

Supplemental Table 1. Demographics for [¹⁸F]florbetapir Groups

	<i>N</i>	Skull Binding Group		<i>p</i> -value*
		High Binding	Low Binding	
Sex	313			<0.001
<i>Female</i>		62 (94%)	115 (47%)	
<i>Male</i>		4 (6%)	132 (53%)	
Age: years	312			0.10
<i>Mean (SD)</i>		71 (8)	69 (8)	
Education: years	299			0.15
<i>Mean (SD)</i>		15.61 (2.40)	16.10 (2.22)	
CDR	313			0.67
0		56 (85%)	217 (88%)	
0.5		9 (14%)	23 (9.3%)	
≥ 1		1 (1.5%)	7 (2.8%)	
MMSE	311			0.26
<i>Mean (SD)</i>		28.55 (2.80)	28.96 (1.74)	
Amyloid Status	313			0.46
<i>Negative</i>		43 (65%)	173 (70%)	
<i>Positive</i>		23 (35%)	74 (30%)	

Abbreviations: MMSE=Mini-Mental State Examination, CDR=Clinical Dementia Rating®.

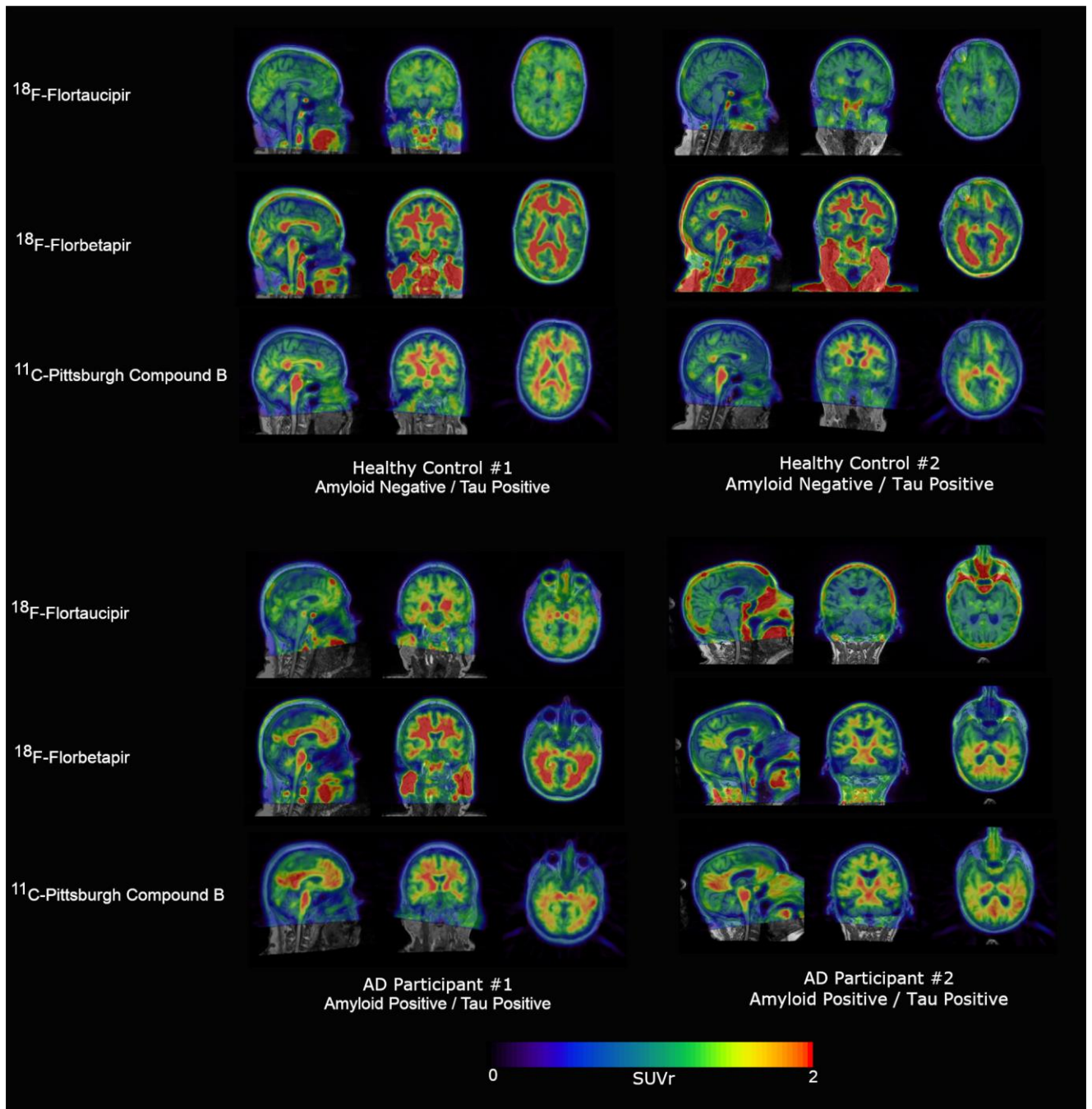
*Differences assessed using Welch two sample t-tests and Fisher's exact test

Supplemental Table 2. Demographics for [¹¹C]Pittsburgh Compound B Groups

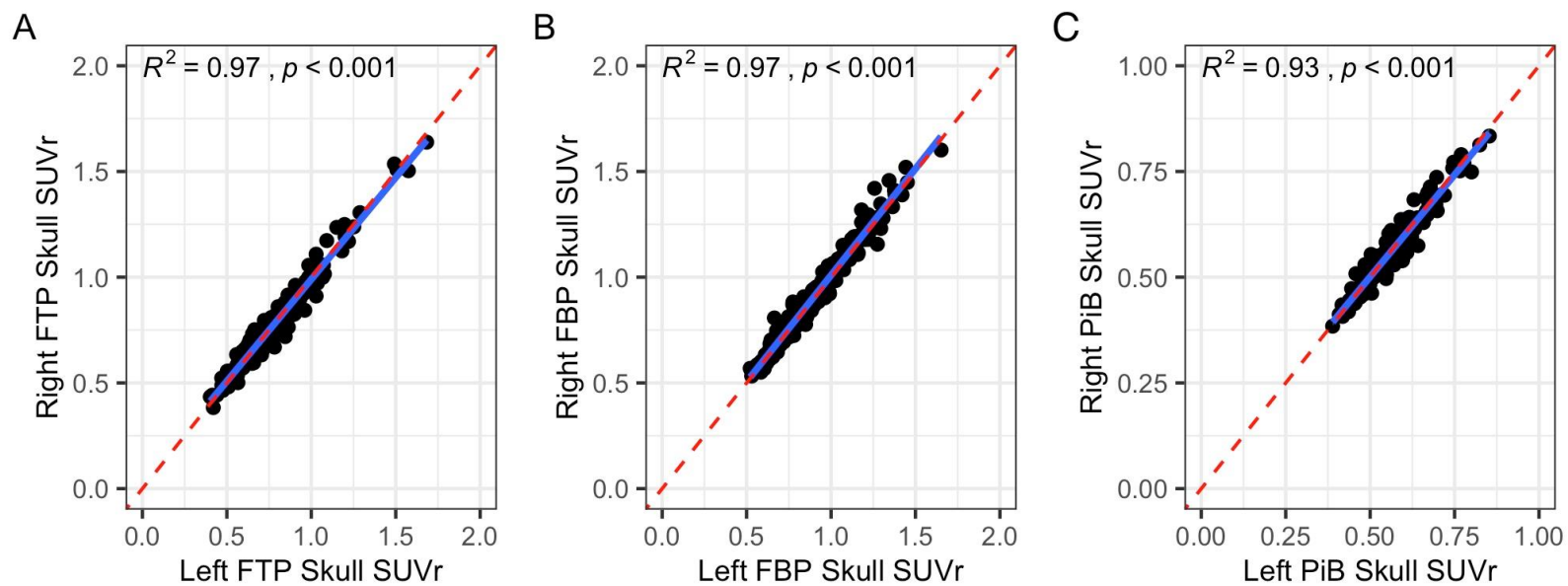
	<i>N</i>	Skull Binding Group		<i>p</i> -value*
		High Binding	Low Binding	
Sex	152			≥0.99
<i>Female</i>		7 (58%)	84 (60%)	
<i>Male</i>		5 (42%)	56 (40%)	
Age: years	152			0.82
<i>Mean (SD)</i>		70 (9)	70 (8)	
Education: years	145			0.61
<i>Mean (SD)</i>		15.75 (1.91)	16.06 (2.40)	
CDR	150			≥0.99
0		12 (100%)	131 (95%)	
0.5		0 (0%)	6 (4.3%)	
≥ 1		0 (0%)	1 (0.7%)	
MMSE	150			0.96
<i>Mean (SD)</i>		29.25 (1.14)	29.27 (1.18)	
Amyloid Status	152			0.47
<i>Negative</i>		8 (67%)	110 (79%)	
<i>Positive</i>		4 (33%)	30 (21%)	

Abbreviations: MMSE=Mini-Mental State Examination, CDR=Clinical Dementia Rating®.

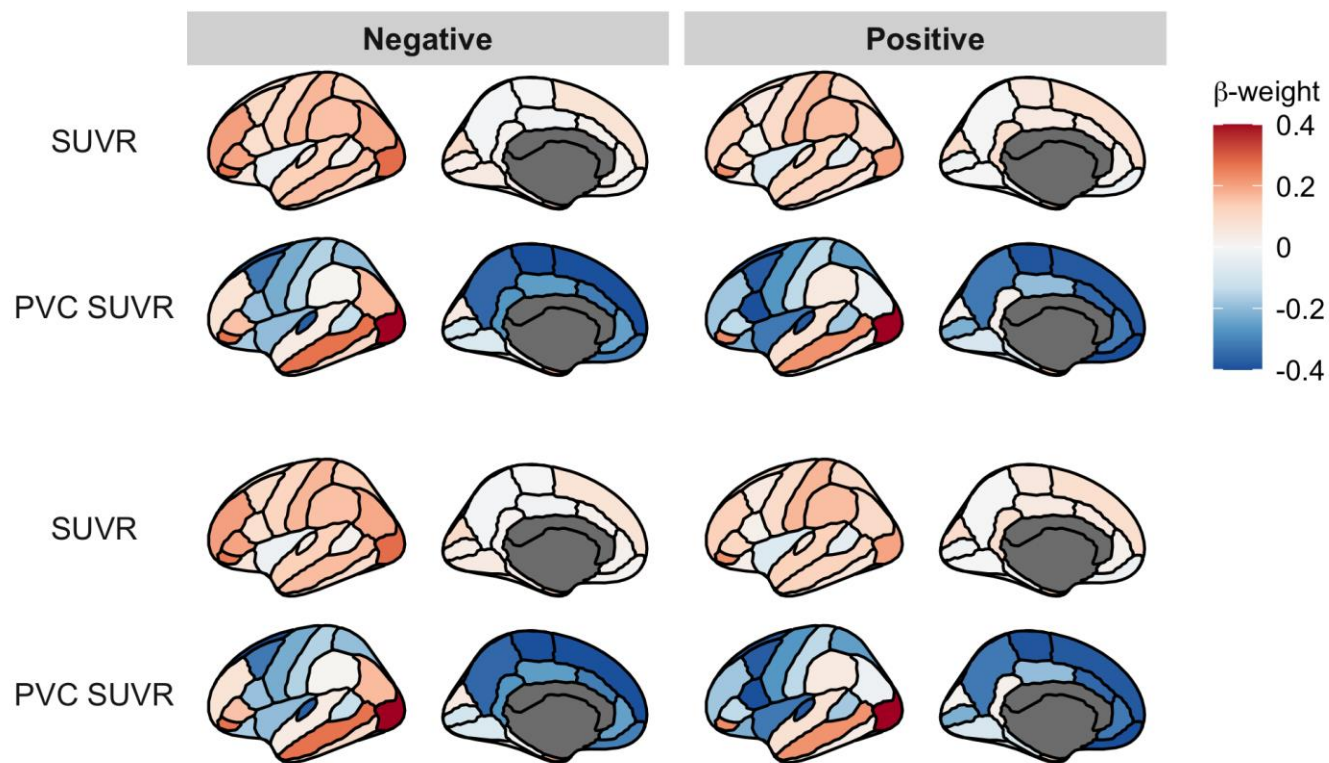
*Differences assessed using Welch two sample t-tests and Fisher's exact test



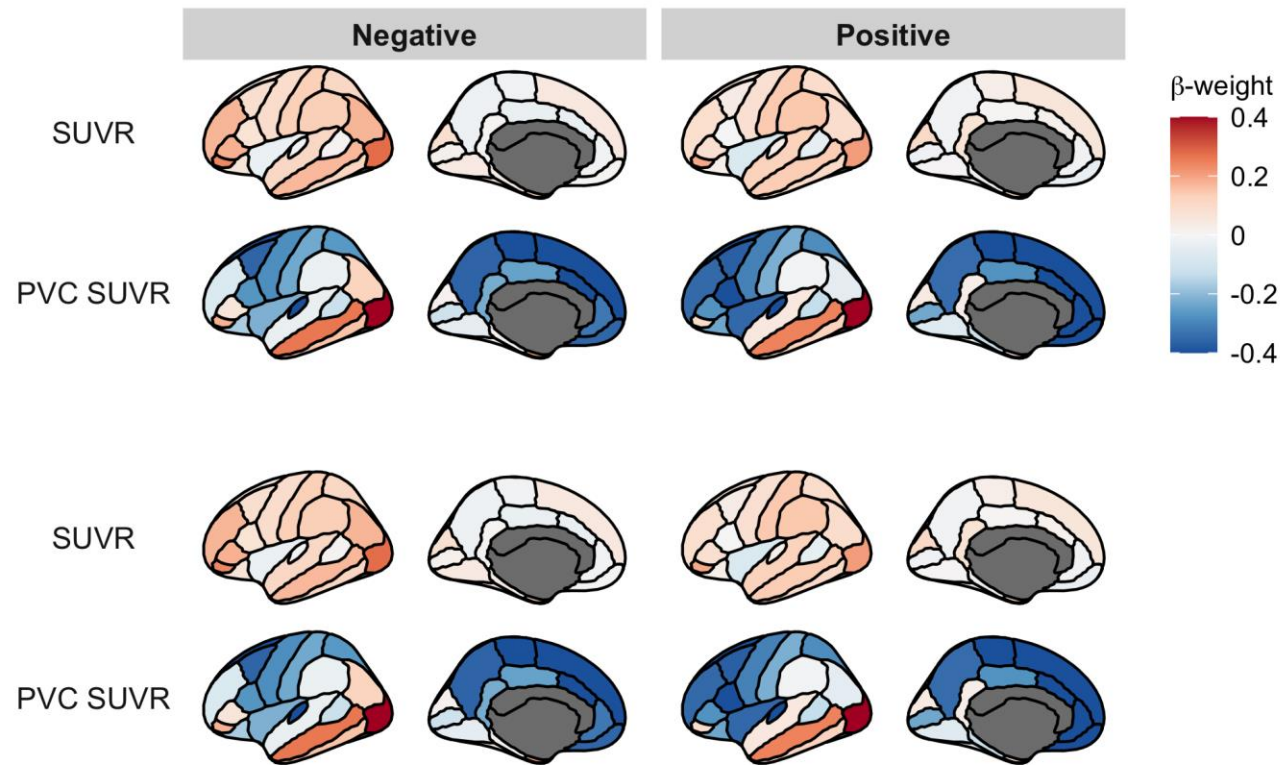
Supplemental Figure 1. Voxel-wise standard uptake value ratio (SUVR) images overlaid on anatomical T1-weighted images from four unique participants classified as having high levels skull binding for ^{18}F -flortaucipir (FTP), ^{18}F -florbetapir (FBP), and ^{11}C -Pittsburgh Compound B (^{11}C -PiB). Images are in participant native space. Amyloid positivity is based off both amyloid PET tracers (i.e., an amyloid negative individual is negative for both FBP and ^{11}C -PiB). Tau positivity is based on the tauopathy summary measure.



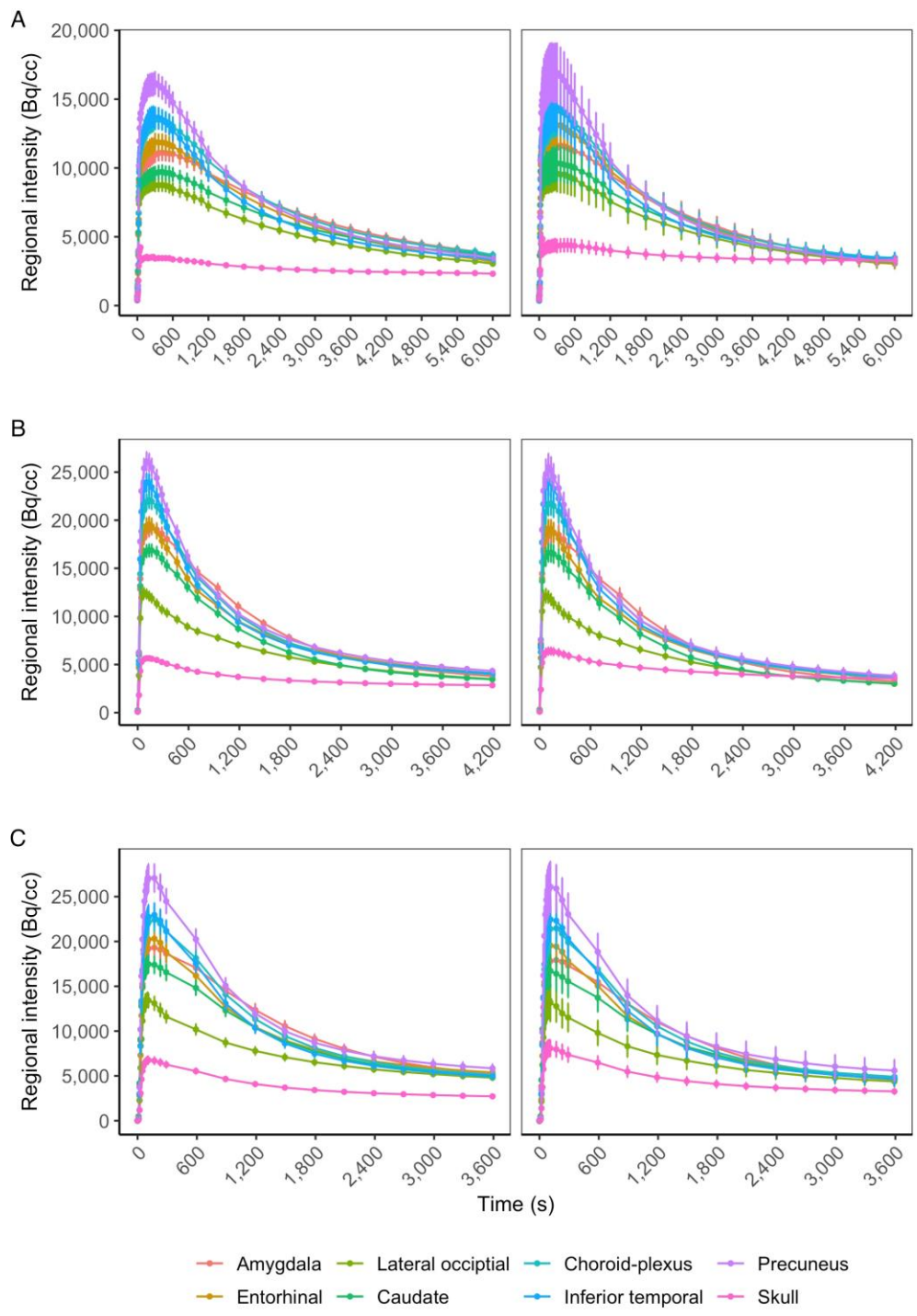
Supplemental Figure 2. Correlations between SUVrs for left and right portions of the skull region of interest (ROI) for (A) ^{18}F flortaucipir (FTP), (B) ^{18}F florbetapir (FBP), (C) ^{11}C Pittsburgh Compound B (PiB). To obtain the left and right portions of the skull ROI, the ROI was divided in half along the midline and SUVrs were obtained for each half.



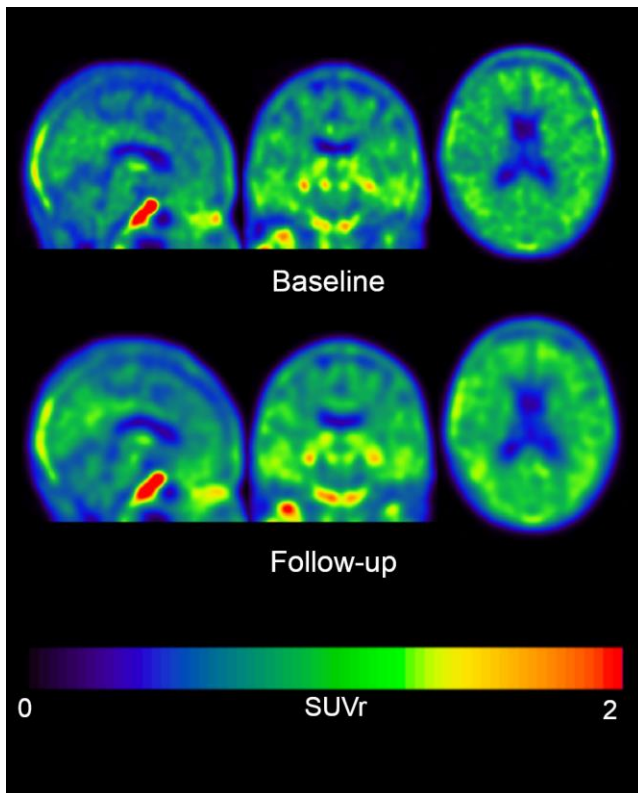
Supplemental Figure 3. Regional cortical SUVrs as a function of $[^{18}\text{F}]$ flortaucipir (FTP) skull SUVr for amyloid negative (left) and positive (right) individuals. Multiple comparisons uncorrected (top panel) and corrected using a Benjamini and Hochberg false discovery rate of 5% (bottom panel) are shown without any significance threshold. Non-partial volume correction (PVC) SUVrs were elevated with increased skull signal for many parietal, frontal, and temporal regions for both amyloid negative individuals. Once PVC was applied, many regions show an inverted relationship between regional SUVr and skull SUVr, suggesting PVC can to some extent moderate the bias introduced by proximal skull signal for cortical SUVrs.



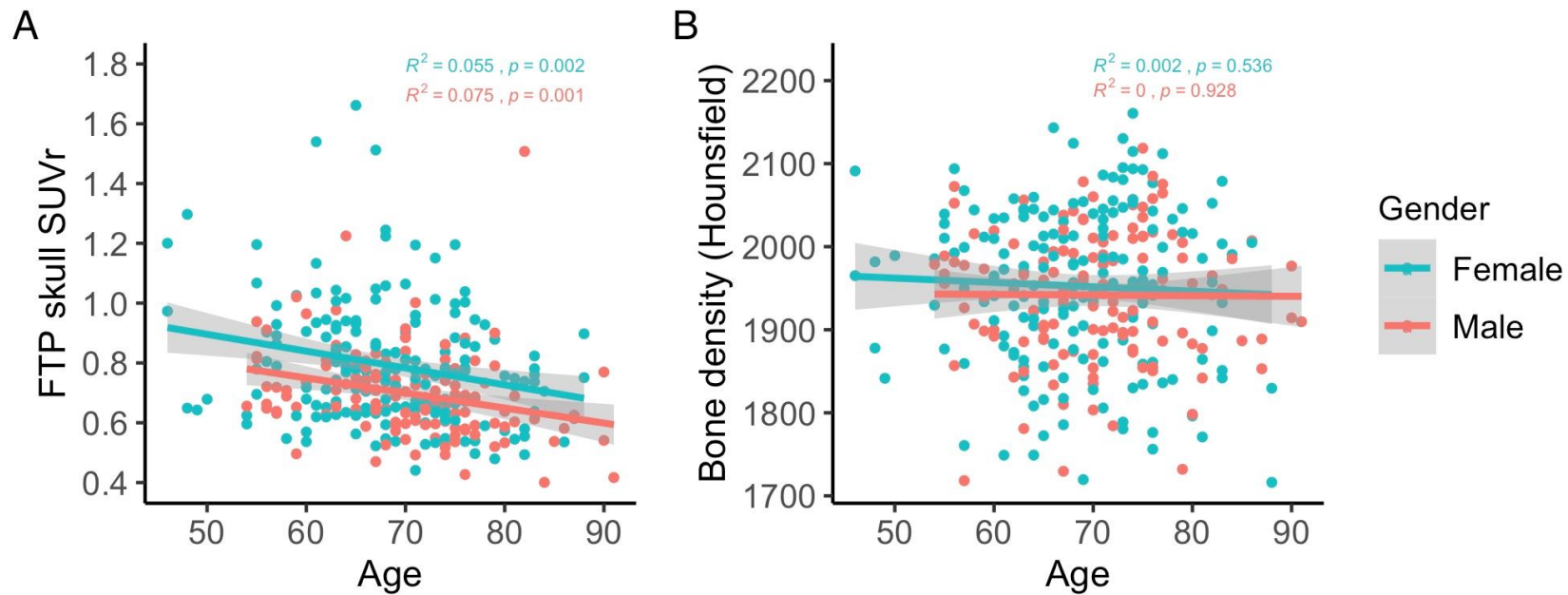
Supplemental Figure 4. Regional cortical SUVRs as a function of $[^{18}\text{F}]$ flortaucipir (FTP) skull SUVR after controlling for age and sex for amyloid negative (left) and positive (right) individuals. Multiple comparisons uncorrected (top panel) and corrected using a Benjamini and Hochberg false discovery rate of 5% (bottom panel) are shown without any significance threshold. Similar regional impacts to those seen in a model with only skull SUVR were observed for both amyloid negative and positive individuals. Both medial temporal and lateral occipital showed elevated SUVRs with increased skull SUVR, suggesting that these regions should be scrutinized in any quantitative PET study of Alzheimer disease-related tauopathy.



Supplemental Figure 5. Time activity curves for select regions of interest and the skull using (A) [^{18}F]flortaucipir, (B) [^{18}F]florbetapir, and (C) [^{11}C]Pittsburgh Compound B. TACs were generated separately for those with low skull uptake (left) and high skull uptake (right). Error bars are 95% confidence intervals.



Supplemental Figure 6. Exemplar baseline and follow-up [^{18}F]Flortaucipir (FTP) longitudinal scans from a participant with high FTP skull binding. Images are registered to MNI-152 space.



Supplemental Figure 7. Relationship of (A) ^{18}F -flortaucipir (FTP) skull SUVr and (B) cranial bone density as measured by a CT scan with age. Although skull signal was more prevalent in younger individuals, neither sex showed any differences in cranial bone density across the age range of the study. Off-target skull binding does not appear to be a solely age-related phenomenon.