: inferior frontooccipital fasciculus; SLF: superior longitudinal fasciculus; WMH: white matter hyperintensities; JHU-ICBM: Johns Hopkins University International Consortium for Brain Mapping probabilistic fiber tract atlas; DMN: default mode network. Figure 4.2 Scatterplots show association between WMH volume IN JHU-ICBM-tracts atlas and $A\beta$ burden in DMN regions



Figure 4.2 shows the scatterplot of the fitted regression line of the WMH volumes as independent variable and regional SUVr as the dependent variable. All p values are adjusted for the covariates age, sex, ApoE and total intracranial volumes. R square is the proportion of variance in the DMN regions SUVr that was explained by the WMH volumes in JHU-ICBM-tracts without any adjustment. Abbreviations: Aβ: amyloid β; SUVr: Standardized Uptake Value ratio; PCC: posterior cingulate; MPFC: medial prefrontal cortex; IPL: inferior parietal lobules; MTL: medial temporal lobe; IFOF: inferior frontooccipital fasciculus; SLF: superior longitudinal fasciculus; WMH: white matter hyperintensities; CING-

hippo: cingulum-hippocampus tract.

4.4 Discussion:

The present data demonstrate that WMH volumes in major fiber tracts projecting from DMN regions are associated with upstream A β levels in connected DMN cortical regions. These data are consistent with recent studies demonstrating that WMH volumes in individual tracts explain more variance in the pathogenesis of AD than total or regional WMH burden, emphasizing the importance of lesion location when evaluating the clinical consequences of WMH [212]. These data suggest the possibility of a retrograde hypothesis wherein SVD in DMN pathways may lead to an upregulation of A β production in proximal neuronal cell bodies, initiating and or accelerating the pathogenesis of AD. Indeed, it is well established that ischemic injury proximal to neuronal cell bodies leads to an upregulation of A β production [213, 214], and so a retrograde hypothesis whereby more distal injury to connected axons, also leading to an

upregulation of A β production remains a plausible explanation for the association of AD and SVD seen across many studies [61, 132, 149] that is further supported by the present data.

In contrast to the present findings, a recent study that used ADNI (recruitment phases GO and II) found no association between the levels of global amyloid burden and WMH in any of the fiber tracts of the DMN [196]. The present study using regional amyloid burden rather than global measures of A β refines such analyses, establishing a direct relationship between WMH volumes in SLF and A^β burden in IPL. A similar, albeit not statistically significant relationship was seen between WMH volumes in IFOF and A β burden in MPF. It is noteworthy that no such significant relationships were found between CING with PCC and CING-Hippo with MTL in the pAD cases studied. This discrepancy may be explained by understanding the neuroanatomic involvement of DMN regional involvement at distinct stages of AD, especially given that the present study sought to evaluate pAD specifically. Post-mortem pathologic studies have demonstrated that $A\beta$ deposition follows a specific pattern of spread [215]. The topographical pattern of A β accumulation in pAD begins in the precuneus, medial orbitofrontal, and posterior cingulate cortices [5, 216-219], then the inferior parietal [102], and finally occipital and medial temporal lobes in the later stages of the disease. As such, in the pAD cohort studied, amyloid levels may have already reached a zenith in the PCC and may not have yet begun in the MTL narrowing the distributions of A β SUVr in these regions required to see associations with downstream tract WMH-mediated injury. Conversely, at the stage of pAD, accumulation of A β in the IPL and MPF cortices is an active process, broadening the distribution and allowing detection of the influences of WMH on A β accumulation in these DMN regions. Further work exploring the association of regional WMH and cortical A^β deposition in connected DMN regions is needed to advance our understanding of the interplay between WMH and A β across the pathologic and clinical continuum of AD.

It is also possible that the involvement of only some DMN pathways could be due to the small sample size (only 25 participants) that had WMH involving the CING and CING-Hippo tracts. WMH affects WM tracts differently [212], some tracts, including IFOF and SLF, appear to be particularly vulnerable to WMH development compared to CING and CING-Hippo [196, 220]. It is also possible that these findings are related to the population studied, as ADNI excludes participants with significant vascular risk factors and or WMH burden that may limit analysis of the full impact of WMH within discrete WM tracts evident in a more generalizable population.

It is important to understand that the present study cannot determine causality as it investigated associations only. While our hypothesis is that WMH influences upstream Aβ deposition through increased Aβ production, it is also possible that Aβ -mediated neuronal injury leads to Wallerian degeneration, inflammation and or demyelination of axonal projection pathways that are supported by many prior studies [150, 221-225] that may eventually manifest as WMH in these DMN tracts. Indeed, WMH are not always caused by SVD, but are well recognized to be caused by Wallerian degeneration after any injury, inflammation in a variety of CNS diseases, and by the prototypic demyelination seen in multiple sclerosis and related disorders [226-228]. Unfortunately, definitive imaging characteristics distinguishing these causes of WMH are limited at present, further animal model work in the area of mixed AD-SVD is needed to explore the human associations demonstrated in the present study.

The main limitations of our study include the relatively small sample size available for this analysis from ADNI 3. Additional exploration after ADNI 3 and other cohorts with both A β - PET and 3D FLAIR is warranted. Another limitation of this study is applying an atlas-based fiber tract ROI approach to assessing DMN brain regions rather than using direct DTI measures. Due to natural variability in precise neuroanatomic localization of such pathways, it is possible that the true contributions of WMH within DMN tracts was over or underrepresented in specific individuals in the cohort. It should be noted, however, that an atlas-based approach has the advantage of avoiding problems of fiber tracking in degenerating pathways. Another major limitation of the present study is the selection bias as ADNI excludes participants with significant evidence for cerebrovascular disease, which may limit analysis of the full impact of WMH and other cerebrovascular injuries in relation to A β . Despite these limitations, it should be noted that focusing on the type, location, and connectivity of lesions rather than simply the presence or absence of lesions is the main strength of the present work.

In conclusion, the current results support the hypothesis of localized effects of WMH in axonal projections on cortical A β SUVr in DMN regions and tracts. Further studies testing our hypothesis at the level of microstructural damage are needed, especially given the findings from recent DTI studies demonstrating that WM microstructural alterations (even in the absence of overt WMH) are anatomically connected to the cortical brain regions with significant A β deposition at the earliest stages of disease within the DMN [100-102]. Further studies are also needed to define longitudinal patterns involved in the association of WMH on A β deposition in participants with mild cognitive impairment and dementia to allow a complete understanding of

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the full disease course. Such work is critical for the optimal timing of disease modifying interventions that may target AD, SVD, and mixed pathologic processes that are most common in the general population.

CHAPTER 5. THESIS SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

This thesis first tested the hypothesis that early focal regional amyloid deposition in the brain is associated with cognitive performance in specific cognitive domain scores in pAD (**chapter 2**). Since mixed dementia is widely recognized as the norm rather than the exception, the second study aimed to explore the potential causal relationships between regional and global A β and WMH with cognitive function (EF and memory) scores in CN older adults (**chapter 3**). Finally, the relationship between WMH and A β is strongly determined by the spatial distribution of the two pathologies, so the third study aimed to quantify A β in Default mode network (DMN) regions to examine whether cerebral small vessel disease (SVD) affects A β deposition in connected DMN regions (**chapter 4**).

5.1 The relation between A β and cognition in pAD

Previous studies evaluating the relationship between brain A β (measured on PET, or in CSF), and cognitive function have shown variation in the results in which cognitive domains are most affected by early A β deposition in pAD. Several such studies have demonstrated early memory decline in pAD [44-50], on contrary to deficits in EF or other domain involvement [51-55, 229]. These inconsistencies between studies could be due to the amyloid burden being often low or focal in pAD, and all of them used global rather than regional measures of A β deposition, which may limit detection of the earliest signs of A β pathology. Findings from clinical-pathological studies support the clinical meaningfulness of early regional A β deposition [124] and the predictive role of early precuneus pathology in the development of future global amyloid deposition in the brain and cognitive decline [123], steer the field toward studying the correlation between spatial distribution of A β and cognitive performance, especially in early pAD [5, 230].

Recent therapeutic attempts aiming at A β plaques have demonstrated limited success [231]. Potential reasons could include attempting anti-amyloid therapies too late in the disease course after downstream consequences on neurodegeneration and cognitive decline have taken hold [4]. Focusing on regional A β -PET SUVr levels in the precuneus and posterior cingulate demonstrates the benefit of using regional amyloid status rather than relying solely on global amyloid status to identify pAD for future amyloid targeted treatment studies and clinical trials.

A primary focus on memory domain impairment in relation to regional quantification of amyloid rather than examining a broader array of cognitive domain involvement [123-125] introduces bias that limits our complete understanding of the impact of early preclinical A β deposition. While the existing literature has shown that global A β burden has more robust associations with memory decline than any other cognitive domains in healthy older adults, the present data demonstrate that patients with early focal AB deposition have clinical features that differ from persons with more diffuse global A β [232]. The results from our first study clearly demonstrate that increased A β deposition in the precuneus and posterior cingulate (the earliest brain regions affected with Aβ pathology[3, 102]) are associated with changes in EF that may precede memory decline in pAD (Figure 5.1). Both posterior cingulate gyri and precuneus are highly anatomically connected [233], and are part of DMN that is involved in attention and executive function [234-236]. Moreover, A β accumulation in regions associated with DMN (i.e. the prefrontal cortex, inferior parietal lobule, posterior cingulate cortex, and precuneus) have been shown to be correlated with neuropsychological performance on multiple measures [230]. In summary, accumulating evidences from our study and two other independent samples [124, 237] indicate that assessing regional changes in amyloid, particularly in posterior cortical regions, enhances the early detection of subclinical amyloid-related cognitive decline.

Figure 5.1 Amyloid-PET levels in the Precuneus and Posterior Cingulate Cortices are Associated with Executive Function Scores in Preclinical Alzheimer's Disease Prior to Overt Global Amyloid Positivity



Regional amyloid deposition in the precuneus and posterior cingulate are associated with early preclinical decline in executive function in pAD, irrespective of global SUVr.

*Abbreviations A β : amyloid β , SUVr: Standardized Uptake Value ratio; pAD: preclinical Alzheimer's disease.

5.2 The relation between WMH burden, Aβ deposition, and cognition

EF refers to "higher-level" cognitive function [238]. Deficits in EF have been shown to predict the development of dementia [239-242] and are linked to both WMH burden and A β deposition in the brain [66, 71, 81, 243, 244]. EF performance is dependent on both intact white matter pathway connectivity, as well as pathologic integrity of the cortical regions themselves [167, 168]. The mechanisms contributing to EF decline in CN older adults are not fully understood and frequently overlap [66]. In fact, WMH burden and A β deposition are considered the two primary drivers of dementia and are associated with each other, suggesting a possible interaction of these two pathologies rather than a purely additive effect. (Figure 5.2)

Figure 5.2 Amyloid-PET and white matter hyperintensities have independent effects on baseline cognitive function and synergistic effects on longitudinal executive function



A β and WMHs contribute to baseline cognition independently (A), and there is a synergistic interaction between these baseline biomarkers of pathology on longitudinal EF performance (B). Furthermore, WMH dependent changes in cognitive performance are related to direct effect of WMH (C) and an indirect effect through both global and regional A β burden (D).

Data from our second study demonstrated that WMHs contribute to global pathology, exerting an effect on baseline cognitive performance through the direct effect of WMH and an indirect effect moderated through global and regional A β burden. The relationship between WMH and A β burden may be related to impaired general cerebral perfusion [74, 173] or to vascular pathology affecting amyloid clearance pathways [139], however the exact mechanisms remain unclear. Some preclinical studies suggest that WMHs may directly induce amyloid burden [145, 146, 182, 183], and others have highlighted that baseline WMH predicted higher A β deposition over time [61, 147, 245]. It also remains possible that WMHs interact with the β -amyloid cascade at a mechanistic level[90]. The pathogenesis of both WMH and A β may involve a vicious circle, of which the initiating event remains unclear.

5.3 The spatial distribution and heterogeneity of WMH and $A\beta$

Evidence from recent studies has suggested that the relationship between WMH and $A\beta$ is strongly determined by the spatial distribution of the two pathologies [150]. The majority of published studies have emphasized the spatial heterogeneity of WMH [98, 151] with posterior WMH predominance in relation to global $A\beta$ measures [96-98, 145, 185]. Such prior studies have left the potential heterogeneous influences of regional $A\beta$ deposition relatively unexplored. The topographic patterns of regional $A\beta$ deposition in relation to WMH was investigated in chapter 3 of this thesis demonstrating that WMHs contribute to parietal and frontal $A\beta$ burden. With these findings in mind and from a mechanistic point of view, there are many questions that remain unanswered. Why certain brain regions might be more vulnerable to WMH –related $A\beta$ deposition, and are there biological mechanisms that can explain an interaction or are the observed associations simply due to confounding?

Recent studies on brain connectivity and functional neuroanatomy have resulted in a better understanding of the mechanism through which WMHs might lead to cognitive symptoms by disrupting the structurally connected cortical regions that represent the major networks of the brain [186, 187]. A possible mechanism explaining the contribution of WMH to the topographic pattern of A β may be due to the changes in structural connectivity in the frontal and frontalparietal node [246, 247], which has been shown to lead to neuroinflammation that is hypothesized to spread trans-axonally to cortical regions [92, 190]. To explore the pathological interaction and biological link between WMH and A β within discrete WM tracts and cortical regions we conducted the third experiment.

The pathology underlying AD might be varied according to the Aβ regional distribution and is likely further influenced by WMH pathology [92]. WMH volumes in individual tracts explain more variance in the pathogenesis of AD than total or regional WMH [212]. With these data in mind, our third study demonstrates that increased WMH volumes in SLF was associated with increased regional SUVr in IPL, supporting our contention that the WMH–A β relationship is region dependent. (Figure 5.3)





A: This study aimed to test the hypothesis that vascular injury (WMH) distal to the neuronal cell body, might upregulate amyloid production in connected cortical regions initiating and or accelerating the pathogenesis of AD in cognitively normal older adults with early $A\beta$ deposition (pAD). B: After evaluation the association of WMH volumes in major fiber tracts projecting from cortical DMN regions and $A\beta$ -PET SUVr in the connected cortical DMN regions, we found increased WMH volumes in the superior longitudinal fasciculus (SLF) was associated with increased regional SUVr in the inferior parietal lobule (IPL).

5.4 Conclusion

In conclusion, the results from the present set of experiments demonstrate that many factors may affect the interplay between A β and WMH during the preclinical phase of dementia. The first factor to consider is the temporal sequence and the spatial distribution of A β accumulation. Post-mortem pathologic studies showed that A β deposition follows a specific pattern of spread [215]. The topographical pattern of A β accumulation in pAD begins in the precuneus, medial orbitofrontal, and posterior cingulate cortices, spreading to core regions of the DMN [5, 216-219], then the inferior parietal[102], and finally occipital lobe, and temporal lobe in late stages of the disease. The data presented in this thesis demonstrate a significant association between WMH volumes in SLF and A β burden in IPL. In contrast, our studies failed to detect a

similar association in brain regions affected very early or late in the course of the disease. The second factor that needs to be understood involves the nature of the population studied. The majority of large-cohort studies in dementia that investigated the effects of WMH on neurodegeneration and cognition as ADNI excluded participants with severe vascular risk factors and considerable WMH burden (studies 2 and 3), which may limit analysis of the full impact of WMH and other cerebrovascular injuries in relation to A β . Finally, focusing on cognitively normal elderly participants affords an accurate and thorough understanding of the cognitive and brain changes accompanying pAD that is critical [248], however this approach limits the generalizability of the results, and it remains unclear how the relationships studied in this thesis might be altered at the later stages of mild cognitively impairment or in clinical AD patients. Molecular imaging studies of A β in pAD suggest that, on average, aged CN participants with pAD exhibit mean cortical levels of A β between those of healthy controls and AD patients.

5.5 Future direction and studies:

Neuroimaging data acquired at one point in time does not contain enough information to identify potential causal relationships between WMH and A β deposition. Further Longitudinal studies are needed to show that elevated WMH burden within discrete WM tracts at baseline worsened A β -PET SUVr in discrete cortical regions over time in AD cohorts. WM degeneration is a continuous process over time with microstructure alternation in WM integrity, which ultimately leads to macrostructure change, as reflected by WMH. Future investigations to evaluate A β SUVr in the cortical regions containing the neuron cell bodies that have preclinical WM alternation evidence (from DTI) to their downstream axon tracts are needed. Finally, further studies are needed to complete the dynamic understanding of WMH and A β pathology by exploring the interaction and spatial relation between the two pathologies in mild cognitively impaired or AD patients.

Initial A β deposition often falls below the global A β SUVr cut-off scores for the diagnosis of pAD and the majority of clinical trials. The field is at a crossroads about whether to continue to pursue anti-A β therapy or more actively pursue alternative targets for the pAD stage that may allow potentially more effective interventions with disease-modifying therapies that are on the horizon. The relation between A β and SVD in influencing executive function in pAD is partially driven directly by WMH and is additionally contributed to by WMH injury that accelerates A β deposition ultimately leading to the deficits in executive function seen in pAD. Efforts targeting

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WMH may potentially augment and be needed in a staged approach in addition to anti-amyloid and other AD-focused disease modifying therapies.

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CURRICULUM VITAE

Doaa Ali, M.D., MSc

Education and Post-graduate Training

INSTITUTION AND LOCATION	DEGREE	Starting Date	Completion Date	FIELD OF STUDY
Faculty of Medicine, Tanta University	MD	09/2004	02/2011	Medicine
Tanta, Egypt				
Department of Internal Medicine and	Internship	03/2011	02/2012	Medicine – Surgery
Department of Surgery				
Tanta University Hospitals, Tanta, Egypt				
Faculty of Medicine, Tanta University, Egypt	MSc	10/2012	04/2015	Master's Degree
				Neurology and
				Psychiatry
Department of Behavioral Science, College of Medicine, University of	PhD student	01/2020	present	Clinical and Translational science
кенциску				

Professional Position

2012 – 2014: Resident, Neurology and Psychiatry department, Faculty of Medicine, Tanta University.

2014 – 2015: Chief Resident of Neurology and Psychiatry, Department of Neurology and Psychiatry, Tanta University Hospitals, Tanta, Egypt

2015 – 2019: Assistant Lecturer of Neurology and Psychiatry, Tanta University, Egypt

2019 – 2020: Research Assistant, Sanders Brown Center on Aging, University of Kentucky

2020 – 2023: Graduate Research Assistant, Sanders Brown Center on Aging, University of Kentucky

2023 – present: Imaging Research Scientist, Sanders Brown Center on Aging, University of Kentucky

Professional Membership

08/2018 - ongoing American Academy of Neurology

06/2012 - ongoing Egyptian Society of Neurology

08/2010 – 12/2015 Member Egyptian White Coat Association (Medical Charity)

Awards & Recognitions

06/2015 – Honors Degree Award – For MSc thesis entitled "Study of the psychiatric impact of political unrest on a sample of students at Tanta university"

03/2012 – Graduated Medical School with Honors Degree

Scientific Publications:

a. Ali DG, Abner EL, Bahrani AA, El Khouli R, Gold BT, Jiang Y, Wilcock DM, Jicha GA. Amyloid-PET and White Matter Hyperintensities Have Independent Effects on

Baseline Cognitive Function and Synergistic Effects on Longitudinal Executive Function. Brain Sciences. 2023;13(2):218.

- b. Ali DG, Bahrani AA, Barber JM, El Khouli RH, Gold BT, Harp JP, Jiang Y, Wilcock DM, Jicha GA. Amyloid-PET levels in the precuneus and posterior cingulate cortices are associated with executive function scores in preclinical Alzheimer's disease prior to overt global amyloid positivity. Journal of Alzheimer's Disease. 2022(Preprint):1-9.
- c. Moga DC, Abner E, Schmitt F, Eckmann L, Huffmyer M, Martinez A, Beech B, George R, El Khouli R, Ali D. Intervention for Cognitive Reserve Enhancement in Delaying the Onset of Alzheimer's Symptomatic Expression (INCREASE) Study: Results from a Randomized Controlled Study of Medication Therapy Management Targeting a Delay in Prodromal Dementia Symptom Progression. The Journal of Prevention of Alzheimer's Disease. 2022;9(4):646-54.

Conference Abstracts and Presentations:

International Conferences:

1. "Cognitive reserve for memory performance is mediated by preclinical frontotemporal and limbic amyloid deposition in subjects with normal cognition in early MCI"

Doaa Ali, Daniela Moga, Riham El-Khouli, Ashely Martinez, Erin Abner, and Gregory Jicha Alzheimer's Association International Conference 2020 (AAIC 2020)

2. "Preclinical amyloid-PET SUVr in the precuneus and posterior cingulate associations with MoCA scores are driven by language domain subscores"

Doaa Ali, Justin M Barber, Riham H El Khouli, Brian T. Gold, Jordan Harp, Linda J Van Eldik, Donna M Wilcock, Gregory A Jicha. Alzheimer's Association International Conference 2021 (AAIC 2021)

3. "Executive dysfunction is the earliest sign of preclinical Alzheimer's disease detected by regional Ab-PET SUVr in the precuneus and posterior cingulate cortex"

Doaa Ali, Justin M. Barber, Riham H. El Khouli, Brian T. Gold, Jordan Harp, Linda J. Van Eldik, Donna M. Wilcock, Gregory A. Jicha. Alzheimer's Association International Conference 2021 (AAIC 2021)

4. "Does targeted medication therapy management increase cognitive reserve? Results from the INtervention for Cognitive Reserve Enhancement in delaying the onset of Alzheimer's Symptomatic Expression (INCREASE) study"

Daniela C Moga, Erin L Abner, Frederick A Schmitt, Lynne Eckmann, Mark Huffmyer, Ashley I Martinez, Brooke F Beech, Rosmy George, Riham H El Khouli, **Doaa Ali**, Gregory A Jicha . Alzheimer's Association International Conference 2021 (AAIC 2021)

5. "Longitudinal plasma Alzheimer's disease biomarkers in an Alzheimer's disease research center cohort suggest pTau181 as the most reliable plasma biomarker for brain Alzheimer's pathology"

Tiffany L. Sudduth, Zachary Winder, Frederick A. Schmitt, Jordan Harp, Peter T. Nelson, **Doaa Ali**, Gregory A. Jicha, Donna M. Wilcock. Alzheimer's Association International Conference 2021 (AAIC 2021)

6. "The Combined Effect of β -Amyloid and White Matter Hyperintensities on Present and Future Executive Function Performance in Cognitively Normal Older Adults"

Doaa Ali, Riham H El Khouli, Erin L Abner, Ahmed Bahrani, Brian T. Gold, Yang Jiang, Donna M Wilcock, and Gregory A Jicha. Alzheimer's Association International Conference 2022 (AAIC 2022)

7. "Discrete white matter hyperintensity (WMH) growth quantification is superior to measurements of total longitudinal WMH volume change: implications for clinical trials in VCID"

Ahmed Ali Bahrani, Justin M Barber, Brian T. Gold, **Doaa Ali**, David K Powell, Linda J Van Eldik, Larry B Goldstein, Donna M Wilcock, Gregory A Jicha. Alzheimer's Association International Conference 2022 (AAIC 2022)

National Conferences:

"F-18 Amyvid PET CT In Asymptomatic Patients: Manual Versus Automated Analysis And Association With Patients' Global Cognitive Function." **Doaa G Ali,** Daniela C Moga, Riham H. El Khouli, Gregory A. Jicha. Radiology society of North America 2021 (RSNA 2021) Chicago, IL