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White matter reference region in PET studies of ^{11}C-Pittsburgh Compound B uptake: effects of age and amyloid-β deposition

Short running Title: PiB uptake in white matter

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ABSTRACT

Amyloid-β (Aβ) deposition as seen on positron emission tomography (PET) using an Aβ binding agent is a critical diagnostic biomarker for Alzheimer's disease (AD). Some reports suggest using white matter (WM) as a reference region for quantification of serial Aβ PET studies; however, nonspecific WM retention in Aβ PET in people with dementia or in cognitively unimpaired (CU) has been widely reported and is poorly understood. **Methods:** To investigate the suitability of WM as a reference region and the factors affecting WM ^{11}C-Pittsburgh Compound B (PiB) uptake variability, we conducted a retrospective study on two large data sets: 1) a longitudinal study of participants (n=577) who were CU, had mild cognitive impairment (MCI), or had dementia likely due to AD (ADD); and 2) a cross-sectional study of single-scan PET imaging in CU subjects (n=1349). In the longitudinal study, annual changes in WM PiB uptake were assessed, and in the cross-sectional study, WM PiB uptake was assessed relative to subject age. **Results:** Overall, we found that WM PiB uptake showed age-related increases which varied with the WM regions selected. Further, variable annual WM PiB uptake changes were seen with different GM PiB baseline uptake levels. **Conclusion:** WM binding increases with age and varies with GM PiB. These correlations should be considered when using WM for normalization in PiB PET studies. The cerebellar crus1+crus2 showed no increase with age and cerebellar GM+WM showed minimal increase, supporting their use as reference regions for cross-sectional studies comparing wide age spans. In longitudinal studies, the increase in WM uptake may be minimal in the short-term and thus using WM as a reference region in these studies seems reasonable. However, as participants age, the findings may be affected by changes in WM uptake. Changes in WM PiB uptake may relate to disease progression, warranting examination of the causes of WM PiB uptake.

Key Words: AD, ^{11}C-PiB, white matter; amyloid-β, PET

INTRODUCTION

Amyloid-β (Aβ) plaque accumulation in the brain as measured by positron emission tomography (PET) has become a critical diagnostic biomarker for Alzheimer's disease (AD) (*1*). Given its implications for prognosis and potential early intervention (*2*), reliable quantitative measurement of Aβ deposition using PET has been an important topic of discussion (*3-5*).

For inter- and intra-subject semi-quantitative Aβ PET imaging, obtaining the Standardized Uptake Value Ratio (SUVR) of cortical areas relative to a reference region was initially shown to closely mimic the Logan graphical distribution volume ratio shown in a ^{11}C-Pittsburgh Compound B (PiB) Aβ PET study (*6*). For this reason, most large studies of Aβ deposition have used delayed imaging and have used the cerebellum as a reference region for normalization (*7*).

Recently, several longitudinal Aβ PET studies have suggested including white matter (WM) regions as reference areas for SUVR (*5,8-10*). Longitudinal ^{18}F-Florbetapir Aβ PET studies report that as a reference region, WM has stronger correlations with cerebrospinal fluid $A\beta_{1-42}$ level and has less variability than the cerebellum (*8,10*). In addition, a cross-sectional ^{18}F-AV45 Aβ PET study showed that SUVR using the entire subcortical WM as a reference region had a higher correlation with distribution volume ratio than did SUVR of the cerebellum (*11*). In a PiB PET study of AD patients at three different points in time, we showed that supratentorial WM with the cerebellum included was the most reliable reference region in representing disease progression over time (*5*).

The benefit of WM over the cerebellum as a reference region is that there is a larger region over which to average the signal, potentially leading to less noise. WM measurements may also be more resistant to small degrees of misregistration during image quantification (*12*). In addition, the cerebellar signal is collected at the edge of the scanner field of view where sensitivity is lower (*8,9*).

A pervasive finding in Aβ PET studies is the substantial retention of the tracer in the WM of both subjects with dementia patients and healthy controls (*13*). WM uptake has been observed with every Aβ PET imaging agent to a greater or lesser degree, independent of the presence of Aβ deposition (*14-17*). The mechanism of this binding is poorly understood, and its non-specificity is attributed mainly to its non-displaceable and non-saturable characteristics seen in several PiB PET studies (*7,18,19*).

Generally, WM uptake has not been a point of contention in disease categorization (*13*). However, because WM is being considered as a reference region, it is important to understand factors that affect WM uptake so as to assess its suitability for longitudinal studies for disease progression assessment and therapy evaluation studies where changes in individual amyloid levels may be small and more easily impacted by small changes in normalization region effects.

To investigate potential variables affecting WM PiB uptake, we conducted a retrospective study evaluating the WM PiB binding in two large population data sets: 1) a longitudinal study of serial PiB PET uptake in cognitively unimpaired (CU), MCI, and dementia likely due to AD (ADD) groups; and 2) a cross-sectional study of single scan PiB imaging vs age in a CU group. Further, we evaluated annual WM PiB uptake increases as they related to changes in gray matter (GM) uptake to assess its relationship to disease progression. These findings are discussed relative to the implications and potential confounds in using WM SUVR normalization and categorizing levels of amyloid deposition.

MATERIALS AND METHODS

Participants

Participants were drawn from the Mayo Clinic Study of Aging epidemiological study (*20*). The study was approved by Mayo Clinic and Olmstead Medical Center

Institutional Review Boards and all subjects signed an informed consent (Clinical trial #NCT00950430). Two large population data sets were extracted from this study: 1) a longitudinal data (n=577); and 2) a cross-sectional data (n=1349) in which PiB imaging was collected from 2006 to 2015, as described in Table 1. The longitudinal data consisted of subjects who were categorized as CU, MCI, or ADD. ADD defined as being clinical diagnosis of Alzheimer's disease without biomarker verification. Each clinical classification was further divided into Aβ negative (A-) and Aβ positive (A+) based on the global GM PiB SUVR cut-off value of 1.4 SUVR (*21*). For the present analysis, we re-labeled the study groups into A- (CU-, MCI-, and ADD-), and A+ (CU+, MCI+, and ADD+).

Imaging Method

See supplemental information for detailed description.

Image and Statistical Analysis

Magnetic resonance imaging (MRI) T1 and PiB scans were coregistered using SPM12 with 6 degrees of freedom. Resampling between MRI and PET resolutions was performed using ANTs software tools with 3rd order B-Spline interpolation. Two-compartment partial volume correction (PVC) was applied for cerebrospinal fluid correction. Atlas region of interest (ROI) were resampled to subject spaces also using ANTs with nearest-neighbor interpolation (*5*).

Two representative ROIs within WM were used for analysis as shown in Fig. 1: periventricular and subcortical (*22*). These ROIs were subdivided to frontal, occipital, parietal, and temporal areas based on the anatomical lobe discrimination of the STAND400 brain template (*23*). Additional ROIs were used for comparison as well, including corpus callosum (anterior and posterior), brainstem, cerebellum WM and

cerebellum WM+GM, as well as eroded subcortical WM and composite (voxel-weighted median average of cerebellum WM+GM, brainstem/pons and eroded subcortical WM), which was designed to emulate regions from the paper by Landau et. al. (*8*). The global GM PiB ROI included GM of parietal, cingulate precuneus, prefrontal, orbitofrontal, temporal, and anterior cingulate regions (*24*). If not stated otherwise, the cerebellar crus1+crus2 voxel signal were used as the normalization region (denominator) for all SUVRs. In addition to and separate from the SUVR, we also assessed the standardized uptake value (SUV) calculated from dose and weight normalization to describe the age associations of the ROIs. See supplemental information for detailed description of the statistical analysis.

RESULTS

Annual WM PiB SUVR % change in longitudinal data

The estimated annual WM PiB SUVR % change using a linear mixed effects model in the longitudinal data is shown in Figure 2 and Supplemental Table 1. Figure 2A shows annual WM PiB SUVR % increase in CU, MCI, and ADD. The annual global GM PiB SUVR showed a 1.9% increase. The subcortical WM area showed the highest annual % increase among the WM ROIs ranging from 1.2 - 1.5%. The periventricular WM area showed annual increase ranging from 0.4 - 1.1%. The eroded subcortical WM and composite had a similar range as periventricular, having 0.9% and 0.6% annual increase respectively. The corpus callosum (anterior and posterior), brainstem, and cerebellum WM annual increase ranged from 0.3 - 0.9%, with cerebellum GM+WM showing the lowest annual increase of 0.2%. The slope is significantly different from 0 at the 0.05 level, if the 95% CI excludes zero; therefore, all WM ROIs showed significant annual increases in SUVR % change.

While both A- and A+ groups showed annual WM PiB SUVR % increase, the increase rate varied between A- and A+ for each of the ROIs (Fig. 2B). The A+ group showed faster annual increase for the global GM (as would be expected from the cortical amyloid accumulation signal bleed-in) and subcortical WM (likely a bleed in effect), while the A- group showed faster annual increase for the periventricular WM, corpus callosum, brainstem, cerebellum WM and eroded subcortical WM. Cerebellum GM+WM showed no rate difference between A- and A+.

Age-dependent WM uptake change in cross-sectional CU data

To confirm whether the annual WM uptake increase is also observable in cross-sectional data, we selected a CU group and compared the WM PiB uptake related to age using different reference regions (Fig. 3 and Supplemental Table 2). We confirmed an age-related increase in the periventricular WM SUVR (slope=0.03, rho=0.19), subcortical WM SUVR (slope = 0.07, rho = 0.37), and cerebellum GM+WM (slope=0.01, rho=0.34) when normalized to cerebellar crus (Fig. 3A). Changing the reference region to cerebellum GM+WM showed a similar trend (Fig. 3B) with a trend towards a smaller slope in supratentorial WM; periventricular WM SUVR (slope=0.02, rho=0.12) and subcortical WM SUVR (slope=0.05, rho=0.33). The cerebellum crus1+crus2 GM slope (slope=-0.01, rho=-0.31) became slightly negative with the inclusion of the cerebellar WM in the denominator. In addition to and separate from the SUVR, we assessed SUV with age as an alternate normalization method. The SUV of perventricular (slope=0.04, rho=0.17), subcortical (slope=0.07, rho=0.28) and cerebellum crus1+crus2 (slope=0.01, rho=0.06) regions showed similar slopes to SUVR normalization (Fig. 3C and Supplemental Table 2). Finally, we evaluated the cerebellar reference region atrophy effect by applying 3-compartment PVC to the cerebellar GM reference region (atrophy corrected) and confirmed the WM age trend was still present and that the slope was

similar to that of the 2-compartment PVC results (atrophy uncorrected) (Supplemental Fig. 1).

Comparing annual WM PiB SUVR change with annual GM PiB SUVR change

We saw a correlation between annual WM PiB SUVR change and annual global GM PiB SUVR change in the longitudinal data shown in Figure 4. Periventricular WM showed a correlation between annual WM and global GM PiB SUVR change (A-; slope=1.21, $p<0.001$ and A+; slope=0.69, $p<0.001$). Subcortical WM showed correlation between annual WM and global GM PiB SUVR change (A-; slope=1.07, $p<0.001$ and A+; slope=0.76, $p<0.001$). Cerebellum GM+WM showed low correlation with the global GM PiB SUVR change (A-; slope=0.16, $p<0.001$ and A+; slope=0.08, $p<0.001$).

Comparing annual WM PiB SUVR change with GM PiB SUVR baseline values

Figure 5 shows the relationship between the annual WM uptake change and baseline GM PiB in the longitudinal data. Depending on the global GM PiB SUVR baseline there are different rates in the annual WM PiB SUVR change. In A+ participants, both ROIs (periventricular WM and subcortical WM) showed a trend of greatest change in the WM PiB annual increase at 1.9 - 2.1 GM PiB SUVR baseline values and the rate showed decrease at the higher GM PiB SUVR baseline levels (~2.7>). At the lowest global GM PiB SUVR baseline values (representing the A- group (blue circles)), increases of WM PiB annual change for both periventricular and subcortical WM ROIs were the highest. The relationship between within-subject annual SUVR change and baseline age had no distanced effect, implying the annual increase rate itself shows minimum age related effect (Supplementary Fig. 2).

DISCUSSION

The causes of WM PiB uptake in Aβ PET imaging remain largely unknown, but its effects are important to understand when WM is used as a normalization region for quantification of cortical Aβ tracer binding. Changes over time in WM uptake could affect cortical GM SUVR results. In this study we found that WM PiB uptake increases with age and varies with GM Aβ deposition and with the area of WM sampled.

The simplest explanation for some variations in signal in subcortical WM PiB would be spillover of the GM Aβ signal into subcortical WM as this region includes the area of WM closest to GM. The fact that the subcortical WM had the highest annual increase and a steeper age-dependent increase compared to periventricular WM would support this, as would the fact that the A+ group had a greater annual uptake increase in subcortical WM than the A- group. For this reason, investigators using WM as a reference region tend to avoid selecting WM regions close to GM (*5,8,9*). Our results support this approach in that we observed a lower level of annual PiB uptake increase in periventricular or eroded subcortical WM ROIs in both longitudinal and cross-sectional samples.

Nevertheless, annual WM PiB increases are seen in periventricular WM and other WM regions such as corpus callosum, cerebellum WM and also in eroded subcortical WM. These values are moderate (0.4 - 1.1%) compared to the annual GM increase (1.9%), but are statistically significant. These increases are found in both A- and A+ population and appear in WM areas at a great enough distance from GM that cannot be explained by a GM spillover effect.

The relatively slower kinetics of WM compared to GM, which results in a slower clearance rate (*13,18*), may explain WM PiB uptake. This could also explain the age related increase in WM PiB binding, because cerebral perfusion on average declines with age (*25*), thus slowing WM clearance of the tracer in old vs young. Blood flow has

been reported to be slower in WM than GM (*26,27*). Delays in delivery (*28*) and slower clearance of the tracers (*29*) in WM have been previously described in molecular imaging studies. For example, PiB clearance was reported to be slower in WM compared to GM in AD and CU subjects (*18*).

Studies using MRI to measure white matter hyperintensity has proposed that cerebral small-vessel disease can lead to reduced Aβ clearance and to increased cerebral GM PiB in AD (*30,31*). However, white matter hyperintensity measurements in studies of WM PiB uptake have found reduction in binding (*32*) and that WM lesions can reduce WM PiB binding in cognitively impaired (*33*) as well as in multiple sclerosis patients (*34*).

Another possible explanation of WM uptake may be the lipophilic nature of Aβ PET tracers that may enhance binding of the high lipid content of WM (*7*). This possibility is further supported by histopathologic studies (*35*). However, given the generally agreed upon concept of age-related myelin loss, our age-related WM PiB uptake increase is not explained by this theory. These data are inconsistent with our findings and our work suggests that alternate mechanisms must be at play to explain the increased uptake of WM PiB with age.

One of the findings in our study was that the annual increase in WM PiB uptake correlated with annual increases in GM PiB uptake in WM regions even when spill over is an unlikely component (periventricular WM). The trends in GM change with age were previously reported in a comparison of annual increase in GM PiB uptake with GM baseline SUVR (*21*), but have not been described previously for WM annual change.

Previously, PiB was also shown to bind a wide range of fibrillar Aβ pathology, including diffuse plaques (DP) and cerebrovascular amyloid angiopathy, which affects both GM and WM (*36*). DP are common in the brains of elderly individuals and can be

seen in relatively large numbers in the absence of any associated evidence of cognitive impairment and could be a WM component to PiB binding in some (*37-39*).

The implications of the present findings are that the use of WM normalization could affect the characterization of A+ or A- subjects and the quantification of Aβ accumulation over time. The cerebellar crus1+crus2 showed no increase with age and cerebellar GM+WM showed minimal increase, supporting their use as reference regions for cross-sectional studies comparing wide age spans. Relative to longitudinal studies, the increase in WM uptake over short-term may be minimal, but as the longitudinal observation continues for a longer time frame, the results may be affected by changes in WM uptake. For example, the WM annual increase maximized within A+ individuals at a GM baseline SUVR range of 1.9 - 2.1. The highest WM increase in the entire population was seen when global GM PiB SUVR values were the lowest in A- individuals. In contrast, individuals with higher GM PiB SUVR baseline levels (~2.7>) showed a trend of annual WM decrease. These data demonstrate that the annual WM change rate varies based on population selection with different amyloid status and different age ranges.

These observations may also help to reconcile findings related to seeing better stabilities in longitudinal Aβ PET studies when using WM normalization (*5,8,9*), where the reports describe five years or less of serial PET images. In a short-term longitudinal study (<5 years), the improved noise characteristics of a large WM normalization region would add stability and hence reliability, therefore may be beneficial (i.e., a small WM rate change in those with a GM SUVR range of 2.1 - 2.7 would add to stability). It could also be the case that small GM Aβ accumulation could be “masked” by WM increase leading to the impression of improved reliability, especially when reliability is compared against cognitive change (i.e., participants with no or minimal cognitive change could still have Aβ accumulation).

For longer-term longitudinal study, age-related increases in WM will ultimately result in underestimation of longitudinal GM increases in most populations (i.e., overly conservative estimation). Possible approaches suggested by these data for longitudinal data include using deep WM for short-term datasets and/or age correction in the WM region. More longitudinal data and additional analyses would be needed to test the utility of age correction for reference regions.

CONCLUSION

In summary, we found that WM PiB uptake has notable variability among those who are cognitively unimpaired (with and without evidence of Aβ deposition) and those diagnosed with either MCI or ADD. WM PiB uptake increases with age and is seen in both cross-sectional and serial evaluations. These findings are important relative to the quantitative and visual interpretation of PiB PET scans. The variability of WM PiB uptake may hamper accurate characterization. Increases in WM PiB uptake over time appear to occur in association with increasing global GM PiB SUVR, even in WM ROIs far from GM. Eroded subcortical WM and composite regions (cerebellum WM+GM, brainstem/pons, and eroded subcortical WM) are an important consideration to reduce but not eliminate WM PiB uptake effects. This study was specific to Aβ PET imaging using PiB, and thus, future investigations should address the characteristics of other Aβ tracers.

DISCLOSURES

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Schering Pharma, Piramal Imaging Inc, and receives research support from GE Healthcare, Siemens Molecular Imaging, and AVID Radiopharmaceuticals. Dr. Knopman serves on a Data Safety Monitoring Board for the DIAN study, and is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the Alzheimer's Disease Cooperative Study. Dr. Petersen serves on scientific advisory boards for Pfizer, Inc., Janssen Alzheimer Immunotherapy, Elan Pharmaceuticals, and GE Healthcare. No other potential conflict of interest relevant to this article was reported.

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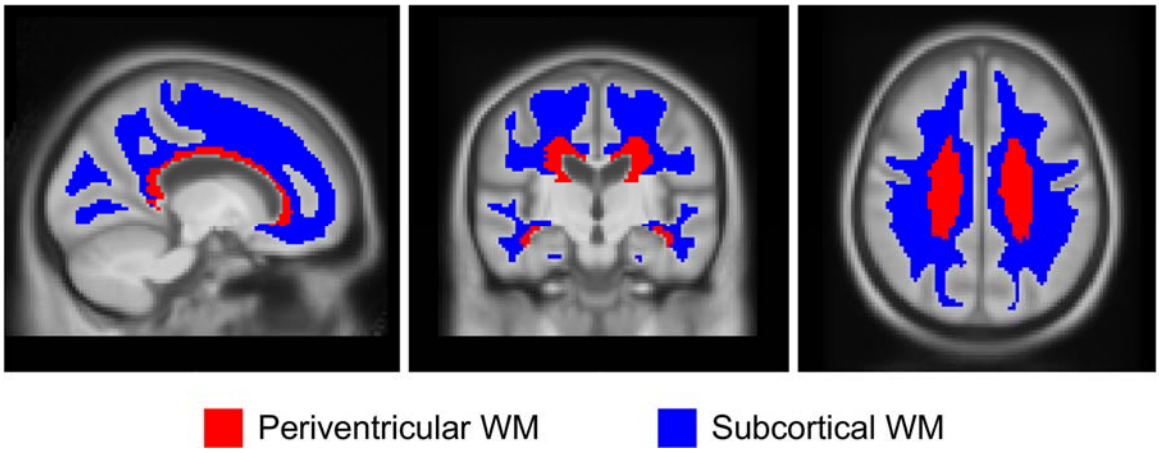


Figure 1. **Regions of interests (ROIs) in the WM.** Two ROIs, periventricular and subcortical, within the WM reference regions are shown.

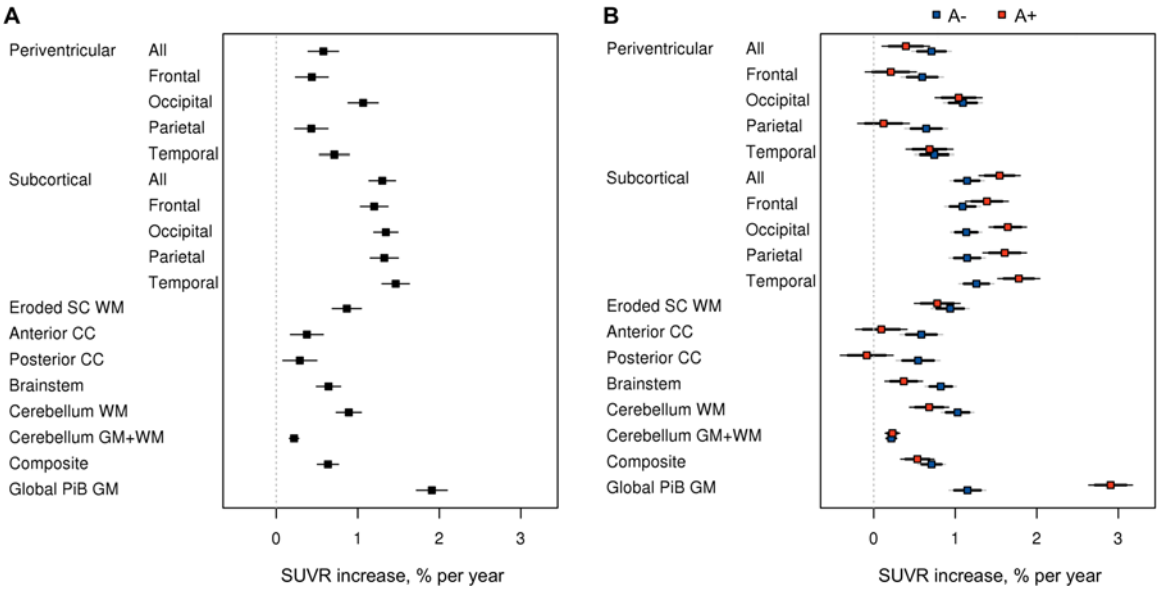


Figure 2. Annual WM PiB SUVR % change in longitudinal data. A. Regional increase in WM PiB uptake. B. Difference in WM accumulation (A- vs A+).

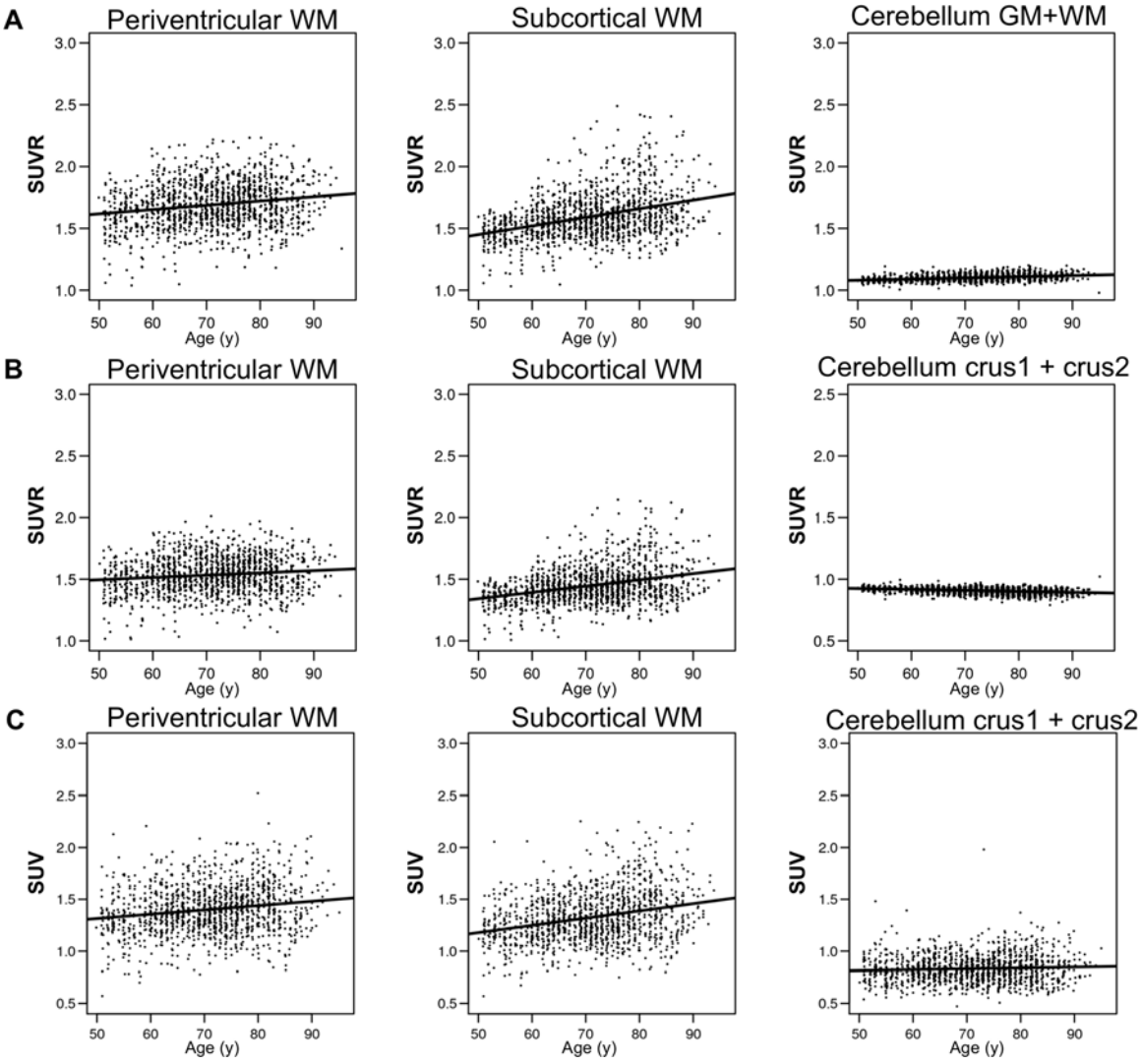


Figure 3. Age-dependent WM uptake change in cross-sectional CU data (SUVR and SUV). A. Age and SUVR scatterplot with linear regression using cerebellum crus1+crus2 GM as a reference region. B. Age and SUVR scatterplot with linear regression using cerebellum GM+WM as a reference region. C. Age and SUV scatterplot with linear regression.

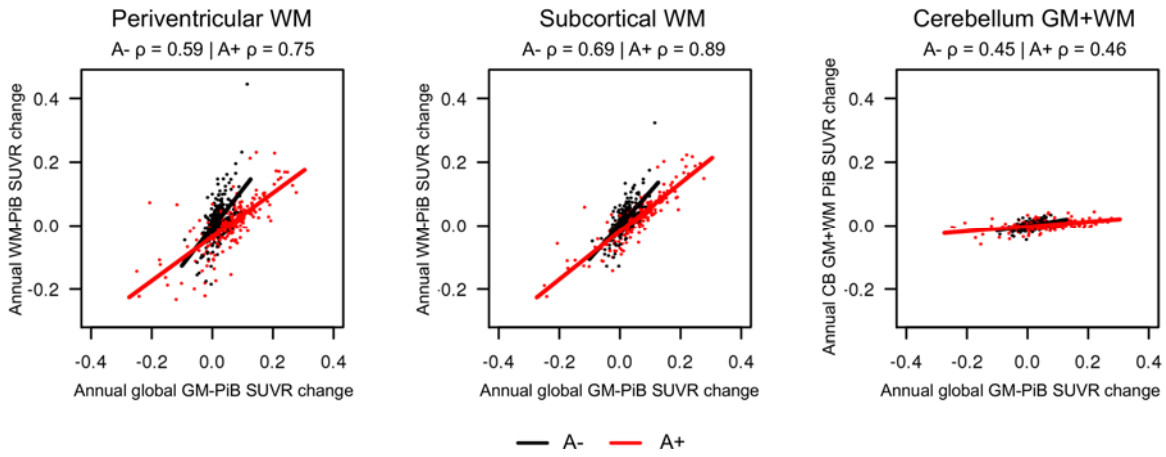


Figure 4. Comparison of annual WM PiB SUVR change with annual GM PiB SUVR change. Scatterplot between annual change in global GM PiB SUVR and annual change in regional WM PiB SUVR by Aβ status with linear regression line among A- (black) and A+ (red).

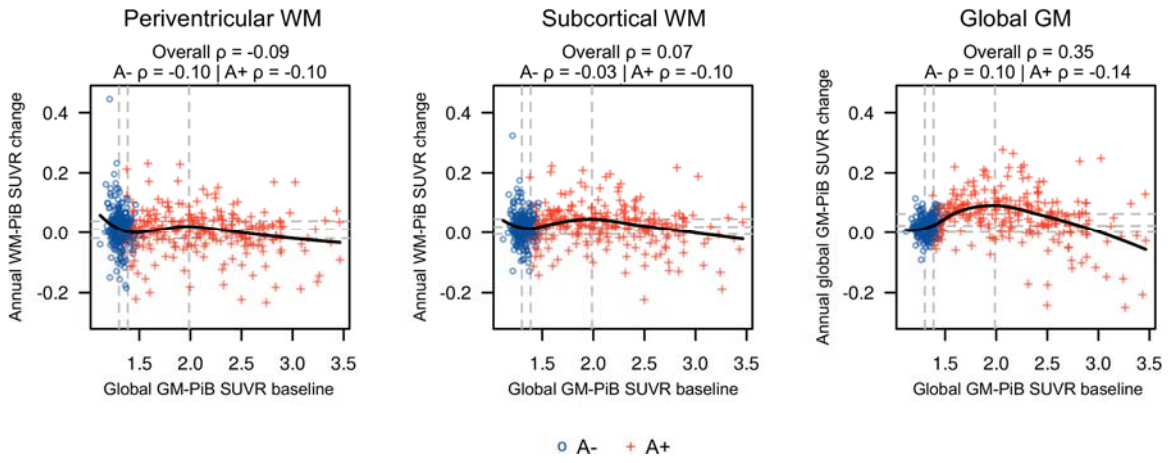


Figure 5. Comparison of annual WM uptake change and baseline global GM PiB in the longitudinal data. Spearman's correlations of the Loess curve are shown at the top of each panel overall subjects, among A- (blue) and A+ (red).

Table 1. **Participants Demographics.**

	Longitudinal data			Cross-sectional data
Variable	CU	MCI	ADD	CU
Number of subjects	421	116	40	1349
Age, years				
Mean (SD)	77 (7)	75 (9)	69 (11)	71 (10)
Range	51 to 94	54 to 90	50 to 91	50 to 95
Male, no. (%)	256 (61%)	80 (69%)	24 (60%)	706 (52%)
Education, years, mean (SD)	15 (3)	15 (4)	15 (2)	15 (3)
Abnormal PiB, no. (%)	149 (35%)	73 (63%)	37 (92%)	429 (32%)
Global GM PiB SUVR (cere, GM+WM, PVC), mean (SD)	1.5 (0.34)	1.8 (0.53)	2.2 (0.41)	1.43 (0.31)
APOE ε4 carrier, no. (%)	115 (27%)	53 (46%)	24 (60%)	361 (27%)
Scans per person				
1				1349 (100%)
2	300 (71%)	79 (68%)	26 (65%)	
3	101 (24%)	27 (23%)	7 (18%)	
4	17 (4%)	5 (4%)	5 (12%)	
5	3 (1%)	6 (5%)	2 (5%)	
Time between first and last scan, years				
Mean (SD)	2.8 (1.2)	2.1 (1.1)	1.9 (1.3)	

Abbreviation: SD, standard deviation

White matter reference region in PET studies of ^{11}C-Pittsburgh Compound B uptake: effects of age and amyloid-β deposition

SUPPLEMENTAL INFORMATION

MATERIALS AND METHODS

Participants

All subjects were categorized by neurologists, neuropsychologists, and study nurses through our consensus diagnosis using quantitative data from a brief mental status examination, nine neuropsychological tests, and the Clinical Dementia Rating Scale (*1*).

Imaging Methods

^{11}C-PiB PET image was performed under Food and Drug Administration Investigational New Drug approval (#77924) and synthesized on-site at the Mayo Clinic Cyclotron Facility. PiB PET/CT studies were performed as previously described in Lowe, et al. (*2*), using GE scanners (Discovery 690XT and Discovery RX; GE Healthcare, Waukesha, WI). Standard iterative reconstruction (256 matrix, 300 mm field of view, 1.17 mm 1.17 mm 3.27 mm voxel size) with corrections for attenuation, scatter, random coincidences and radioactive decay were applied as well as a 5 mm Gaussian post filter as previously described (*3*). T1-weighted magnetic resonance imaging (MRI) scans were acquired on 3 T scanners (Discovery MR750, Signa HDx, Signa HDxt, and Signa Excite, GE Healthcare, Waukesha, WI) for region localization and masking, and for partial volume correction (PVC).

Image and Statistical Analysis

ROI voxels that were deemed primarily non-tissue according to the T1 MRI segmentations were omitted. Median values were computed for each of these regions and averaged, weighted by region size, to produce the composite median value.

All analyses were conducted using R statistical software version 3.3.1 (*4*). Mixed-effects linear regression models using age at baseline as the time scale were used to estimate change in WM SUVR over time in the longitudinal dataset. Random subject-specific intercepts and slopes were included. We fit separate models for each region. To evaluate the effect of Aβ, a second linear mixed effects model was fit including abnormal PiB and an abnormal PiB by time interaction. Together these fixed effects allowed WM SUVR to change with possibly different rates of decline by A- or A+ PiB status. All outcome measures were log-transformed to reduce skewness and to allow for interpretation of slope estimates as approximate annual percent change (*5*). This procedure also enables the comparison of several different regions across a similar scale. We modeled the log of SUVR to estimate rate of accumulation expressed as percentage per year.

The age relationship to WM-uptake was analyzed in a cross-sectional sample of CU subjects by fitting a linear regression model between age and SUV (or SUVR). To test for evidence of age-related differences between groups, we summarized the p-values from an age by abnormal PiB interaction.

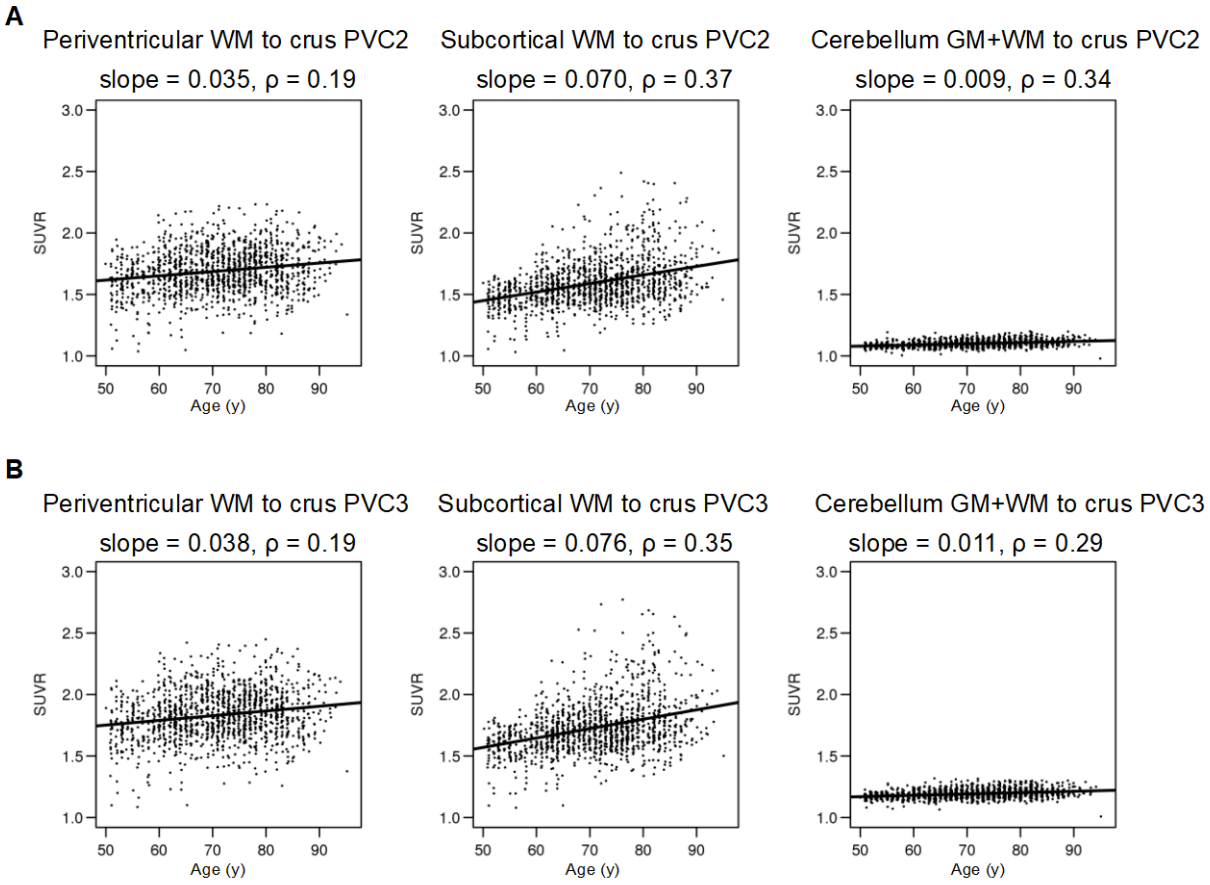
We compared annual change in global GM-PiB SUVR and annual change in WM-PiB SUVR using a 2-stage approach. First, we applied linear regression to examine the relationship between age and SUVR for each subject. The slope of the linear regression represents an estimate of the annual SUVR change for a given subject. Given the varying number of scans per subject, this technique has the advantage of allowing all scan data for a given subject to be used in the estimation of change. Change

was estimated separately for global GM-PiB SUVR and WM-PiB SUVR, and the two measures were compared. To allow for differing rates of accumulation, we conducted linear regression between the two change measures by Aβ status, and the strength of association was determined by Pearson's correlation coefficient. Additionally, to compare annual WM-PiB SUVR change and GM-PiB SUVR at baseline, we calculated Spearman's correlations and fit local polynomial regression (loess) models to allow for nonlinear trends.

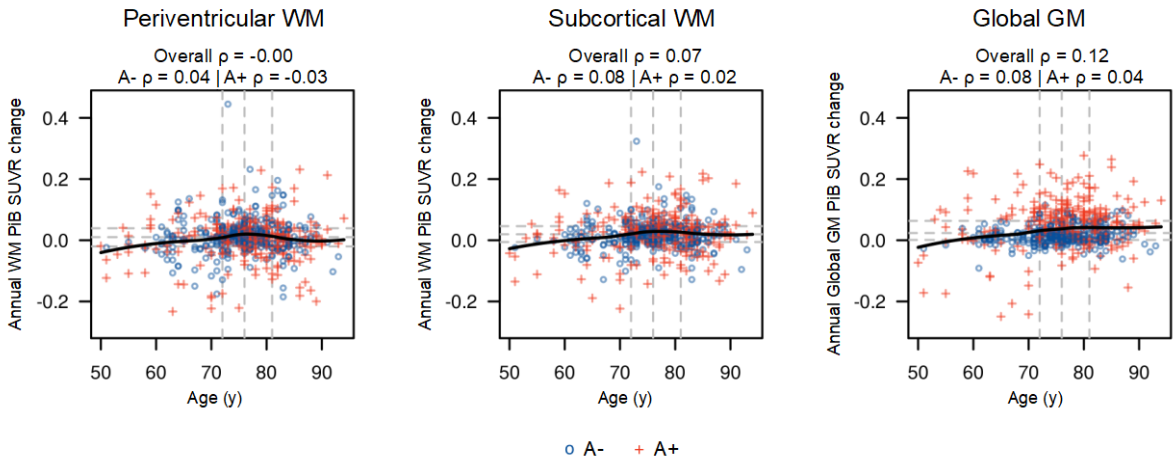
DISCUSSION

We used two-compartmental PVC correction in this study, correcting only for cerebrospinal fluid (*6*). It would be possible to use more sophisticated PVC methods, such as GTM (*7*), in an attempt to measure the WM signal, but GTM PVC assumes that individual regions each have homogeneous uptake, which is a questionable assumption for PiB in WM. Instead, in our analysis, we opted to include eroded subcortical WM ROI and other variants which consist of voxels that were sufficiently far from the cortex so as to ensure that bleed-in of the cortical signal was not a factor in the measured signal.

RESULTS



Supplemental Figure 1. Confirming cerebellum reference region atrophy effect. Assessing cerebellum reference region atrophy effect by applying PVC3 on the cerebellum GM compared to PVC2. A WM age trend is present and the slop is similar between atrophy uncorrected (A, using PVC2) and corrected (B, using PV3), lending support that the age effect is not due to age-related cerebellar GM atrophy effect.



Supplemental Figure 2. The relationship between within-subject annual change in SUVR and baseline age. The relationship between within-subject annual SUVR change and baseline age had no distanced effect, implying the annual increase rate itself shows minimum age related effect; PV WM (rho = -0.00), SC WM (rho =0.07), and global GM (rho = 0.12).

Supplemental Table 1. Annual WMPiB SUVR % change in longitudinal data. Mixed effects models on SUVR were fit within each region adjusting for time and baseline age with subject specific intercept and slope. Log transformation on SUVR allows the predictions to be interpreted as approximate annual percentage change. We summarize the model-based mean difference between A- and A+ SUVR (Positive values indicate A+ group increasing faster).

		SUVR increase		**A- vs A+**	
Region		percent per year (95% CI)	*P*-value	percent per year (95% CI)	*P*-value
Periventricular	All	0.6 (0.4, 0.8)	<0.001	-0.3 (-0.7, 0.1)	0.10
	Frontal	0.4 (0.2, 0.6)	<0.001	-0.4 (-0.8, 0.0)	0.06
	Occipital	1.1 (0.9, 1.3)	<0.001	-0.1 (-0.4, 0.3)	0.78
	Parietal	0.4 (0.2, 0.6)	<0.001	-0.5 (-0.9, -0.1)	0.01
	Temporal	0.7 (0.5, 0.9)	<0.001	-0.3 (-0.6, 0.1)	0.76
Subcortical	All	1.3 (1.1, 1.5)	<0.001	0.4 (0.1, 0.7)	0.02
	Frontal	1.2 (1.0, 1.4)	<0.001	0.3 (-0.0, 0.6)	0.09
	Occipital	1.3 (1.2, 1.5)	<0.001	0.5 (0.2, 0.8)	<0.001
	Parietal	1.3 (1.2, 1.5)	<0.001	0.5 (0.1, 0.8)	0.009
	Temporal	1.5 (1.3, 1.6)	<0.001	0.5 (0.2, 0.9)	0.002
Eroded SC		0.9 (0.7, 1.0)	<0.001	-0.2 (-0.5, 0.2)	0.39
Anterior CC		0.4 (0.2, 0.6)	<0.001	-0.5 (-0.9, -0.1)	0.02
Posterior CC		0.3 (0.1, 0.5)	0.007	-0.6 (-1.1, -0.2)	0.003
Brainstem		0.6 (0.5, 0.8)	<0.001	-0.5 (-0.8, -0.2)	0.003
Cerebellum WM		0.9 (0.7, 1.0)	<0.001	-0.3 (-0.7, -0.0)	0.03
Cerebellum GM+WM		0.2 (0.2, 0.3)	<0.001	0 (-0.1, 0.1)	0.82
Composite		0.6 (0.5, 0.8)	<0.001	-0.2 (-0.4, 0.1)	0.20
Global GM-PiB		1.9 (1.7, 2.1)	<0.001	1.8 (1.4, 2.1)	<0.001

Abbreviation: A-, Aβ negative; A+, Aβ positive; CC, corpus callosum; CI, confidence interval; GM, gray matter; PiB, ^{11}C-Pittsburgh Compound B; SC, subcortical; SUVR, Standardized uptake value ratio; WM, white matter

Supplemental Table 2. SUVR and SUV linear regression slopes for 10-years in CU cross-sectional data. Summary of slopes of linear regression model on SUVR and SUV adjusting for age and age by abnormal PiB interaction in cross-sectional data are shown with the slope for a 10-year increase in age among CU.

	SUVR		SUV	
Region	slope	rho	slope	rho
Periventricular	0.03	0.19**	0.04	0.17**
PV frontal	0.04	0.19**	0.04	0.17**
PV occipital	0.05	0.30**	0.05	0.23**
PV partietal	0.03	0.16**	0.04	0.15**
PV temporal	0.03	0.20**	0.04	0.17**
Subcortical	0.07	0.37**	0.07	0.28**
SC frontal	0.07	0.37**	0.07	0.29**
SC occipital	0.05	0.35**	0.06	0.26**
SC parietal	0.07	0.36**	0.07	0.28**
SC temporal	0.07	0.36**	0.07	0.28**
Eroded SC WM	0.05	0.27**	0.05	0.22**
Anterior CC	0.05	0.25**	0.05	0.21**
Posterior CC	0.03	0.17**	0.04	0.16**
Brainstem	0.04	0.26**	0.05	0.18**
Cerebellum WM	0.03	0.19**	0.03	0.14**
Cerebellum GM+WM	0.01	0.34**	0.02	0.12**
Cerebellum crus1+crus2 GM	NA	NA	0.01	0.06*
Composite	0.02	0.23**	0.03	0.16**
Global GM-PiB	0.14	0.38**	0.12	0.35**

Abbreviation: CC, corpus callosum; CU, cognitively unimpaired; GM, gray matter; PiB, ^{11}C-Pittsburgh Compound B; PV, periventricular; SC, subcortical; SUV, standardized uptake value; SUVR, standardized uptake value ratio; WM, white matter.

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