

## Comparison of $^{11}\text{C}$ -Pittsburgh compound-B and $^{18}\text{F}$ -Flutemetamol

### White Matter Binding in PET

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**ABSTRACT**

PET imaging with  $\beta$ -amyloid ligands is emerging as a molecular imaging technique targeting white matter integrity and demyelination.  $\beta$ -amyloid PET ligands such as “ $^{11}\text{C}$ -Pittsburgh compound-B” ( $^{11}\text{C}$ -PiB) have been considered for quantitative measurement of myelin content changes in multiple sclerosis (MS), but  $^{11}\text{C}$ -PiB is not commercially available given its short half-life. A “ $^{18}\text{F}$ -PET” ligand such as flutemetamol with a longer half-life may be an alternative, but its ability to differentiate white matter hyperintensities (WMH) from normal appearing white matter (NAWM) and its relationship with age remains to be investigated.

**Methods:**

Cognitively unimpaired (CU) older and younger adults (N=61) were recruited from the community responding to a study advertisement for  $\beta$ -amyloid PET. Participants prospectively underwent MRI,  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol PET scans. MRI-FLAIR images were segmented into WMH and NAWM and registered to the T1-weighted MRI.  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol PET images were also registered to the T1-weighted image MRI.  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol standard uptake value ratios (SUVrs) from the WMH and NAWM were calculated using cerebellar crus uptake as a reference for both  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol.

**Results:**

Median age was 38 years (range 30-48) in younger adults and 67 years (range 61-83) in older adults. WMH and NAWM SUVrs were higher with  $^{18}\text{F}$ -Flutemetamol than  $^{11}\text{C}$ -PiB both in older ( $p<0.001$ ) and in younger ( $p<0.001$ ) CU adults.  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol SUVrs were higher in older compared to younger CU adults in both WMH ( $p<0.001$ ) and in NAWM ( $p<0.001$ ).  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol SUVrs were higher in NAWM compared to WMH in both older ( $p<0.001$ ) and in younger ( $p<0.001$ ) CU

adults. There was no apparent difference between  $^{11}\text{C}$ -PiB versus  $^{18}\text{F}$ -Flutemetamol SUVrs in differentiating WMH from NAWM in older and in younger adults.

**Conclusion:**

$^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol show a similar topographical pattern of uptake in white matter with a similar association with age in WMH and NAWM.  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol can also effectively distinguish between WMH and NAWM. However, given its longer half-life, commercial availability, and higher binding potential,  $^{18}\text{F}$ -Flutemetamol can be an alternative to  $^{11}\text{C}$ -PiB in molecular imaging studies specifically targeting MS to evaluate white matter integrity.

**Key words:** PET, white matter hyperintensity, normal appearing white matter,  $^{11}\text{C}$ -Pittsburgh compound-B,  $^{18}\text{F}$ -Flutemetamol

## Introduction

PET imaging with  $\beta$ -amyloid ligands is largely used in the field of dementia clinically, but it is also emerging as a molecular imaging technique targeting various aspects in multiple sclerosis (MS) including demyelination (1-10), which correlate well with clinical disability (11) and cognition (7,9).

Although advanced MRI techniques such as diffusion tensor imaging are widely used in evaluating white matter (WM) integrity, they are not specific measures of myelin. Over the last decade, PET ligands have been utilized to study myelin kinetics (1-10,12). PET ligands are also being used to understand the underlying mechanisms such as neuroinflammation, neurodegeneration, microglia activation and myelin kinetics (12,13). PET ligands are also explored as a potential outcome measure in clinical trials (12). This would especially be important for future remyelination trials potentially adding value to MRI imaging alone. Among these ligands, “ $^{11}\text{C}$ -Pittsburgh compound-B” ( $^{11}\text{C}$ -PiB) seems to be a sensitive and reliable imaging marker in measuring WM integrity and potentially myelin integrity both in animal and human studies (2,3,5-8).

$^{11}\text{C}$ -PiB uptake in the WM correlates with well-established WM integrity imaging markers such as diffusion tensor imaging (8) as well as cognitive function (7-9). Consistent with that, WM  $^{11}\text{C}$ -PiB uptake is lower in white matter hyperintensities (WMH). On the other hand, white matter  $^{11}\text{C}$ -PiB uptake increases with aging (8,14). This seems rather contradictory as WMH volume also increases with aging and  $^{11}\text{C}$ -PiB uptake is lower in WMH than normal appearing white matter (NAWM), with uptake in both compartments increasing with aging suggesting that the aging and WMH effects are independently influencing  $^{11}\text{C}$ -PiB uptake in the WM.  $^{11}\text{C}$ -PiB shows high affinity for WM, however given its short half-life (20 min), it is not commercially available. To conduct multi-center clinical trials using PET imaging to investigate WM integrity and to make PET imaging more accessible, “ $^{18}\text{F}$ -PET” ligands such as  $^{18}\text{F}$ -Flutemetamol may be a more reliable alternative.

Furthermore, PET ligand uptake in the WM is increasingly being used as a reference region to calculate the standard uptake value ratios (SUVR) in longitudinal  $\beta$ -amyloid PET studies (15-19). Thus, the association between WM  $^{11}\text{C}$ -PiB uptake and aging should be carefully considered in serial amyloid- $\beta$  PET studies and should be investigated further with different PET ligands such as flutemetamol to see if there is a similar variation of WM  $^{18}\text{F}$ -Flutemetamol uptake.

Both  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol PET ligands have been investigated as potential WM integrity markers in animal and human studies on PET imaging (12). Although PET ligands are not identical in their uptake characteristics, their topographic patterns of uptake may be comparable. In the current study, WM was evaluated in two compartments, WMH and NAWM, in cognitively unimpaired younger and older adults, and the ability of  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol PET ligands to differentiate WMH from NAWM was investigated.

## Materials and methods

### Study population

Cognitively unimpaired (CU) older adults with age range of 61-83 and younger adults with age range of 30-49 were recruited from the community responding to a study advertisement for  $\beta$ -amyloid PET (14).

Although it is expected to be more significant in older adults, WMH increases with aging across the adult lifespan including younger adults. Moreover, WMH is clinically relevant in terms of its association with higher blood pressure and higher HbA1C even in younger adults with low WMH (20).

To compare WM binding characteristics of two ligands ( $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol), the participants prospectively underwent magnetic resonance imaging (MRI),  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol PET scans. The  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol scans were completed within a median of 4 days. No adverse events were seen from imaging.

### Imaging acquisitions and analyses

PET imaging was performed on a PET/CT scanner (DRX or DRXT; GE Healthcare) operating in 3D mode using  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol tracers.  $^{11}\text{C}$ -PiB PET images were acquired in 20 minutes (in four 5-minute dynamic frames), after an injection of  $^{11}\text{C}$ -PiB (555MBq; range, 292–729MBq) with a 40-minute uptake delay.  $^{18}\text{F}$ -Flutemetamol PET images were also acquired in 20 minutes, after an injection of  $^{18}\text{F}$ -Flutemetamol (370 MBq; range, 333–407 MBq) with an 80-minute uptake delay (21). To create a single static PET image, dynamic frame images were averaged. An iterative reconstruction algorithm was applied with a 5-mm Gaussian postfilter, and attenuation, scatter, random coincidences as well as radioactive decay were corrected (19).

An automated imaging processing pipeline was used to analyze PET images (19). The cerebellar crus gray matter was used as a reference region to create normalized  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol PET standardized uptake value ratio (SUV<sub>r</sub>) images, which is a previously established reference region in PET

studies that target WM in both cognitively unimpaired individuals and patients with MS (7,8). For anatomic segmentation and labeling of WMH and NAWM, MRIs were performed on 3.0 T scanners (GE Healthcare, Milwaukee, WI), which included a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence and a T1-weighted 3D high-resolution magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence (22). First, using a semiautomated segmentation algorithm on FLAIR-MRI, WM was segmented into WMH and NAWM (23). Then, FLAIR images were co-registered to MPRAGE images and MPRAGE images were segmented using SPM12 with the Mayo Clinic Adult Lifespan Template (<https://www.nitrc.org/projects/mcalt/>). (24) A WM mask was generated by using a threshold for SPM12 WM segmentation to include voxels with probability  $\geq 0.5$ . To account for T1-hypointense lesions being erroneously called gray matter, voxels segmented as WMH in the co-registered FLAIR images were also included as WM. To exclude voxels severely affected by partial volume averaging of gray matter and cerebrospinal fluid, the WM mask was eroded by 3 mm. The remaining WM voxels were divided into two subclass masks, WMH and NAWM. Finally, the mean value for each of  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol PET SUVr over all voxels in each of the WMH and NAWM segmentation masks was calculated.

#### Study consent

The study protocol was approved by the Mayo Clinic Institutional Review Board. Informed consent was obtained from each participant.

#### Statistical analysis

Participants' characteristics were compared among younger and older CU adults using t-tests for continuous variables or chi-squared tests for categorical variables. Due to the gap in ages from 48 to 61, all analyses were stratified by younger and older adult age groups. Amyloid imaging SUVrs were compared using paired t-tests for pairwise group comparisons. Linear regression models and Pearson correlations were used for testing the association of age with  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol SUVr in

WMH and NAWM. To compare associations of  $^{11}\text{C}$ -PiB SUV<sub>r</sub> with  $^{18}\text{F}$ -Flutemetamol between WMH and NAWM, we used linear mixed models adjusted for age, across all participants, with two values (WMH and NAWM) per participant. The mixed models accounted for within participant correlations. We used a group variable for WMH/NAWM and tested for an interaction by group. A significant interaction would indicate a difference in slopes for WMH and NAWM. To compare the performance of  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol tracers in group-wise regional differentiation (WMH versus NAWM), the area under the receiver operating characteristic curve (AUROC) generated using a simultaneous two-stage parameter estimation approach (25) was used. Each AUROC had 95% confidence intervals estimated using the bootstrap. All tests used an alpha level of 0.05 for significance.



## Results

Cognitively unimpaired older adults (N=31) had a median age of 67 (range 61-83) years, and CU younger adults (N=30) had a median age of 38.5 (range 30-48) years. Sex, *APOE* ε4 carrier status and years of education were not different between the groups. As expected, the WMH volume was higher ( $p < 0.001$ ) in older CU (16.74±27.01 cc) than younger CU adults (2.90±1.65 cc). (Table 1).

### <sup>11</sup>C-PiB SUVr compared to <sup>18</sup>F-Flutemetamol SUVr in WMH and NAWM

WMH SUVrs were higher with <sup>18</sup>F-Flutemetamol than <sup>11</sup>C-PiB both in younger ( $p < 0.001$ ) and older CU ( $p < 0.001$ ) adults. Similarly, NAWM SUVrs were higher with <sup>18</sup>F-Flutemetamol than <sup>11</sup>C-PiB both in younger ( $p < 0.001$ ) and older CU ( $p < 0.001$ ) adults.

### WM <sup>11</sup>C-PiB and <sup>18</sup>F-Flutemetamol SUVr in younger compared to older CU adults

<sup>11</sup>C-PiB SUVr was lower in WMH ( $p < 0.001$ ) in younger compared to older CU adults. <sup>11</sup>C-PiB SUVr was also lower in NAWM ( $p < 0.001$ ) in younger compared to older CU adults. Similarly, <sup>18</sup>F-Flutemetamol SUVr was lower in the WMH ( $p < 0.001$ ) and NAWM ( $p < 0.001$ ) in younger compared to older CU adults (Table 1, Figure 1). In addition, age correlated with higher WMH <sup>11</sup>C-PiB SUVr in younger CU adults ( $r = 0.43$ ;  $p = 0.018$ ) and with higher NAWM <sup>11</sup>C-PiB SUVr in older CU adults ( $r = 0.38$ ;  $p = 0.037$ ) (Figure 2). The slopes of the association between age and <sup>11</sup>C-PiB compared to age and <sup>18</sup>F-Flutemetamol in WMH was not different in older CU adults ( $p = 0.16$ ). The slopes of the association between age and <sup>11</sup>C-PiB compared to age and <sup>18</sup>F-Flutemetamol in WMH was not different in younger CU adults ( $p = 0.41$ ). Similarly, the slopes of association between age and <sup>11</sup>C-PiB compared to age and <sup>18</sup>F-Flutemetamol in NAWM was not different in older CU adults ( $p = 0.26$ ). The slopes of association between age and <sup>11</sup>C-PiB compared to age and <sup>18</sup>F-Flutemetamol in NAWM was not different in younger CU adults ( $p = 0.16$ ) (Figure 2).

$^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol SUVr in WMH compared to  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol SUVr in NAWM

$^{11}\text{C}$ -PiB SUVr in WMH was lower than in NAWM both in younger and older CU adults ( $p < 0.001$ ). Similarly,  $^{18}\text{F}$ -Flutemetamol SUVr in WMH was lower than in NAWM ( $p < 0.001$ ) both in younger and older CU adults (Figure 1). In younger CU adults, the AUROC comparing WMH versus NAWM for  $^{11}\text{C}$ -PiB was 0.828 (95% CI 0.747-0.903) and for  $^{18}\text{F}$ -Flutemetamol it was 0.902 (0.821-0.982). In older CU adults, the AUROC comparing WMH versus NAWM for  $^{11}\text{C}$ -PiB was 0.751 (95% CI 0.692-0.794) and for  $^{18}\text{F}$ -Flutemetamol it was 0.787 (95% CI 0.725-0.845). AUROC analysis suggested no difference between  $^{11}\text{C}$ -PiB versus  $^{18}\text{F}$ -Flutemetamol SUVr in differentiating WMH from NAWM both in younger and in older adults.

## Discussion

$\beta$ -amyloid PET ligands were originally developed for measuring cortical  $\beta$ -amyloid deposition in Alzheimer's disease. However, independent of the presence of cortical  $\beta$ -amyloid deposition, WM uptake is also observed in  $\beta$ -amyloid PET studies (26,27). Recently,  $\beta$ -amyloid PET ligands have been specifically repurposed as potential markers of WM integrity in MS due to an ongoing need for molecular imaging ligands for myelin in MS. None of the existing advanced imaging techniques target myelin specifically. By contrast,  $\beta$ -amyloid PET ligands have showed high affinity to WM with high sensitivity and sensitivity to myelin (1,28). Therefore,  $\beta$ -amyloid PET ligands can successfully differentiate WMH from NAWM (7,8). Moreover,  $\beta$ -amyloid PET ligand uptake decreases in demyelinating lesions and increases in ensuing remyelinated lesions (2,29), which generates the possibility of using molecular imaging as a biomarker for potential remyelination therapies. Changes in  $\beta$ -amyloid PET ligand uptake also correlate well with clinical disability scales (11) and cognitive performance (7,9) in patients with MS. Therefore,  $\beta$ -amyloid PET ligand uptake can be a perfect complementary metric to MRI in clinical trials targeting myelin integrity in MS.

Among the  $\beta$ -amyloid PET ligands,  $^{11}\text{C}$ -PiB has emerged as a sensitive and reliable imaging marker in measuring WM integrity both in animal and human studies (2,3,5-8). However, it also has a suboptimal signal-to-noise ratio and a short half-life ( $T_{1/2}=20$ minutes), which makes it challenging to be widely used and commercially available.  $^{18}\text{F}$ -Flutemetamol, which is a fluorinated analogue of  $^{11}\text{C}$ -PiB, has been developed to increase the availability of  $\beta$ -amyloid PET by compensating for the short half-life of  $^{11}\text{C}$ -PiB ligand (21).

In the current study, we compared  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol PET ligands in WMH and NAWM in different age groups. We found that 1) WMH and NAWM SUVrs were higher with  $^{18}\text{F}$ -Flutemetamol than  $^{11}\text{C}$ -PiB in both older and in younger CU adults. 2)  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol uptakes were

higher in older compared to younger CU adults in both WMH and in NAWM. 3)  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol showed a similar topographic pattern of uptake in the WM with higher uptake in NAWM compared to WMH in both older and in younger CU adults. 4) There was no difference between  $^{11}\text{C}$ -PiB versus  $^{18}\text{F}$ -Flutemetamol SUVrs in differentiating WMH from NAWM in both younger and in older adults.

$^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol have a similar diagnostic performance for detecting cortical  $\beta$ -amyloid deposition in CU adults and patients with AD (30,31). Although, compared to  $^{11}\text{C}$ -PiB, a higher  $^{18}\text{F}$ -Flutemetamol uptake is commonly observed in the WM both visually (30) and quantitatively (14,32). However, less is known about the WMH and NAWM uptake differences between  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol. In the current study,  $^{18}\text{F}$ -Flutemetamol SUVrs in the WMH and NAWM were higher than  $^{11}\text{C}$ -PiB both in older and in younger CU adults. Nevertheless,  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol ligands were not superior to one another in differentiating WMH from NAWM in either age group. Similarly, a recent animal study showed a head-to-head comparison of WM binding using  $^{11}\text{C}$  ( $^{11}\text{C}$ -PiB and  $^{11}\text{C}$ -MEDAS) and  $^{18}\text{F}$  ( $^{18}\text{F}$ -Flutemetamol,  $^{18}\text{F}$ -Florbetaben,  $^{18}\text{F}$ -Florbetapir) PET ligands in four healthy nonhuman primates (baboons) (32) to study their ability to distinguish WM from gray matter binding. Consistent with our findings, “ $^{18}\text{F}$ -PET” ligands showed higher SUVrs and higher binding potentials than “ $^{11}\text{C}$ -PET” ligands in the WM. It is speculated that several mechanisms may partially contribute to the variability in the amount of WM uptake between different PET ligands such as differences in molar activities, brain penetrance through the blood brain barrier and duration to reach a WM/gray matter equilibrium (32).

Both  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol ligands showed a similar topographic pattern of uptake in the WM with higher uptake in NAWM compared to WMH. This is in line with previous findings where  $^{11}\text{C}$ -PiB PET imaging was used as a plausible WM integrity marker (1,3,4,7,11,29). Both animal and human studies show that  $^{11}\text{C}$ -PiB PET may differentiate between myelinated tracts, demyelinated lesions (2,7)

and remyelinated regions (3,11). A recent study demonstrated that lower  $^{18}\text{F}$ -Florbetapir uptake in WM correlated with large-caliber axon degeneration in Alzheimer's disease spectrum, reinforcing previous findings on  $\beta$ -amyloid PET ligand uptake in the WM being myelin-dependent (33). The mechanism of  $\beta$ -amyloid tracers' uptake in the WM is not very well understood. However, the beta-pleated structure of both the  $\beta$ -amyloid peptide and the myelin basic protein seems to be the common target of  $\beta$ -amyloid PET ligands (34,35). Moreover, the  $\beta$ -amyloid PET ligands are lipophilic in nature and this potentially contributes to the higher binding in the WM, which is also high in lipid content (36). The mechanism of PET ligand uptake in the WM may partly be also attributed to specific WM kinetics, mainly slower rates of regional clearance of the ligands in the WM (37). Alternatively, a dynamic PET acquisition method could be used to compare and explore further WM binding patterns of  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol (5). Furthermore, to better understand the differences in topographic uptake patterns of  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol WM, a future study including patients with MS would be of interest.

$^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol ligands also showed a similar pattern of uptake in both WMH and NAWM in association with age. There was higher  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol uptake in older compared to younger CU adults in both WMH and in NAWM. The comparison of slopes of association between age and PiB compared to age and  $^{18}\text{F}$ -Flutemetamol in WMH was not different in older or younger CU adults. Similarly, the comparison of slopes of association between age and  $^{11}\text{C}$ -PiB compared to age and  $^{18}\text{F}$ -Flutemetamol in NAWM was also not different in older or younger CU adults. WM uptake significantly increases with aging (14,38). In parallel, WMH and NAWM uptake increase with aging as well (8,14). This may be in part due to reduced kinetics (37,39,40) and reduced global blood perfusion rate (41) in the WM with aging. The increase in PET ligand uptake in the WM with aging is an important factor to consider, because WM is increasingly used as a reference region in longitudinal PET imaging studies. Aging is associated with an increase of WMH volume along with a decrease in myelin integrity, which is expected to result in an overall decrease in PET ligand uptake in the WM. However, in the current study, higher WMH and NAWM  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol uptake was observed in the older compared to

younger adults in line with previous studies (8,38). This suggests that additional aging-related mechanisms may be influencing WM PET ligand uptake (8,38). Moreover, although  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol show a similar topographical WMH and NAWM uptake in different age groups, there is also a quantitative difference between  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol as  $^{18}\text{F}$ -Flutemetamol shows a higher uptake in WMH as well as in NAWM compared to  $^{11}\text{C}$ -PiB. Therefore, when WM uptake is used as a reference region for the evaluation of cortical uptake in serial PET studies; age, WMH volume and the type of the PET tracer should be carefully taken into account in these calculations (8).

### **Conclusion**

$^{11}\text{C}$ -PiB can effectively distinguish between WMH and NAWM, but its lower overall binding capacity to WM and to the compartments of WMH and NAWM compared to  $^{18}\text{F}$ -Flutemetamol may result in a suboptimal signal to noise ratio (32). However, a lower signal to noise ratio seems to have no impact on the differentiation of WMH and NAWM with  $^{11}\text{C}$ -PiB compared to  $^{18}\text{F}$ -Flutemetamol. With higher binding potentials along with longer half-lives, “ $^{18}\text{F}$ -PET” ligands such as  $^{18}\text{F}$ -Flutemetamol are alternatively positioned to be utilized in multi-center clinical trials targeting myelin repair as a secondary outcome in demyelinating diseases including MS. Such an outcome measure can potentially provide more myelin specific information than MR diffusion tensor imaging metrics alone both as a complementary and a stand-alone metric.

**KEY POINTS****QUESTION:**

Do  $^{18}\text{F}$ -Flutemetamol and  $^{11}\text{C}$ -Pittsburgh compound-B ( $^{11}\text{C}$ -PiB) show a similar topographic pattern of uptake in the white matter hyperintensity (WMH) and normal appearing white matter (NAWM) as there is an ongoing need in multiple sclerosis for molecular imaging of white matter integrity?

**PERTINENT FINDINGS:**

We prospectively investigated  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol uptakes in WMH and NAWM in 61 cognitively unimpaired (CU) adults.

- 1) WMH and NAWM SUVrs were higher with  $^{18}\text{F}$ -Flutemetamol than  $^{11}\text{C}$ -PiB in both older and in younger CU adults.
- 2)  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol SUVrs were higher in older compared to younger CU adults in both WMH and in NAWM.
- 3)  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol showed a similar topographic pattern of uptake with higher SUVr in NAWM compared to WMH in both older and in younger CU adults.
- 4) There was no difference between  $^{11}\text{C}$ -PiB versus  $^{18}\text{F}$ -Flutemetamol SUVrs in differentiating WMH from NAWM in both older and in younger CU adults.

**IMPLICATIONS FOR PATIENT CARE:**

With a longer half-life and commercial availability,  $^{18}\text{F}$ -Flutemetamol may be an appealing alternative to  $^{11}\text{C}$ -PiB for molecular imaging in demyelinating diseases such as multiple sclerosis to evaluate myelin integrity in clinical trials targeting myelin repair.

Table 1. Participants' demographic and imaging characteristics

	All n = 61	Young CU n = 30	Older CU n = 31	P-value
Age, years	53.7 (15.8)	38.9 (6.0)	68.1 (5.8)	<0.001
Males, no. (%)	23 (38%)	12 (40%)	11 (35%)	0.72
<i>APOE</i> $\epsilon$ 4, no. (%)*	17 (29%)	11 (38%)	6 (21%)	0.15
Education, years	15.1 (2.0)	15.5 (2.0)	14.7 (2.0)	0.17
WMH Volume cc	9.94 (20.36)	2.90 (1.65)	16.74 (27.01)	<0.001
PiB SUV <sub>r</sub> WM	1.92 (0.20)	1.81 (0.13)	2.02 (0.20)	<0.001
PiB SUV <sub>r</sub> WMH	1.75 (0.19)	1.65 (0.13)	1.85 (0.20)	<0.001
PiB SUV <sub>r</sub> NAWM	1.92 (0.21)	1.81 (0.13)	2.04 (0.20)	<0.001
FMT SUV <sub>r</sub> WM	2.42 (0.25)	2.29 (0.14)	2.53 (0.28)	<0.001
FMT SUV <sub>r</sub> WMH	2.14 (0.25)	2.03 (0.15)	2.25 (0.28)	<0.001
FMT SUV <sub>r</sub> NAWM	2.43 (0.25)	2.29 (0.14)	2.56 (0.27)	<0.001

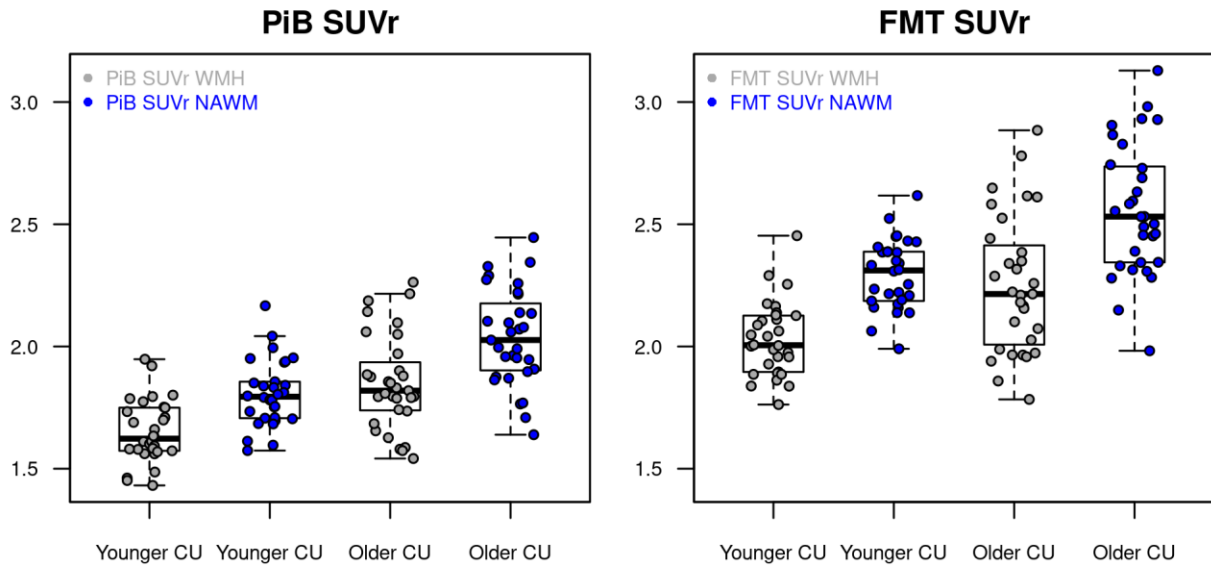
mean (SD) listed for the continuous variables and count (%) for the categorical variables.

P-values comparing groups are from a t-test or chi-squared test

\*3 are missing *APOE*  $\epsilon$ 4

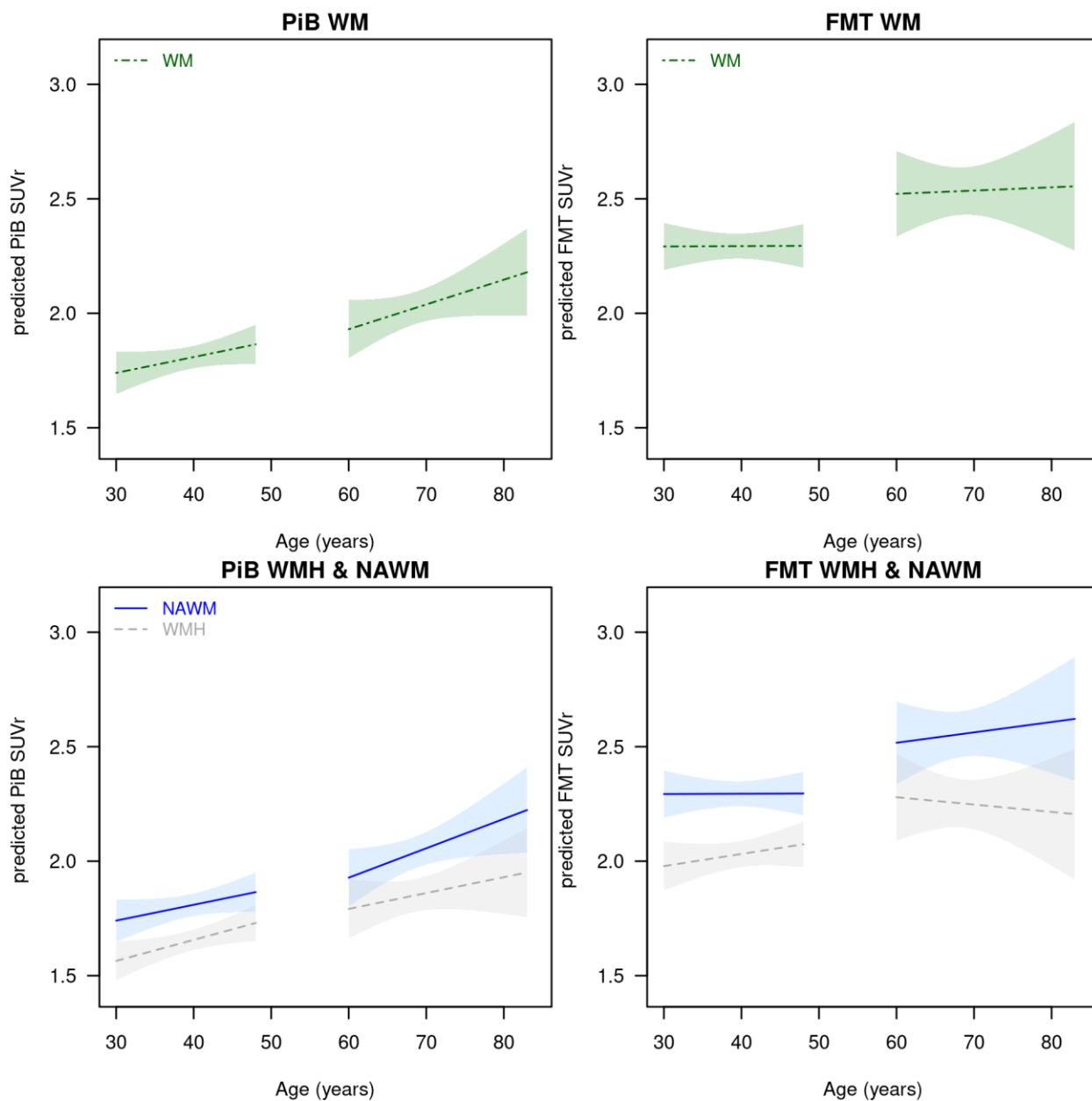
CU= cognitively unimpaired, NAWM= normal appearing white matter, FMT= <sup>18</sup>F-Flutemetamol, PiB= <sup>11</sup>C-Pittsburgh compound-B, SUV<sub>r</sub>= standard uptake value ratio, WMH= white matter hyperintensity





**Figure 1.  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol SUVr in WMH and NAWM in younger and older CU adults.**

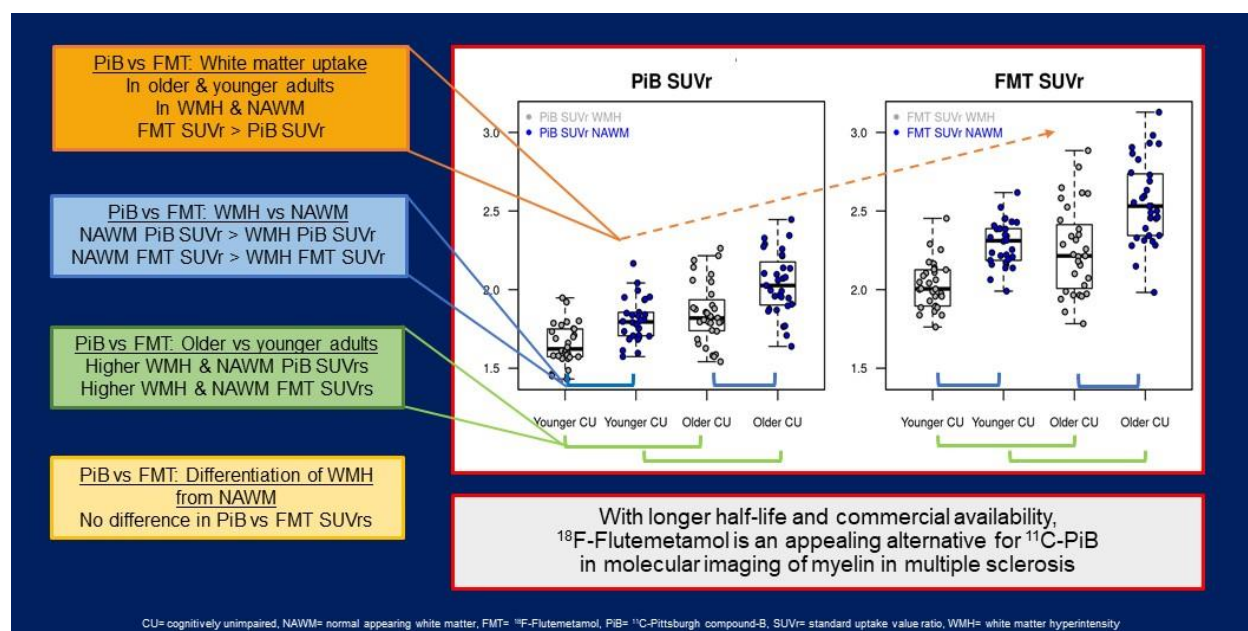
$^{11}\text{C}$ -PiB SUVr was lower in WMH and NAWM in younger compared to older CU adults.  $^{11}\text{C}$ -PiB SUVr in WMH was lower than in NAWM in younger and in older CU adults.  $^{18}\text{F}$ -Flutemetamol SUVr was lower in the WMH and NAWM in younger compared to older CU adults.  $^{18}\text{F}$ -Flutemetamol SUVr in WMH was lower than in NAWM in younger and in older CU adults. CU= cognitively unimpaired, NAWM= normal appearing white matter, FMT=  $^{18}\text{F}$ -Flutemetamol, PiB= Pittsburgh compound-B, SUVr= standard uptake value ratio, WMH= white matter hyperintensity



**Figure 2. Association between age and  $^{11}\text{C}$ -PiB/ $^{18}\text{F}$ -Flutemetamol in the white matter.**

In the upper panel, the associations of  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol radioligand uptake with age were compared in the WM. In the lower panel, the associations of  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -Flutemetamol radioligand uptake with age were compared in the WMH and NAWM compartments individually. The slopes of association between age and  $^{11}\text{C}$ -PiB compared to age and  $^{18}\text{F}$ -Flutemetamol in WMH were not different in older CU adults. The slopes of association between age and  $^{11}\text{C}$ -PiB compared to age and  $^{18}\text{F}$ -Flutemetamol in WMH were not different in younger CU adults. The slopes of association between age and  $^{11}\text{C}$ -PiB compared to age and  $^{18}\text{F}$ -Flutemetamol in NAWM were not different in older CU adults. The

slopes of association between age and  $^{11}\text{C}$ -PiB compared to age and  $^{18}\text{F}$ -Flutemetamol in NAWM were not different in younger CU adults. CU= cognitively unimpaired, NAWM= normal appearing white matter, FMT=  $^{18}\text{F}$ -Flutemetamol, PiB=  $^{11}\text{C}$ -Pittsburgh compound-B, SUVr= standard uptake value ratio, WM= white matter, WMH= white matter hyperintensity



## Graphical Abstract

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