

Research Article

Amyloid Burden and White Matter Hyperintensities Mediate Age-Related Cognitive Differences

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ABSTRACT

This study examined the additive vs synergistic contribution of beta-amyloid ($A\beta$) and white matter hyperintensities (WMH) across seven cognitive domains in 104 cognitively normal older adults. It also measured the extent to which age-related differences in cognition are driven by measurable brain pathology. All participants underwent neuropsychological assessment along with MRI and PiB-PET imaging for $A\beta$ quantification. WMH severity was quantified using the ARWMC scale. Stepwise regressions, moderation and mediation modelling were performed. Our findings show that $A\beta$ deposition single-handedly predicts poorer episodic memory performance, and that $A\beta$ and WMH contribute additively to poorer performance in working memory and language while carrying synergistic associations with executive functions and attention. Through mediation modelling, we demonstrated that the influence of age over episodic memory, working memory, executive functions and language is fully mediated by brain pathology. This study permits to conclude that, in healthy older adults; 1) $A\beta$ burden and WMH have synergistic associations with some cognitive domains and; 2) age-related differences in most cognitive domains are driven by brain pathology associated with dementia.

Keywords: Cognitive aging; Alzheimer's disease; Neuroimaging

Abbreviations: $A\beta$ = beta-amyloid; AD = Alzheimer's disease; MCI = mild cognitive impairment; PiB = Pittsburgh Compound B; SUVR = standard uptake value ratio; WMH = white matter hyperintensities

Introduction

Pathological changes are common in the aging brain, even in older adults who remain fully functional. For example, it has been consistently shown that significant cerebral beta-amyloid deposition ($A\beta$) – one of the pathological hallmarks of Alzheimer’s disease (AD) along with neurofibrillary tangles – is present in about a third of cognitively normal older adults (Jack et al., 2017; Jansen et al., 2015). Longitudinal studies suggest that healthy older adults harbouring high $A\beta$ burden are about fourfold more likely to convert to mild cognitive impairment (MCI) and that MCI individuals are also more likely to convert to AD in the following years compared to their same-aged peers with low $A\beta$ (Chen et al., 2014; Doraiswamy et al., 2012; Villemagne et al., 2011).

The amyloid cascade hypothesis, which posits that $A\beta$ deposition is the initiating event in a sequence of neuropathological changes leading to dementia, has remained for a long time the dominant explanation for AD (Hardy and Selkoe, 2002; Jack et al., 2013). More recently, though, the impact of other pathologies coexisting with $A\beta$ burden - especially of presumed vascular origin - is gaining increasing recognition in the pathogenesis of AD (Gorelick et al., 2011; Iadecola, 2013). For instance, in a comprehensive data-driven model of the spatiotemporal ordering of preclinical AD progression, vascular dysregulation was identified as the first pathological event, followed by $A\beta$ deposition, metabolic dysfunction, functional impairment and cortical atrophy (Iturria-Medina et al., 2016).

White matter hyperintensities (WMH), which reflect vascular brain pathology (i.e., small vessel disease), have been linked to an increased risk of developing dementia, whether in combination with $A\beta$ or independently (Mortamais et al., 2014). WMH and $A\beta$ have received considerable attention as

potential biomarkers of preclinical dementia because: 1) they occur in a significant proportion of healthy older adults (Burns et al., 2005; de Leeuw et al., 2001); and 2) they are key drivers of age-related cognitive decline in healthy older adults (Vemuri et al., 2015). Although the deleterious influence of WMH on cognition in healthy older adults is viewed as largely global, the bulk of research points towards a more direct link with executive components of cognition and processing speed (Hedden et al., 2012; Moon et al., 2017; Murray et al., 2010; Papp et al., 2014). In contrast, high A β burden in cognitively normal older adults has been associated with decline primarily in episodic memory, although some studies have shown decline in semantic memory, working memory, executive functions and visuospatial functions as well (Baker et al., 2017; Duke Han et al., 2017; Hedden et al., 2013).

The specific nature of age-associated changes across specific cognitive domains remains to be better understood, however, since many studies have used relatively rudimentary neuropsychological testing. Finer discrimination between multiple cognitive domains in the context of preclinical dementia is valuable in order to distinguish subtle changes in cognition most suggestive of underlying pathology from those which are more likely benign in nature. In the same way, the question as to whether the effects of A β burden and WMH on cognition are independent or interactive also remains open. Some authors have advanced that A β and WMH yield an additive effect on cognition in healthy older adults (Lo et al., 2012; Vemuri et al., 2015), while others have suggested a synergistic interaction, whereby cognitive deterioration associated with coexisting pathologies is greater than the sum of their distinctive effects (Iadecola, 2010; Zekry et al., 2002). A more comprehensive view of the interrelationships between AD and cerebrovascular disease pathophysiology and how they relate to specific cognitive changes in aging is needed to improve

early identification of at-risk individuals. So far, clinical trials targeting A β have shown very limited success in altering the clinical course of AD, which may be attributable to treatment being administered tardily in the disease course, when significant neurodegeneration has already occurred (Gauthier et al., 2016; Mangialasche et al., 2010; Musiek and Holtzman, 2015). Thus, timely intervention (at the presymptomatic stage) holds a better promise of achieving therapeutic efficacy. For that purpose, the first step is to hone our ability to reliably recognize the earliest signs of pathological aging.

The first objective of this study was to investigate the independent contribution of A β and WMH across seven cognitive domains, and to examine whether there was an interaction between these pathological biomarkers on cognition. Another main objective was to assess the extent to which age-related differences in cognitive function may be driven by A β deposition and WMH using partial least squares path (mediation) modelling. We sought to answer these questions in a cross-sectional study carried out in a cohort of cognitively normal older adults. A β deposition was modelled on PET imaging with ¹¹C-Pittsburgh Compound B ligand (PiB), and WMH were quantified with a semi-quantitative visual rating scale.

Methods

Participants

In this cross-sectional study, we recruited 104 participants aged 65 years and older. The majority of participants in our study was recruited from the CRIUGM pool of healthy older participants, but a portion of our sample was also recruited through advertisements (73 and 27%, respectively), because we wanted to recruit participants across a broader range of educational achievement (i.e.,

overrepresentation of educated participants in the CRIUGM pool). All participants underwent a detailed neuropsychological assessment, an MRI scan and a PiB-PET scan. Volunteers with untreated diabetes or heart disease, and other health conditions known to adversely impact cognition including untreated mental health disorders were excluded. A history of moderate to severe traumatic brain injury, substance abuse or neurological disorders, as well as general anaesthesia in the last six months, were also criteria for exclusion. Participants expressed no significant cognitive complaint and were judged to be free of dementia or MCI at the time of their participation, using the following criteria. Participants had to perform within 2 SD of the mean on a self-reported memory questionnaire (van der Linden et al., 1989). Two specific domains of the questionnaire were used for screening, “Conversations” and “Movies and books”, which have been shown to be particularly sensitive to objective memory decline (Clement et al., 2008). We further screened for general cognitive decline using the Montreal Cognitive Assessment (MoCA), on which participants had to score ≥ 23 . This cut-off has been deemed optimal in a recent meta-analysis (Carson et al., 2018). Additionally, performance of participants had to be > -1.5 SD when compared to the mean of age-matched controls on at least one of two learning tasks used for screening, the Logical Memory subtest of the Wechsler Memory Scale (WMS-III; delayed recall) and the Delayed Matching-to-Sample - 48 items (DMS-48; 2 min. delay). In an effort to screen for depressive symptoms, participants had to score $< 11/30$ on the Geriatric Depression Scale (GDS). This study protocol was reviewed and approved by the CRIUGM and the Montreal Neurological Institute and Hospital (MNIH) Research Ethics Boards. All participants provided written informed consent prior to their participation in the study.

Measures of Cognition

Participants underwent detailed neuropsychological testing covering the following cognitive domains: episodic memory, working memory, executive functions, language, attention, processing speed and visuospatial abilities. Composite scores were calculated for each of these cognitive domains. In order to do so, we computed correlation matrices including all performance indices of subtests related to a specific cognitive domain based on their theoretical framework. For each matrix (or cognitive domain), all performance scores significantly intercorrelated at $r \geq 0.30$ were selected, thereby ensuring internal validity of our composite measures (this cut-off corresponds to a medium effect size according to accepted standards) (Cohen, 1988). These raw scores were then converted into standardized z-scores (based on our sample's mean and SD). Cognitive measures for which a higher score indicates a poorer performance (such as z-scores reflecting errors or execution times) were reversed scored. The z-scores were then averaged together to produce composite cognitive scores, which were themselves converted into z-scores to facilitate data interpretation. When only one test score was available in a participant for a specific cognitive domain, a composite score was not calculated. This resulted respectively in 3 and 4 missing values for executive functions and attention. Outliers were defined as $z \pm 3.29$ ($P < 0.001$); and then two extreme scores ($z < -3.29$) were replaced with the minimum threshold value (-3.29). The distribution normality of the composite cognitive scores was verified upon visual inspection of frequency distributions and normal probability plots. Detailed information on the neuropsychological battery and the list of performance indices (by cognitive domain) are shown in Supplemental Table S1. Matrices showing correlation coefficients between composite cognitive scores and between performance scores included in the composites are provided in Supplemental Tables S2. and S3.

Brain Imaging

PET imaging of cerebral A β was done with ^{11}C - PiB, which is the most widely used radiotracer for

A β quantification in individuals without dementia (Mintun et al., 2006). PET images of A β were acquired on a Siemens/CTI ECAT HR+ scanner in 3D imaging mode at the McConnell Brain Imaging Centre. Each scanning session yielded a collection of 7 dynamic frames comprised of 63 axial slices, using a 128x128 matrix (voxel dimensions: x,y = 2.059 mm, z = 2.425 mm). In order to minimize in-scanner time, scanning was started 50 minutes following bolus injection, during which time 7 frames (6x300 sec, 1x600 sec) were collected. Global standard uptake value ratios (SUVR) were computed by creating a region-weighted average of PiB ratio values, which, in turn, were derived by normalizing cortical tissue radioactivity concentration to cerebellar grey matter counts. Cerebellar grey matter was used as a reference region because it is largely spared from A β deposition (Klunk et al., 2004). These SUVR units were regarded as a continuous measure of A β burden in this study. PiB PET and MRI imaging each took place within an average of 85.12 days (SD = 73.26) and 5.62 days (SD = 34.11) of the last neuropsychological testing date.

MRI scans were obtained on a 3T Siemens Trio MRI at the Unit  de Neuroimagerie Fonctionnelle. High resolution anatomical images were acquired using an optimized MPRAGE protocol (TR = 2.3 s, TE = 2.94 ms, TI = 900 ms, flip angle = 9, FOV = 256x240, voxel 1mmx1mmx1.2mm). This MPRAGE protocol allowed co-registration of PiB PET to each subject's MRI image. In addition to this sequence, an Axial Proton Density (PD)/T2 weighted protocol (TR 3000 ms, TE 12ms and 99 ms, FOV 240 mm, matrix 228 x 256, 48 slices, slice thickness 3mm) and a FLAIR protocol (TR 9000ms, TE 105 ms, T1 2500 ms, FOV 220 mm, matrix 256 x 256, slice thickness 4mm) was used for quantification of WMH in participants.

Severity of WMH was assessed by a certified neurologist in our team (C.B.) using the ARWMC scale, a semi-quantitative visual rating tool yielding a 4-point scale (0 = no lesion; 1 = focal lesion(s); 2 = confluent lesions; 3 = diffuse lesions) over five cerebral regions (frontal, parieto-

occipital, temporal, infratentorial and basal ganglia) for the right and left hemispheres separately (Wahlund et al., 2001). A global brain measure of WMH was calculated by summing scores on all five regions bilaterally and was treated as a continuous variable in our analyses.

Statistical Analysis

Pearson correlations were calculated between age and all studied variables. We used partial correlations adjusted for age in a first attempt to explore associations between A β burden, WMH and cognitive domains. Independent samples t-tests were also conducted to assess possible sex differences in biomarkers, cognitive abilities and number of years of education. Independence between A β and WMH was verified and confirmed prior to carrying out the main analyses.

We then employed a stepwise multiple regression approach to estimate the additive and distinctive contribution of different potential predictors on cognition. A stepwise regression analysis was conducted for each cognitive domain by entering age, sex, A β and WMH as independent variables and cognitive composite score as the outcome. The same regression analyses were then repeated including number of years of education as an independent variable. The stepwise procedure allowed for the selection of predictor variables in a step-by-step iterative manner, adding variables in order of their additive contribution to the model while simultaneously removing variables no longer reaching significance levels, until no variable could be further added or removed. Statistical criteria for the inclusion and removal of predictor variables in the final model were set to an F probability (P -value) ≤ 0.050 and ≥ 0.051 , respectively. Potential multicollinearity issues were tested using the tolerance ($1-R^2$) and the Variance Inflation Factor (VIF) diagnostic indexes. Normality of the residuals was verified using normal probability plots.

In order to verify the presence of an interaction between A β and WMH pathologies on cognitive abilities, we used multiple regression models with an added interaction term. A significant interaction could be of two types: 1) one (more plausible) synergistic, whereby A β and WMH's combined effects on cognition are greater than the sum of their individual effects; 2) and the other antagonistic, where both biomarkers cancel out each other's effects, either partially or completely. To answer that question, simple linear moderation models were computed based on the following equation: $\hat{Y} = i_1 + b_1X + b_2M + b_3XM$, where X represents WMH and M represents A β . The function of such a model is to determine whether the effect of a one-unit change in X on \hat{Y} is dependent upon M (or *conditional*). Otherwise stated, the moderation analysis establishes whether WMH's effect on cognitive performance varies across different values of A β (or vice-versa). In our analyses, A β was selected as the moderator variable (M) and WMH as the independent variable (X), but this choice was arbitrary as interchanging the position of X and M would not affect the interaction term. Age, sex and education were entered as covariates in the moderated regressions. An interaction was deemed significant at $P < 0.05$. The moderated regression models were built using Hayes' PROCESS macro for SPSS (model 1) (Hayes, 2013).

As one of our main objectives was to test whether age's influence on cognition was driven by A β deposition and WMH, we constructed parallel multiple mediation models using ordinary least squares path analysis with the PROCESS macro (model 4). In these structural equation models, A β burden and WMH were entered as potential mediators of the relationship between age (independent variable) and each composite cognitive score (outcome). In order to control for potential spurious or epiphenomenal associations, sex and education were included in the path models as covariates, thus statistically removing their influence on the mediation paths. Bias-corrected bootstrap confidence intervals for the indirect effect (based on 10,000 bootstrap samples) were used to assess the

significance of mediation effects. A significant mediation effect is indicated when the bootstrapped confidence interval does not contain zero with 95% confidence. Full mediation occurs when path c' (direct effect) is non-significant whereas path a (independent variable's effect on mediator), path b (mediator's effect on outcome) and path c (total effect) are significant at $P < 0.050$. The indirect mediation effect of age on cognitive performance through the mediator variable(s) is obtained from the product of paths a and b ($a \times b$). The direct effect of age on cognition is calculated by subtracting the indirect effect from the total effect [$c' = c - (a \times b)$]. All statistical analyses in this study were conducted with IBM SPSS Statistics (version 24.0; Armonk, NY). False discovery rate (FDR)-corrected P -values accounting for multiple testing across the 7 cognitive domains for the standardized regression coefficients (β), moderation interaction terms and indirect (mediation) effects are displayed in Supplemental Table S4.

Results

Characteristics of participants included in the analyses are displayed in Table 1. Unsurprisingly, age was associated with greater $A\beta$ deposition ($r = 0.388$, $P < 0.001$) and WMH severity ($r = 0.399$, $P < 0.001$), and with poorer cognitive performance across all cognitive domains: episodic memory ($r = -0.223$, $P = 0.023$), working memory ($r = -0.286$, $P = 0.003$), executive functions ($r = -0.360$, $P < 0.001$), language ($r = -0.282$, $P = 0.004$), attention ($r = -0.399$, $P < 0.001$), processing speed ($r = -0.538$, $P < 0.001$) and visuospatial abilities ($r = -0.320$, $P = 0.001$). There was no significant correlation between age and education ($P = 0.759$). Importantly, $A\beta$ burden and WMH were not correlated with one another ($P = 0.342$) when controlling for age; therefore, they were interpreted as independent variables in our statistical analyses. Controlling for age, education correlated marginally and negatively with $A\beta$ ($r = -0.186$, $P = 0.059$) but not with WMH ($P = 0.732$).

When we applied age-corrected partial correlations between biomarkers and cognitive composite

scores, A β burden was inversely associated with episodic memory ($r = -0.359, P < 0.001$), working memory ($r = -0.248, P = 0.012$), attention ($r = -0.296, P = 0.003$) and marginally with executive functions ($r = -0.182, P = 0.070$), while WMH were inversely associated with working memory ($r = -0.284, P = 0.004$), executive functions ($r = -0.272, P = 0.006$), language ($r = -0.326, P = 0.001$) and attention ($r = -0.206, P = 0.041$). Independent samples t -tests revealed a male advantage in working memory ($t(102) = -2.146, P = 0.034$) and visuospatial abilities ($t(102) = -3.585, P < 0.001$). Men were also slightly more educated than women in our sample; $t(102) = -2.099, P = 0.042$. There were no significant sex differences in age ($P = 0.770$), A β burden ($P = 0.673$) or WMH severity ($P = 0.377$).

Testing the independent and additive contribution of A β burden and WMH on cognition

Age, sex, A β and WMH were entered as potential predictors of cognitive composite scores in stepwise regression analyses. As a trend was observed for an inverse relationship between A β and education, the same regressions were repeated in separate analyses this time including education, so as not to overlook A β associations due to the shared variance with education (see Table 2 for detailed stepwise regressions results with and without education). In the first set of analyses (without education), A β burden was the only predictor retained in the stepwise model for episodic memory. Working memory was best predicted by the combination of WMH, A β and sex. Similarly, both biomarkers – but not age and sex – made an additive contribution in the stepwise regression models for executive functions, attention and language. Age did not contribute in predicting episodic memory, working memory, executive functions, attention and language in the stepwise models. In contrast, processing speed was best predicted by age alone, while visuospatial abilities were best predicted by sex and age.

When education was included in the stepwise regression analysis, A β burden was no longer a significant predictor of executive functions and language. Rather, executive functions were best predicted by WMH, education and age, while language was best predicted by WMH and education. Age, A β , WMH and education (that is, all independent variables except for sex) were found to be significant predictors of attention when considering education as a potential predictor. Education was also a significant predictor of visuospatial abilities after sex and age in the stepwise model. However, education made no distinctive contribution to episodic memory, working memory and processing speed.

Consistent with the correlational analyses, A β burden, WMH and age were negative predictors of cognitive performance when selected in the stepwise models. Inversely, education was a positive predictor of cognition when significant. Among collinearity statistics, all tolerance values were well above 0.100 (min = 0.648) and all VIF values were well below 5.00 (max = 1.543), indicating that multicollinearity was not a concern for the regressions. The residuals of the regressions were normally distributed.

Testing the synergistic interaction between A β burden and WMH on cognition

To test the possibility of synergy (or antagonism) between A β burden and WMH on cognition, moderated regressions were run for each composite cognitive score, controlling for age, sex and education. The moderation analysis revealed a significant interaction term between biomarkers on executive functions ($F(1,94) = 14.334, P < 0.001$) and attention ($F(1,93) = 11.556, P = 0.001$). More specifically, a one-unit SUVR increase in A β pathology potentiated WMH's deleterious influence on executive functions and attention by 0.390 SD and 0.298 SD, respectively. The (regression) slopes representing WMH's negative associations with executive functions and attention

for three levels of A β burden and WMH (-1, 0 and 1 SD using sample's mean) are portrayed in Fig. 1. Besides, there was a marginally significant interaction effect between A β burden and WMH for language ($F(1,97) = 2.77, P = 0.0995$) and processing speed ($F(1,97) = 2, P = 0.097$). WMH's negative effects on cognition increased by 0.169 SD for language and 0.167 SD for processing speed consequently to a one unit increase in A β SUVR. The moderation analyses detected no interaction between biomarkers for episodic memory ($P = 0.576$), working memory ($P = 0.582$) and visuospatial abilities ($P = 0.432$). Detailed results of the moderation analyses are provided in Table 3.

Taken together, results from the stepwise and moderated regressions indicate that A β and WMH yield superadditive (synergistic) effects on executive functions and attention, whereas their shared effects on working memory and language are additive in nature.

Mediation of age-related cognitive differences by A β burden and WMH

Mediation analyses were conducted to assess whether A β burden and WMH act as potential mediators of the relationship between age and cognition. Path models with a significant mediation effect are presented in Fig. 2. The path analysis revealed that A β deposition fully mediates the relationship between age and episodic memory (see Fig. 2A). The bootstrap confidence interval for the indirect effect ($a_1 \times b_1 = -0.023$) was entirely under zero ($CI_1: -0.051, -0.008$), indicating that the indirect effect of age on episodic memory performance through A β burden was significant. Both A β and WMH pathologies mediated the effect of age on working memory and attention (see Fig. 2B and 2D). The confidence intervals for the indirect mediation effects of age on working memory through A β [$(a_1 \times b_1 = -0.017)$] and WMH [$(a_2 \times b_2 = -0.020)$] did not contain zero [$(CI_1: -0.038, -0.005), (CI_2: -0.035, -0.010)$] and were thus significant. Similarly, the mediation effects on attention were significant for A β [$(a_1 \times b_1 = -0.015), (CI_1: -0.040, -0.001)$] and WMH [$(a_2 \times b_2 = -0.015), (CI_2: -0.029,$

-0.005)]. However, while A β burden and WMH together fully mediated the influence of age on working memory, the mediation effect was only partial for attention. The indirect mediation effect of age through WMH was significant for executive functions [(a₂ x b₂ = -0.020); (CI₂: -0.04, -0.005)] and for language [(a₂ x b₂ = -0.023), (CI₂: -0.041, -0.010)]; complete mediation by WMH was observed in both cognitive domains (see Fig. 2C and 2E). In contrast, there was no significant mediation effect by either biomarker for processing speed or visuospatial abilities.

Discussion

One of the main findings of this study, as demonstrated through mediation modelling, is that age-dependent differences in episodic memory, working memory, executive functions and language were explained either fully or partially – as is the case for attention – by the presence of brain pathologies associated with AD (A β burden) and cerebrovascular disease (WMH). Changes in other domains such as processing speed and visuospatial skills, however, were explained only by age and/or sex. These results are important because they suggest that the extent of age-dependent changes in specific domains in healthy older individuals is related to the extent of underlying brain pathology. Another significant finding was that A β and WMH were found to contribute additively to decreased performance in working memory and language, while they were found to contribute synergistically to decreased performance in executive functions and attention. Evidence for the existence of a synergistic interaction between both brain pathologies on functions dependent upon frontal-subcortical circuitry contributes in attaining a clearer understanding of the specific role of brain pathology in cognitive aging.

It must be pointed out that episodic memory stood out as the only cognitive domain to be explained solely by A β deposition, and that A β single-handedly predicted episodic memory performance in our

study. This distinctive contribution of A β burden to episodic memory is in agreement with a meta-analysis showing that AD pathology has closer and more robust associations with episodic memory decline than any other cognitive domains in healthy older adults (Hedden et al., 2013). It is noteworthy that A β -dependent memory decline in healthy older adults, as in MCI participants, has been considered to be a signature of preclinical dementia (Pike et al., 2007; Sliwinski et al., 2003). It should also be noted, however, that episodic memory – as a hallmark of AD - has been more systematically investigated than other cognition domains, and this may introduce a bias. Hence, associations between A β and other cognitive skills may have been overlooked in initial studies. In fact, a recent meta-analysis has linked positive A β status in cognitively intact older adults to poorer performance not only in episodic memory, but also in global cognitive functioning, language, visuospatial abilities, processing speed, working memory, attention and executive functions (Duke Han et al., 2017). In the current study, beyond its role in episodic memory performance, A β burden also mediated age-related differences in working memory and attention, along with WMH. Moreover, A β burden and WMH were negatively and synergistically associated with executive functions and attention, which rely to a significant extent on frontal lobe function (Tsuchida and Fellows, 2013). Although mixed findings have been reported previously, some researchers have suggested that specific components of executive functioning (especially switching and inhibition) (Doherty et al., 2015; Kantarci et al., 2012; Mielke et al., 2016) and working memory (Lim et al., 2012) are vulnerable to A β deposition. Our findings are consistent with this view, especially considering that our composite measure of executive functions was composed primarily of tasks assessing switching and inhibition.

The role of WMH in driving age-related differences in working memory, executive functions and attention is also in accordance with previous work relating cerebrovascular pathology and cognition

in normal older adults (Hedden et al., 2012; Moon et al., 2017; Murray et al., 2010; Papp et al., 2014). These particular cognitive functions are thought to be vulnerable to WMH because they depend on prefrontal and subcortical loops, which are more vulnerable to disruption by widespread microvascular lesions (Prins and Scheltens, 2015). Vascular cognitive impairment may also occur through cortical atrophy (Kloppenborg et al., 2012; Rizvi et al., 2018) or other less studied pathophysiological mechanisms, such as damage to the cholinergic neuronal system (Bocti et al., 2005; Richter et al., 2017; Roman and Kalaria, 2006).

More surprisingly, adverse effects of age on language and semantic-related tasks were fully mediated by WMH severity. The current literature reviewing the impact of WMH on verbal abilities in normal aging remains scarce, as most studies have focused primarily on executive functions and processing speed. Lexical and semantic difficulties in AD and even mild cognitive impairment are well documented (Benoit et al., 2017; Joubert et al., 2010; Joubert et al., 2008; Langlois et al., 2016) and have been associated with structural and functional alteration within regions of the semantic network (Barbeau et al., 2012; Joubert et al., 2010; Pineault et al., 2018). There is some evidence for the role of white matter alterations in developmental language disorders such as dyslexia (Zhao et al., 2016). The language-semantic network is complex and involves a wide range of interconnected brain regions, and it is possible that widespread axonal damage may compromise the connectivity of this network. A recent study with a cohort of healthy older participants showed that executive control required to access representations of stored lexical-semantic knowledge relied on the integrity of the arcuate fasciculus, a major language-related white matter pathway (Hoffman et al., 2017). Our results do not allow distinguishing between storage vs access difficulties in language-semantics, but the notion that the integrity of white matter pathways is necessary for executive components of language and efficient communication between distributed cortical regions forming

the language-semantic network is an interesting avenue and deserves future investigation.

In agreement with previous studies in cognitively normal older adults and in individuals with MCI, there was no significant correlation between these two biomarkers when controlling for age, supporting the prevailing notion that A β and vascular pathologies reflect distinct pathological pathways of independent aetiology (Haight et al., 2013; Hedden et al., 2012; Vemuri et al., 2015; Villeneuve and Jagust, 2015). Further, A β and cerebrovascular pathologies also appear to occur independently in preclinical older adults (Knopman et al., 2013). In individuals with AD, however, those with high A β deposition also tend to harbour greater WMH volume; hence, it has been hypothesized that WMH may impart a “second hit” to already existent AD pathology, thus precipitating the clinical expression of the disease (Provenzano et al., 2013). Consistent with this view, there is some evidence suggesting that AD may induce WMH through degenerative, non-vascular processes. Although the pathophysiological mechanisms of interaction between A β and cerebrovascular burden remain elusive, several tentative explanations have been put forward. For instance, accumulation of tau protein in the cortex secondary to A β deposition may promote WMH development (and axonal loss) directly via neuronal death and more indirectly by disrupting fast anterograde axonal transport mechanism (McAleese et al., 2015). WMH, in turn, are thought to potentiate the deleterious impact of AD pathology and accelerate neurodegeneration through various processes including oxidative stress, inflammation and impaired cerebral perfusion (Iadecola, 2010). An alternative hypothesis is that vascular brain damage disrupts lymphatic drainage of vessels located in the periventricular tissue and prevent proper clearance of waste material such as A β peptides (Ramirez et al., 2016; Weller et al., 2009).

It could be reasonably contended that these mechanisms of interaction between AD and vascular pathways may not yet be detectable in asymptomatic individuals because they emerge later in the course of the disease. Challenging this proposition, however, recent work has provided evidence that A β deposition and total WMH volume in healthy older adults have synergistic associations with grey matter neurometabolic alterations typically associated with AD, especially in the posterior cingulate and precuneus (Schreiner et al., 2018). Therefore, AD and cerebrovascular disease pathophysiology may yield mutually potentiating effects which, albeit subtle, are detectable even in the absence of objective cognitive impairment (i.e. in the hypothetical preclinical stage of dementia). Pertaining to cognitive effects of A β deposition and WMH in normal older adults, our results advocate the existence of both additive and synergistic associations, depending on the cognitive domains. It is worth noting that the presence of synergy in several cognitive domains lends support to the notion that A β and WMH interact at a physiological level through one or several of the aforementioned mechanisms. Thus, despite reflecting initially independent disease pathways, A β and WMH pathologies appear to exert interactive effects on cognition in healthy older adults. This finding strongly suggests that AD and cerebrovascular disease pathways converge at some point in time in preclinical individuals, and that their interactive effects and co-occurrence are likely to increase with the disease progression.

In contrast with the results reported above, A β burden and WMH did not significantly predict performance in processing speed and visuospatial abilities when age was accounted for in the regression models. Therefore, other factors or pathogenic mechanisms may be responsible for age-related differences in processing speed and visuospatial function. The lack of an association between biomarkers and processing speed, while not entirely unexpected regarding A β burden, stands against

a body of work suggesting that processing speed is particularly vulnerable to early white matter changes and cerebral small vessel disease (Gunning-Dixon and Raz, 2000; Prins et al., 2005; van den Heuvel et al., 2006; Wright et al., 2008). It could be that other surrogates of cerebrovascular damage, such as vascular risk factors or brain infarcts, would be more readily responsible for slowed information processing with age than WMH (Benjamin et al., 2014; Knopman et al., 2001; Saczynski et al., 2009; Viswanathan et al., 2015). Alternatively, the failure to link higher WMH with reduced processing speed could also be attributable to relatively low WMH severity in our sample. Nonetheless, our findings are fairly in line with those of a recent meta-analysis in which progression of WMH was associated with decline in global cognitive functioning with markedly greater effects for attention and executive functions as opposed to memory and processing speed (Kloppenborg et al., 2014).

On the whole, our results appear quite robust when compared to analogous cross-sectional studies of similar sample size on cognitively normal older adults. One likely explanation is that our carefully selected neuropsychological assessment included the most sensitive and relevant tests specific to each cognitive domain. For instance, we avoided neuropsychological tests with ceiling effects in healthy older adults (e.g. we chose the RAVTL instead of the CVLT for assessing verbal memory). Indeed, many studies have relied on a global cognitive composite score or a single measure of memory, and few studies have sought to assess the distinctive contribution of A β and cerebrovascular pathologies across a wide range of cognitive domains. Another strength to the current study is that in addition to controlling for education in our analyses, we also recruited participants with different levels of education, thus avoiding the common pitfall of recruiting only highly educated participants. Education is often a source of bias because; 1) highly educated adults are more likely to volunteer in cognitive aging studies and; 2) higher education, which is a proxy of

cognitive reserve, may mask associations between brain pathologies and cognition (Stern, 2012).

The use of continuous measures of A β burden and WMH is more statistically powerful and a better reflection of reality than dichotomous measures based on a threshold, which can be viewed as more arbitrary (Farrell et al., 2017).

A few limitations to this study should also be noted. First of all, the cross-sectional nature of the current results limits the scope of interpretation of our findings, as well as our sample size which is relatively modest when compared with some other cohorts. However, we compensated by recruiting participants from a wider spectrum of educational achievement and by using more sensitive neuropsychological tests. Visual rating of WMH severity may prove to be less sensitive to early white matter changes in healthy individuals than automated volumetric assessment of WMH because of potential floor or ceiling effects and does not as readily lend itself to regional characterization.

Conclusions

Altogether, our results demonstrate that age-related changes in multiple components of cognitive functioning are driven by specific neuropathological biomarkers of dementia in healthy older adults. Furthermore, we argue that pathological aging is a multifaceted and insidious process occurring over a continuum of severity rather than a discrete entity. In particular, the present study demonstrates that A β and cerebrovascular pathologies can yield synergistic effects on cognition, especially for functions that rely on frontal-subcortical circuits (i.e., executive functions and attention). Although many have speculated on the existence of superadditive cognitive effects of A β and WMH in healthy older adults, this notion had never, to our knowledge, received tangible empirical support before this study. Most research effort in that direction has failed to find a significant interaction between A β and WMH on cognition, thus pointing towards additive effects (Gordon et al., 2015; Lo et al., 2012;

Vemuri et al., 2015). While it is difficult to pinpoint why our findings differ from those of previous work in this regard, this could be partly imputable to important discrepancies in cognitive assessment, such as reliance on a single composite measure or rating scale in some studies. In another study on this matter, a trend was noticed for worse cognition in healthy older adults harboring significant levels of both AD and cerebrovascular pathologies as compared to other groups, although there was no significant interaction effect (Marchant et al., 2012). Most importantly, our primary finding that brain pathology mediates age-related differences in cognitive performance of older adults has significant implications for future research on cognitive aging and may serve as a leverage for the development of interventions to mitigate cognitive decline associated with aging in individuals without objective cognitive deficits. In light of the current study findings, what truly remains a challenge is to define cognitive aging in the absence of significant brain pathology associated with AD and cerebrovascular disease.

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Author Contributions

P.S.D., S.J., C.B., and H.C. were responsible for conception and design of the study. P.S.D., S.J., M.J., M.M.L. and G.T.V. contributed to acquisition and statistical analysis of data, and J.N., H.C., and C.B. were responsible for MRI/PET preprocessing and interpretation. P.S.D. and S.J.

contributed to drafting the manuscript and P.S.D. was responsible for drafting the figures. All authors reviewed the manuscript and approved the final version of the manuscript.

Potential Conflicts of Interest

We have no conflicts of interest to disclose.

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TABLES

TABLE 1. Characteristics of Participants

77F/27M	Range	Mean (SD)	Median (interquartile range)
Age (years)	65.00-92.92	73.31 (6.17)	72.67 (9.48)
Education (years)	9-24	13.72 (3.27)	13.00 (5.00)
MoCA	23-30	27.32 (1.95)	27.50 (3.00)
A β burden (SUVR)	1.04-2.03	1.24 (0.17)	1.19 (0.11)
WMH (ARWMC)	0-18	3.17 (3.70)	2.00 (6.00)

TABLE 2. Stepwise regressions models by cognitive domain

	Significant Predictors	Std. β (p-value)	F (p-value)	R²
Episodic Memory				
	A β burden	-0.409 (<0.001)	20.513 (<0.001)	0.167
Working Memory				
	WMH	-0.323 (<0.001)	11.870 (<0.001)	0.132
	A β burden	-0.316 (0.001)		0.224
	Sex	0.196 (0.025)		0.263
Executive Functions				
a (without education)	WMH	-0.339 (<0.001)	13.565 (<0.001)	0.143
	A β burden	-0.275 (0.003)		0.217
b (with education)	WMH	-0.287 (0.003)	14.515 (<0.001)	0.143
	Education	0.341 (<0.001)		0.257
	Age	-0.253 (0.007)		0.310
Attention				
a (without education)	A β burden	-0.381 (<0.001)	16.458 (<0.001)	0.158
	WMH	-0.309 (0.001)		0.253
b (with education)	Age	-0.209 (0.039)	11.002 (<0.001)	0.159
	A β burden	-0.276 (0.004)		0.233
	WMH	-0.244 (0.010)		0.280
	Education	0.195 (0.026)		0.317
Language				
a (without education)	WMH	-0.385 (<0.001)	12.425 (<0.001)	0.160
	A β burden	-0.195 (0.032)		0.197
b (with education)	WMH	-0.413 (<0.001)	16.797 (<0.001)	0.160
	Education	0.300 (0.001)		0.250
Processing Speed				
	Age	-0.538 (<0.001)	41.578 (<0.001)	0.290
Visuospatial Abilities				
a (without education)	Sex	0.325 (<0.001)	13.304 (<0.001)	0.112
	Age	-0.311 (0.001)		0.209
b (with education)	Sex	0.272 (0.003)	11.834 (<0.001)	0.112
	Age	-0.320 (<0.001)		0.209
	Education	0.238 (0.008)		0.262

Outcomes (cognitive domains) are identified in the first column of the table. Predictors included in the final model are listed in order of their additive contribution in the stepwise regression model. Results of the stepwise regressions are shown without education (a) and with education (b) separately when inclusion of education as a potential predictor influenced the final model. R²*100 represents the cumulative % of variance explained by each predictor.

TABLE 3. Moderation models by cognitive domain

		Coeff.	SE	t	p-value
Episodic Memory	Intercept	0.541	1.309	0.413	0.680
	WMH (X)	-0.068	0.100	-0.678	0.500
	A β burden (M)	-0.347	0.102	-3.400	0.001
	WMH x A β burden (XM)	0.061	0.108	0.562	0.576
Working Memory	Intercept	-0.106	1.238	-0.086	0.932
	WMH (X)	-0.310	0.094	-3.281	0.001
	A β burden (M)	-0.274	0.096	-2.843	0.005
	WMH x A β burden (XM)	-0.056	0.102	-0.552	0.582
Executive Functions	Intercept	1.122	1.203	0.932	0.354
	WMH (X)	-0.268	0.086	-3.111	0.003
	A β burden (M)	-0.125	0.106	-1.180	0.241
	WMH x A β burden (XM)	-0.390	0.103	-3.786	0.000
Attention	Intercept	1.460	1.050	1.391	0.168
	WMH (X)	-0.219	0.080	-2.732	0.008
	A β burden (M)	-0.282	0.082	-3.443	0.001
	WMH x A β burden (XM)	-0.298	0.088	-3.400	0.001
Language	Intercept	-0.068	1.227	-0.055	0.956
	WMH (X)	-0.345	0.094	-3.691	0.000
	A β burden (M)	-0.140	0.096	-1.466	0.146
	WMH x A β burden (XM)	-0.169	0.101	-1.663	0.010
Processing Speed	Intercept	5.645	1.204	4.690	0.000
	WMH (X)	-0.042	0.092	-0.455	0.650
	A β burden (M)	-0.003	0.094	-0.033	0.974
	WMH x A β burden (XM)	-0.167	0.099	-1.675	0.097
Visuospatial Abilities	Intercept	1.925	1.250	1.540	0.127
	WMH (X)	-0.075	0.095	-0.782	0.436
	A β burden (M)	-0.081	0.097	-0.833	0.407
	WMH x A β burden (XM)	-0.082	0.103	-0.790	0.432

WMH, A β burden and composite cognitive scores are expressed in standardized z-scores (derived from the sample's mean and SD). For simplicity, covariates (age, sex and education) are not shown in this table but were accounted for in all models. The interaction term for the moderation analysis (WMH x A β burden) is shown in the fourth row for each model.

Figure 1. Cognitive performance at low (-1 SD), moderate (0 SD) and high (1 SD) levels of **A β burden and WMH (adjusted for age, sex and education)**

The regression slopes show WMH associations with executive functions (A) and attention (B) at three levels of A β burden and WMH (-1.00 SD, 0.00 SD and 1.00 SD based on our sample's statistics). Differences of slopes illustrate the synergistic interaction between WMH and A β over these cognitive domains. The moderated regression analyses were corrected for age, sex and education.

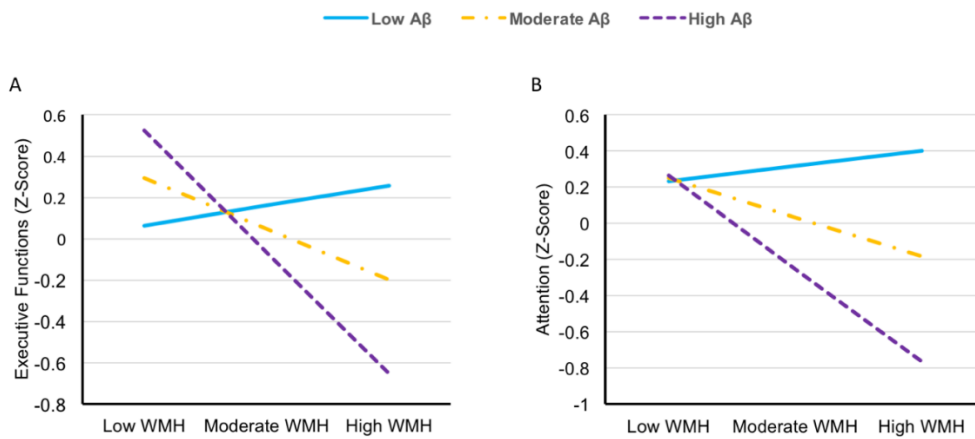


Figure 2. Path models with a significant mediation effect of the biomarkers

A β , WMH and cognitive composite scores are expressed in z-scores (SD units). Age and education are expressed in years. As such, path a is expressed in SD increment of A β (a_1) and WMH (a_2) associated with an increment of one year of age, while path b is expressed in SD decrement of cognitive performance associated with an increment of one SD in A β (b_1) and WMH (b_2). Path c (total effect) is expressed in SD decrement in performance associated with an increment of one year of age regardless of A β and WMH. Significant mediators are highlighted by grey shading. Significant paths are designated by a solid line and non-significant paths by dashed lines. In all the pictured cognitive domains except for attention, the direct effect of age on cognition (c') was non-significant, indicating complete mediation. The mediation effect is only partial for attention. Sex and education were included as covariates in all mediation models. The reported mediations paths (i.e., a, b and c') are adjusted for these covariates. Significant paths between covariates and other variables derived from the mediation analysis are indicated by light lines while non-significant paths are not shown on the figure for simplicity.

