Title

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The Aging Brain: Are two pathologies worse than one? White matter hyperintensities, beta-amyloid, and cognition in normal elderly

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ABSTRACT

White matter hyperintensities (WMH)—areas of increased signal on T2 and Fluid Attenuated Inversion Recovery (FLAIR) MRI images—and beta-amyloid (ABeta) plaques—an Alzheimer's disease pathology—are commonly found in the brains of cognitively normal elderly people. Although previous studies have looked at these pathologies, the interaction between them remains unclear. This study investigated the potential of WMH and ABeta burden in predicting cognition in normal elderly. FLAIRs of 45 local elderly participants were used to quantify WMH volumes to determine WMH load; and a Pittsburg Compound B (PIB) index obtained with positron emission tomography (PET) was used as a measure of ABeta burden. Hierarchical regressions of WMH volume and PIB group predicting executive function, working memory, and episodic memory were done. Results showed a trend towards a WMH and PIB interaction with episodic memory, suggesting that WMH and ABeta burden together may cause worse episodic memory than either of those pathologies by itself. Additionally, we found that education may be modulating the effects of WMH on executive function.

INTRODUCTION

White matter hyperintensities (WMH)—also known as leukoaraiosis, a term coined by Hachinski *et al.* (1)—are hyperintense (bright) areas in cerebral white matter on certain MRI images such as T2 and Fluid Attenuated Inversion Recovery (FLAIR) sequences. They commonly appear in brain scans of normal elderly people (2,3). See Fig. 1 for an example of WMH on a FLAIR image. These hyperintensities can be quantified through fully automated methods (4) and in imaging can act as a measure of aging-related white matter changes.

In terms of pathology, biological causes of the appearance of WMH may include ischemia (by far the most accepted view), blood-brain barrier alterations, chronic edema, and genetic factors (e.g. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy—CADASIL, which also relates to ischemia) (5,6,7). Furthermore, greater WMH burden has been associated with an increased risk of infarcts, stroke, and dementia; increased brain atrophy; decreased mobility; and poorer cognition, particularly frontal function (2,8,9,10,11,12).

However, studies on the association between WMH burden and cognition have not had consis-

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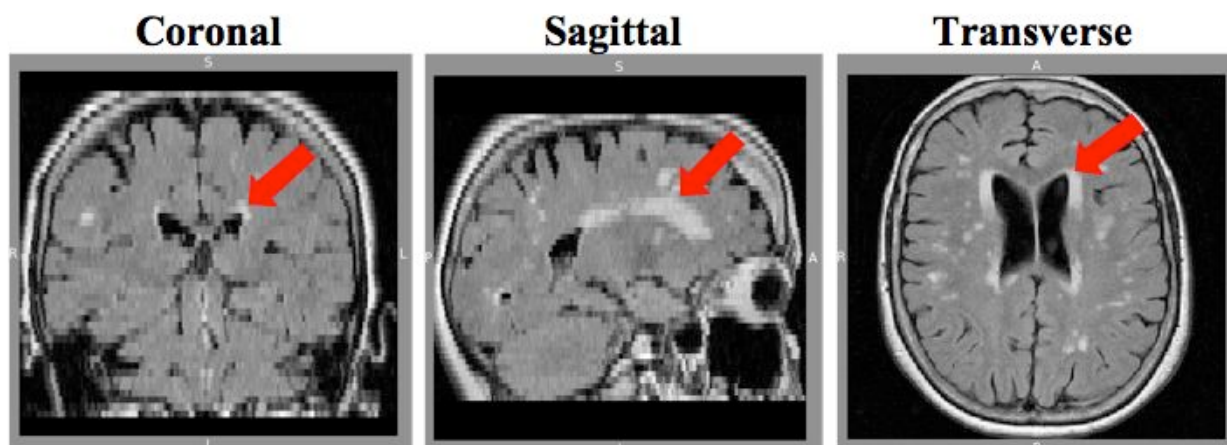
Figure 1: An example of WMH on a FLAIR image in three planes (left to right): coronal, sagittal, and transverse.

	n=	Age	Sample	Methods	Main findings
1	22 (CN) 30 (CI) 26 (Dem)	76.6(6.5) 78.2(7.7) 76.5(8.7)	Normal, cognitively impaired, and demented	Quantitative	Greater WMH volume was associated with worse executive and memory function in non-demented study participants only.
2	53	59(8.1)	Normal	Quantitative	A higher ratio of WMH to WBV was associated with poorer performance on Stroop-like test, Trail Making-like test, and Austin Maze-like test (executive function); Letter (FAS) and Animal Fluency (verbal).
3	88 (ND) 68 (MD)	76.9(8.2) 77.4(7.1)	Non-demented and early AD	Semi-quantitative visual rating	Greater WMH burden (both deep WMH and periventricular WMH) was associated with reduced global cognition (driven by reductions in visual memory, processing speed, and executive function) in AD study participants only.
4	1819	61.1(9.4); 35-88	Framingham Offspring Cohort	Quantitative	Large WMH volumes were associated with worse performance in visual organization; attention, planning and initiation of complex activity (Trail Making test--executive function); and new learning.

Table 1: Summary comparison of four studies on the association between WMH and cognition.

1: Tullberg, M., Fletcher, E., DeCarli, C., Mungas, D., Reed, B.R., Harvey, D.F., *et al.*, White matter lesions impair frontal lobe function regardless of their location, Neurology, 63.2, 246-253, 2004. (13)

2: Paul, R.H., Haque, O., Gunstad, J., Tate, D.F., Grieve, S.M., Hoth, K., *et al.*, Subcortical hyperintensities impact cognitive function among a select subset of healthy elderly, Archives of Neurology, 20.6, 697-704, 2005. (14)

3: Burns, J.M., Church, J.A., Johnson, D.K., Xiong, C., Marcus, D., Fotenos, A.F., *et al.*, White matter lesions are prevalent but differentially related with cognition in aging and early Alzheimer disease, Archives of Neurology, 62.12, 1870-1876, 2005. (15)

4: Au, R., Massaro, J.M., Wolf, P.A., Young, M.E., Beiser, A., Seshadri, S., *et al.*, Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham Heart Study, Archives of Neurology, 63.2, 246-250, 2006. (16)

tent findings. Table 1 summarizes the findings of four such studies. In Tullberg *et al*. (13) and Paul *et al*. (14), greater WMH volume was associated with worse executive function in non-demented and normal elderly, whereas in Burns *et al*. (15) this relationship was found only in early Alzheimer's disease (AD) study participants. Even with large sample sizes such as in Au *et al*. (16), p-values of the correlations between WMH and cognition were within a fairly narrow range of the 0.05 significance cut-off value, emphasizing the small effect size of these findings. Additionally, while these four studies found the relationship between greater WMH burden and worse executive function seen in the literature, results of these four studies varied more in other types of cognition, including memory.

ABeta plaques are a characteristic pathology in AD used in its diagnosis *post mortem* and also found in cognitively normal elderly people (17,18). Plaques are aggregates of various ABeta peptides formed by sequential cleavage of the transmembrane amyloid precursor protein (APP). Through positron emission tomography (PET) and the radiotracer Pittsburg Compound B (PIB), which has been shown to bind to ABeta (19), severity of ABeta burden can be assessed *in vivo*.

	BAC 65 years and older	Study participants	Subset after PIB grouping
n	175	45	38
Age	75.6	73.8	73.4
Gender	112F	30F	24F
Education	17.4	17.3	17.3
eTIV	--	1483668	1504695
MMSE	28.7	29.3	29.3
WMH volume	--	2628.2	2873.6

Table 2: Demographic information on the three groups/subsets of this study (left to right): 1) cognitively normal people 65 years and older from the Berkeley Aging Cohort (BAC), 2) the participants of this study (43 from the first group in addition to two participants from UCSF neuroimaging studies), and 3) a subset of the study participants after PIB grouping. eTIV=estimated total intracranial volume; MMSE=Mini Mental State Examination; WMH volume=average total volume of white matter hyperintensities (after removal of false positives).

Moreover, greater ABeta burden has been associated with worse episodic memory in normal elderly (18).

Multiple brain pathologies can occur simultaneously in normal aging and may affect cognition. Beta-amyloid plaques and white matter disease are commonly found together in clinical diagnoses of dementia and mixed pathologies in *post mortem* "healthy" elderly people (20). Though the tendency is to study pathologies as separate entities, it is likely that a single pathology like WMH will explain only a small part of the individual variability in age-related cognitive changes (21). This study investigates the potential of WMH and PIB in predicting cognitive function in normal elderly, particularly their interaction.

MATERIALS AND METHODS

Of the 45 participants in this study, 43 were community-dwelling, cognitively normal elderly people from the Berkeley Aging Cohort (BAC), recruited through advertisements. Two of the study participants were cognitively normal elderly persons from neuroimaging studies conducted at the University of California, San Francisco (UCSF). The average age of the 45 participants was 73.8 years, 30 of them were female, and the average years of education obtained was 17.3 years (meaning the majority of participants were college graduates). The average Mini Mental State Examination (MMSE) score was 29.3 (the maximum score is 30), which demonstrates the participants' cognitively normal status. This sample did not differ significantly in these variables from the larger BAC sample of 175 cognitively normal people 65 years and older. A smaller sample (n=38) was used in the statistical analyses (because of removal of seven participants for the purpose of high/low PIB grouping, explained later); this subset also did not differ significantly in these demographic variables. See Table 2 for a summary of the demographic information.

Participants underwent a battery of neuropsychological tests including the MMSE, Trail Making (TM), Stroop Task (ST), Digit Span (DS), Listening Span (LS), California Verbal Learning Test (CVLT), and Visual Reproduction (VR), except for the UCSF participants. TM, ST, DS, and LS scores for one of the UCSF participants were missing, as was LS for the other UCSF participant. This study looked at three different cognitive measures—executive function, working memory, and episodic memory—and defined them in the following way. Executive function of the participants was defined as a composite score of the TM and ST tests, working memory was defined as a composite score of the DS and LS tests, and episodic memory was defined as a composite score of the CVLT and VR tests.

Two types of structural MRI images were used for quantification of WMH, Fluid Attenuated Inversion Recovery (FLAIR) and Magnetization Prepared RApid Gradient Echo (MPRAGE) images. These were acquired using a 1.5-T Magnetom (Siemens) scanner at the Lawrence Berkeley National Laboratory (LBNL). An in-house automated white matter hyperintensity segmentation tool was applied to create a WMH

mask. A flow chart of the various processing steps is shown in Fig. 2 and explained below.

Prior to running the tool, FLAIR images were inspected for inter-slice motion. Thirteen cases had significant motion and were re-aligned in SPM2 in an attempt to keep WMH volumes as accurate as possible. All FLAIR images were bias-corrected using FSL Fast to correct for heterogeneities in the magnetic field during image acquisition. Brain masks of grey and white matter (excluding the cerebellum and brainstem, as WMH are rarely found in these areas (3)) were extracted from MPRAGEs with Freesurfer and co-registered to the corresponding FLAIR image with FSL.

The WMH labeling tool was executed using Matlab7 to quantify global WMH volume in the 45 cases. First, the brain mask and FLAIR for each case were inputted into the tool. The brain mask was used to restrict the intensity histogram to voxels within the brain, i.e. the meninges and skull were excluded. Then, an intensity histogram was created from these FLAIR voxels and a cut-off point was determined using an iterative approach (22). Voxels with intensities greater than this cut-off were identified as WMH. Thereafter, a WMH mask was created in native FLAIR space based on these intensity values; the WMH mask was cluster cropped at a threshold of three voxels so that WMH that were three voxels or smaller were excluded in the outputted WMH mask. The masks were examined for accuracy and WMH volumes were extracted from them. Fig. 3 shows examples of the outputted files from two cases, one with the highest and one with the lowest WMH volume.

False positives from this procedure were removed in three ways. First, brain masks excluded hyperintense non-brain areas (e.g. skull, meninges) from being falsely identified as WMH, and at the same time, created more accurate WMH histograms thus possibly greater accuracy in identifying WMH in brain tissue. Second, the WMH masks were cluster cropped at a threshold of three voxels in order to help eliminate falsely identified WMH in cortical grey matter, which tended to be randomly scattered and very small (one to three voxels). Third, a white matter mask of a group specific template was reverse normalized with FSL FNIRT from template to FLAIR space and all WMH outlying this mask were excluded. This last step was used to further exclude cortical grey matter that may have been larger than the cluster crop threshold of three voxels and some deep grey matter areas that
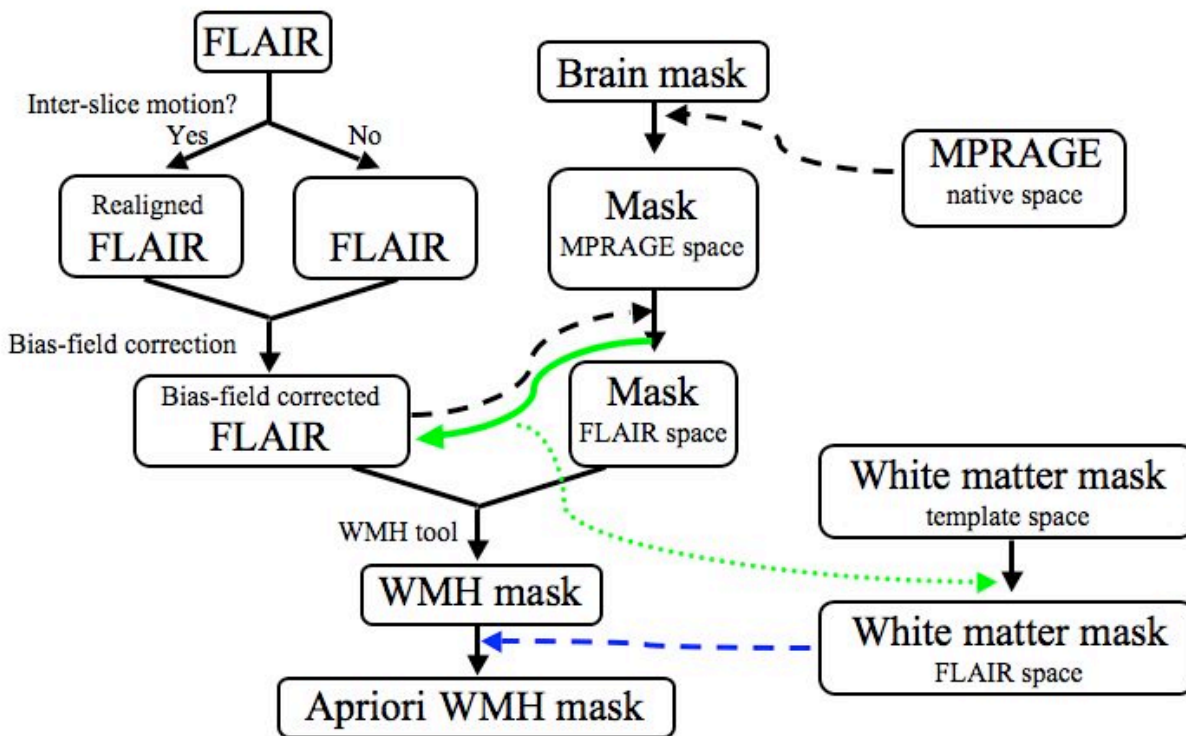

Figure 2. A flow chart of WMH mask processing. Realignment of FLAIR images was done in SPM2. Then FSL Fast was used for bias-field correction. Brain masks were extracted from MPRAGE with Freesurfer. Brain masks and FLAIR images were inputted into the WMH labeling tool. Reverse normalization of white matter mask was done using FSL FNIRT. The white matter mask was applied to the WMH mask and WMH volume was extracted using FSL.
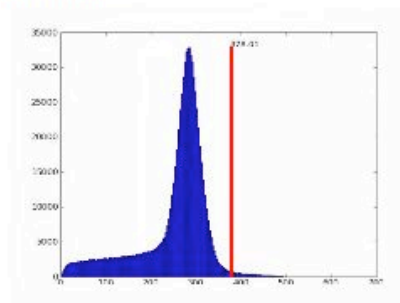
(a) WMH masks

Case with the highest WMH volume
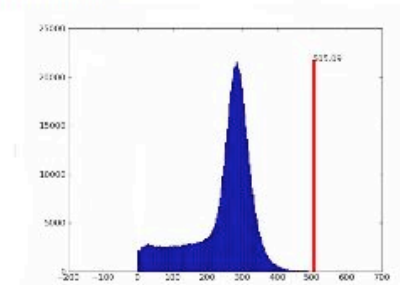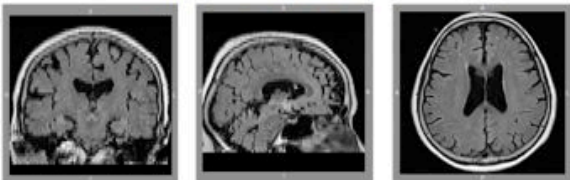
WMH volume / WM volume=0.01393, WMH labeled in red
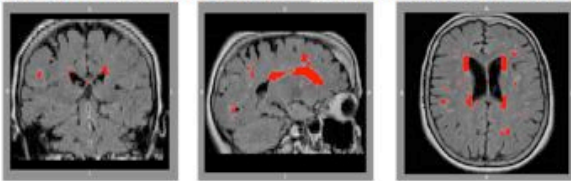
WMH volume / WM volume=0.01393, WMH unlabeled

Case with the lowest WMH volume

WMH volume / total WM volume=0.00007

(b) WMH histograms

Figure 3. Comparison of output files (WMH masks and histograms) of the highest (top) and the lowest (bottom) WMH volume cases. **(a)** Coronal, sagittal, and transverse sections of WMH masks overlaid on FLAIR images of the case with the highest WMH volume (one set of images with the mask overlaid and one without) and another case with the lowest WMH volume, **(b)** intensity histograms created by the tool in order to establish a WMH cut-off value (red line), where intensities greater than the cut-off were deemed WMH.

tended to be falsely identified as WMH.

PIB/PET data were used to extract global PIB index values. PET scans were acquired using a Siemens PET scanner at LBNL. First, PET scans were motion corrected with SPM2. Regional PIB distribution volume ratio (DVR) values were obtained by normalizing to the cerebellum (few plaques occur in this area (23)), partial volume correction was done (to elevate voxels whose signal may be contaminated by cerebrospinal fluid (24)), and DVR values from frontal, cingulate, parietal, and lateral temporal regions were averaged to give global PIB index values.

Because the PIB index values were skewed, the study participants were grouped into high and low PIB groups. Log transformation of PIB values was attempted; but as it did not alleviate the skew, they were not used. The group cut-off (see Fig. 4) was iteratively established similar to the method used by Aizenstein *et al.* (25). Seven borderline cases lying between 2.5% of the cut-off were removed from statistical analyses

in order to make the division between the high and low PIB groups more distinct and more appropriate for statistical analyses. Likewise, WMH volumes were also skewed. Log transforming these values made the distribution more normal (see Fig. 5) and thus these values were used in the statistical analyses.

A series of multivariate analyses predicting the three cognitive measures defined previously—episodic memory, executive function, and working memory—were done in the following manner. The first step in each model had demographic variables, i.e. age, gender, education, and estimated total intracranial volume (eTIV, in order to account for head size differences within the sample), predicting cognition; the second step model had demographic variables plus the log-transformed WMH volumes predicting cognition; the third step model had demographic variables, log-transformed WMH volumes, high/low PIB groups, and a WMH and PIB interaction variable predicting cognition.
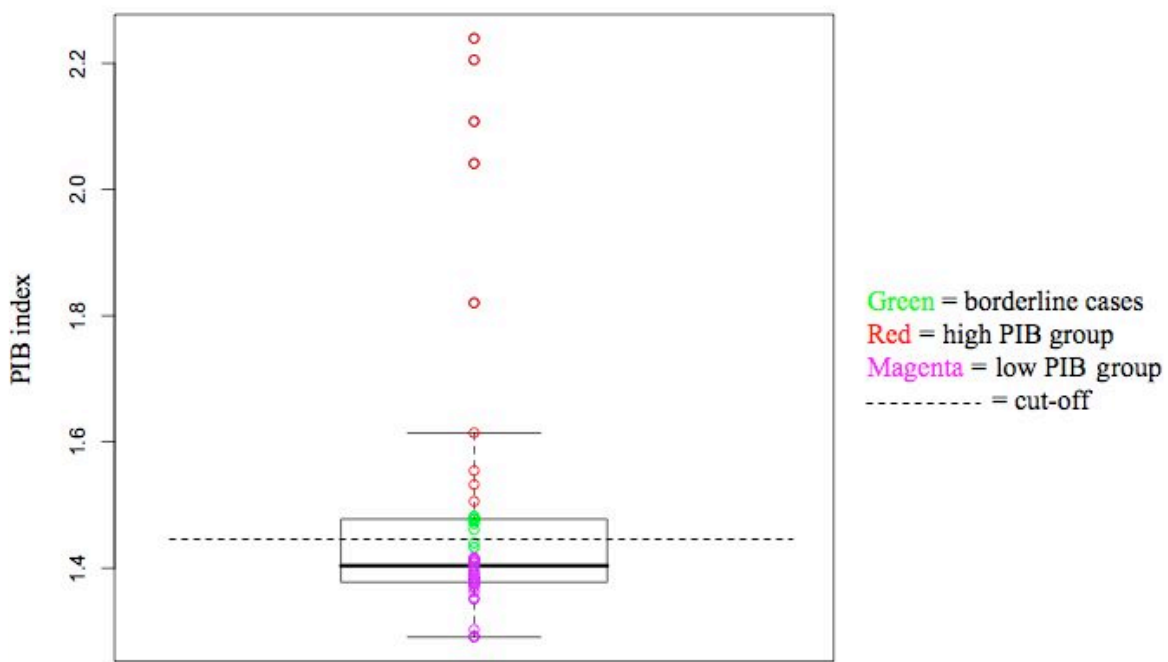
Figure 4. Box and whisker plot of high and low PIB groups (borderline cases defined as within 2.5% of iteratively established cut-off). These seven borderline cases were excluded in statistical analyses, making the sample size from 45 to 38.
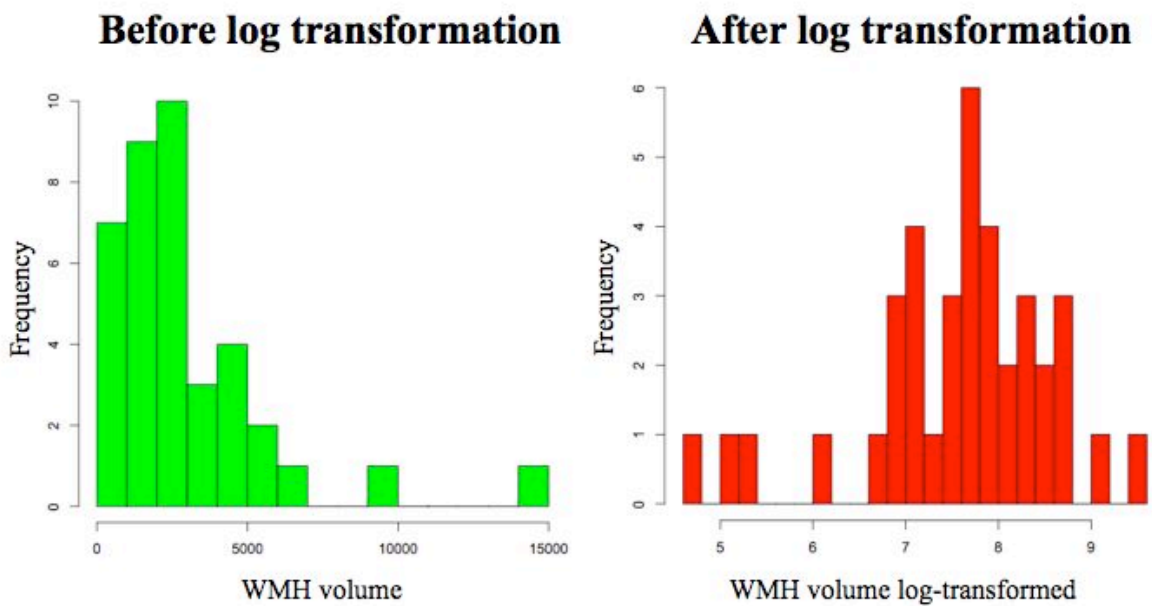
Figure 5. WMH volume histograms before (left) and after (right) log transformation.
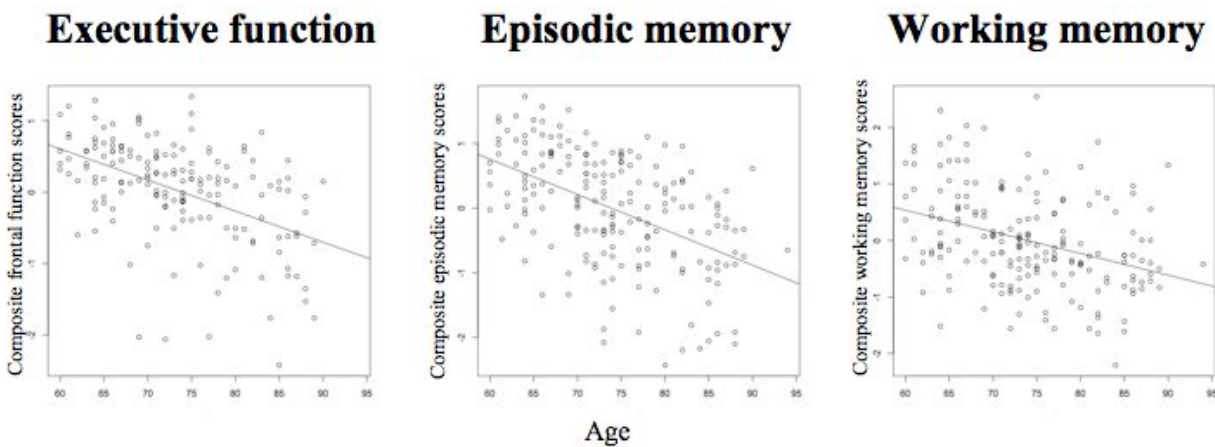
Figure 6. Negative correlations of the three composite scores used as measures of cognition (executive function, episodic memory, and working memory, left to right) against age for 175 cognitively normal, 65 years and older BAC participants.

RESULTS

Composite scores of the cognitive measures were regressed against age in the 175 cognitively normal, 65 years and older BAC participants to ensure that they reflected age-related cognitive decline. See the three plots in Fig. 6. All three composite scores showed a significant, negative correlation with age.

Overall R-squared values of the statistical models and p-values less than 0.2 of individual variables are summarized in Table 3. The models predicting episodic memory steadily improved with each step as evidenced by the increasing R-squared values. In the first two models, age showed a trend; in the last model, WMH and the WMH and PIB interaction showed a trend in predicting episodic memory such that effects of WMH were greater for those with high PIB than for those with low PIB. Notice the red points in the lower right hand corner of Fig. 7 that represent the high PIB participants with both high WMH volumes and low episodic memory scores.

In the models predicting executive function, the baseline R-squared value in the first model was relatively high compared to the first models predicting either episodic memory or working memory. The R-squared values improved minimally with each step, not nearly to the same magnitude as the R-squared values for the models predicting episodic memory. Education was a significant predictor variable in all three models predicting executive function. Age showed a trend in all three models.

For working memory, the R-squared values im-

proved minimally with each step and none of the individual variables showed a trend in predicting it.

DISCUSSION

Our finding that greater age is associated with worse cognition establish our composite scores as reflective of age-related cognitive decline and moreover adds to the existing literature that age is a major factor in cognitive decline. Furthermore, this finding highlights the importance of controlling for age in our models that examined the relationships between cognition and age-related pathologies.

Neither WMH nor the WMH with PIB interaction significantly predicted executive function or working memory—cognitive functions associated with WMH in the literature (2,13,14,16,26). However, these variables did show a trend when predicting episodic memory. Other studies, including Gunning-Dixon and Raz (2), Petkov *et al*. (27), and Charlton *et al*. (28), have likewise shown this relationship between WMH and episodic memory. This finding with episodic memory could mean that WMH pathologies are disrupting certain pathways that affect memory formation. Blumenfeld and Ranganath (29) found that different regions in the prefrontal cortex augment long-term memory formation. WMH that are near these areas or which disconnect them from remote cortical regions could be disrupting these networks so that the ability to create long-term memories is inhibited. The interaction of WMH with PIB could indicate a threshold of ABeta deposition wherein WMH are more detrimen-

Cognition	Variables	R-squared	p
Episodic memory	Age+gender+education+eTIV	0.136	Age: p=0.068
	Age+gender+education+eTIV+ WMH	0.149	Age: p=0.079
	Age+gender+education+eTIV+ WMH*PIB	0.270	WMH: p=0.149 WMH*PIB: p=0.171
Executive function	Age+gender+education+eTIV	0.233	Age: p=0.106 Education: p=0.033
	Age+gender+education+eTIV+ WMH	0.248	Age: p=0.113 Education: p=0.027
	Age+gender+education+eTIV+ WMH*PIB	0.284	Age: p=0.101 Education: p=0.031
Working memory	Age+gender+education+eTIV	0.099	
	Age+gender+education+eTIV+ WMH	0.131	
	Age+gender+education+eTIV+ WMH*PIB	0.141	

Table 3. Summary of R-squared and p-values of multivariate statistical models. eTIV=estimated total intra-cranial volume; WMH=log-transformed WMH volumes; PIB=high/low PIB groups; WMH*PIB=WMH and PIB interaction. *Note*: R-squared values are of the whole model; p-values are of individual variables less than 0.2.
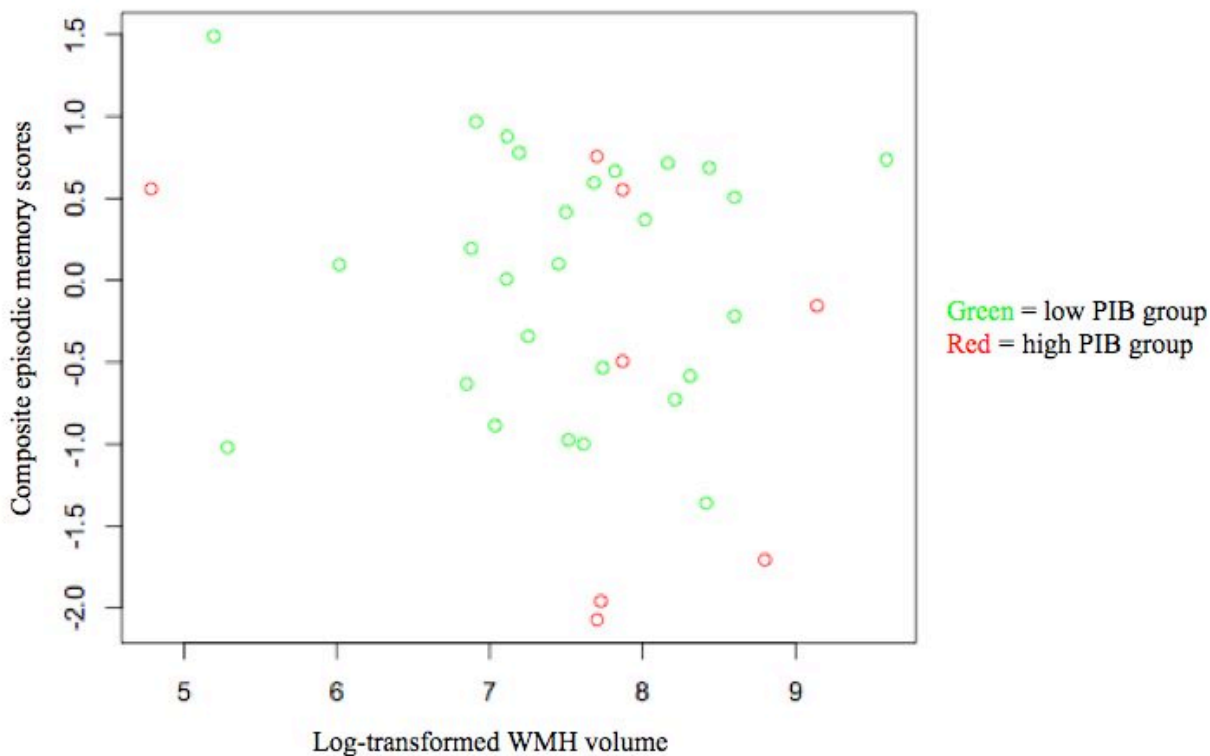
Figure 7. Negative correlation of episodic memory against WMH (controlled for age, education, and gender) shown with different colored PIB groups (low PIB group shown in green and high PIB group shown in red).

tal in those with more ABeta. Although the interaction finding is somewhat weak, especially since one high PIB participant seems to be driving the interaction, there are a few high PIB participants that have both high WMH volumes and low episodic memory scores, which could mean that only high amounts of both pathologies matter in the interaction. In other words, great WMH volumes cause worse episodic memory but only for those with high PIB.

From the literature, we would expect greater WMH burden to be associated with worse executive function; however, we did not find this relationship in this study with WMH alone nor with the WMH and PIB interaction. Because education was a significant predictor variable in all three models predicting executive function, it may have masked a weaker relationship between WMH and/or WMH and PIB interaction with executive function. This finding with education also suggests possible modifying effects of WMH so that individuals with more years of education may be somewhat protected by the detrimental effects that WMH may have on cognition, a relationship found in Dufoil et al. (30). An interaction between WMH and education would need to be investigated to see if this is the case.

We may not have found any relationships with working memory because of the type of working memory test, specifically the DS backward, we used. Oosterman et al. (26) found that the DS backward test was not associated with WMH but other working memory tests were. It may have been that the LS test predicted working memory but the composite score may have created enough noise to mask this result.

This study was strong in that it looked at a possible interaction with two types of pathologies commonly seen in aging. However, it was also limited in a few ways. First, it had a small sample size. Second, some of the data were skewed, e.g. WMH volume and PIB index, so that it could have been analyzed in different ways and in turn affected the outcomes. This study did not look at differential effects that WMH may have depending on their location. The literature on this has been inconsistent. For instance, Yoshita et al. (31) found that spatially different WMH were associated with different degrees of cognitive impairment and Blumemfield and Ranganath (29) found that ventrolateral regions of the prefrontal cortex contributed to encoding the goal-relevancy in long term memory

encoding where as dorsolateral regions of the prefrontal cortex contributed to organizing information in working memory; however, Tullberg et al. (13) found that regardless of the spatial location of WMH, there was always an association with greater WMH burden and worse executive function.

CONCLUSION

This study has looked at the relationship between cognition, WMH, and ABeta. We found that age was significantly related to cognitive decline, WMH and ABeta burden may be interacting with each other to cause worse episodic memory, and education may be modulating the effects of WMH on executive function.

Future studies on these pathologies and cognition can continue to investigate the possibility of spatially different WMH having differential effects on cognition. They can also look at multiple pathologies predicting cognition, especially if they have great statistical power. Additionally, they can employ recent imaging methods, such as diffusion tensor imaging (DTI)—an MRI method shown to be a more sensitive measure of age-related white matter changes than WMH (28). Furthermore, there are certain pathologies, like microinfarcts (32), that cannot be visualized and contribute to cognitive deficits in aging; these pathologies can also be investigated along with pathologies visible in imaging. Lastly, longitudinal studies can be done to see the progression of these pathologies in relation to cognition.

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