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Title: Partial volume correction for PET synaptic density imaging with ^{11}C-UCB-J

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Objectives: The recently developed synaptic vesicle glycoprotein 2A (SV2A) PET tracer, ^{11}C-UCB-J, has demonstrated excellent properties for imaging synaptic density [1]. *In vivo* SV2A PET imaging could provide a highly informative indicator for synaptic density in Alzheimer disease (AD). It is well known that the partial volume effect (PVE) impairs tracer quantification. In addition, for AD and other neuropsychiatric disorders, a decrease in apparent tracer concentration is likely due to a combination of gray matter loss and synaptic density decreases in the remaining tissue. Thus, partial volume correction (PVC) should be performed for absolute tracer quantification. Here, we performed PVC on ^{11}C-UCB-J binding in healthy control (HC) and AD, and assessed its impact on the patient-specific results.

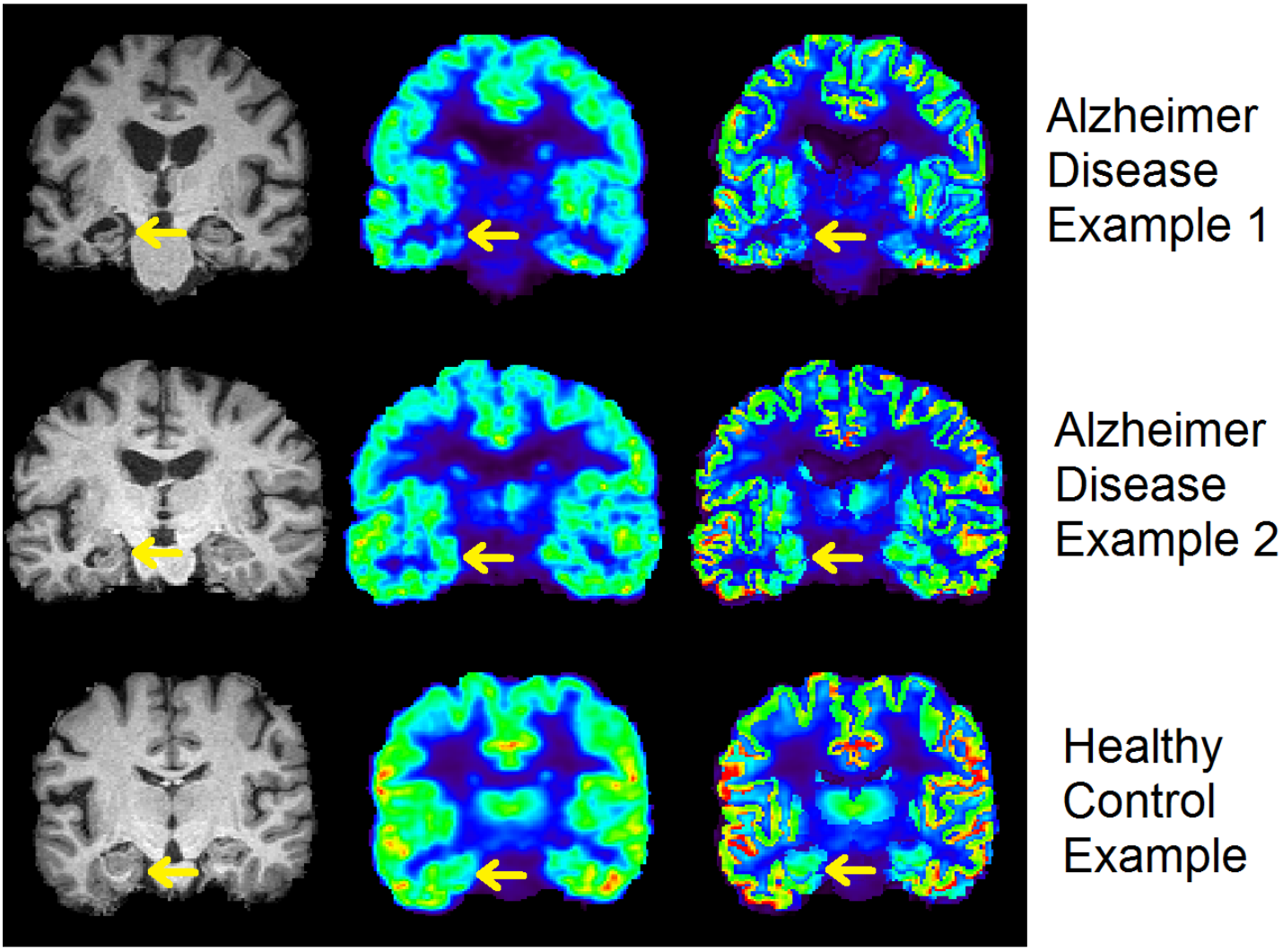
Methods: Seven HC and nine AD subjects were examined using the HRRT with ^{11}C-UCB-J. Iterative Yang (IY) [2] PVC was performed on each dynamic frame. FreeSurfer (FS) -segmented regions of interest (ROIs) were used in the PVC for each subject. IY initializes each ROI's value with the original image, iteratively updates the spill-in and spill-out proportion for each ROI, and finally generates a PVC image. Since the exact point spread function (PSF) is not known, 3 different Gaussian PSFs with 2.5, 3.0, and 3.5 mm in full-width-half-max, were used. Regional time-activity curves were analyzed with the 1-tissue compartment model to estimate volume of distribution (V_T) and binding potential (BP_{ND}). A shrunken version of a centrum semiovale ROI was used as the reference region for calculating BP_{ND}. PVC results were compared to uncorrected data using the FS-segmented ROIs. Seven grey-matter ROIs were evaluated: hippocampus, amygdala, cerebellum, entorhinal cortex, anterior cingulate, posterior cingulate and precuneus.

Results: V_T and BP_{ND} results with and without 3mm-PSF PVC are reported in the table. For some cortical regions, i.e., anterior/posterior cingulate and precuneus, V_T (BP_{ND}) substantially increased with PVC by 34±2% (45±3%). Interestingly, PVC-induced increases were much smaller in hippocampus, entorhinal cortex, amygdala and cerebellum: 12±4% (19±5%). Uptake was significantly lower in the hippocampus of AD compared with HC for uncorrected data, and statistical significance increased after PVC (see Table). The increase in significance was due to the fact that the contrast between hippocampus and its surrounding regions was lower than other cortical regions for HC, and the contrast was even lower for AD. This means the PVE impact on hippocampus was smaller compared with cortical regions for HC, and the impact was even smaller for AD. Thus, after PVC, the uptake in HC hippocampus increased more than in AD. Uptake in the centrum semiovale region changed less than 1% after PVC. For V_T and BP_{ND}, results with 2.5-mm (3.5-mm) PSF were always within -8 % (+8%) in difference compared to 3.0-mm PSF. The FS volume of hippocampus, entorhinal cortex and amygdala were significantly lower for AD. Hippocampus volume was 15% lower in AD but hippocampal SV2A BP_{ND} after PVC was 41% lower, compared to 33% before PVC.

	V_T (mL/cm^3)			V_T PVC			FS Volume (mL)		
	HC	AD		HC	AD		HC	AD	
	Mean(SD)	Mean(SD)	*p*	Mean(SD)	Mean(SD)	*p*	Mean(SD)	Mean(SD)	*p*
hippocampus	13.6(1.7)	10.4(1.8)	**0.004**	15.1(1.9)	11.0(2.0)	**0.002**	7.5(0.6)	6.4(0.7)	**0.007**
amygdala	17.5(2.7)	15.2(3.0)	0.154	20.2(3.2)	17.8(3.4)	0.206	2.8(0.3)	2.4(0.2)	**0.019**
cerebellum	14.4(1.8)	14.4(1.7)	0.993	15.3(2.0)	15.3(2.0)	0.982	102.7(7.3)	104.9(9.9)	0.651
entorhinal	15.8(2.5)	13.0(2.5)	0.061	18.2(3.2)	14.8(3.4)	0.074	3.8(0.5)	2.7(0.5)	**0.001**
ant. cingulate	21.4(2.9)	20.7(3.0)	0.648	28.8(4.0)	27.7(4.5)	0.648	6.8(1.1)	6.9(1.3)	0.814
Post. cingulate	22.0(3.1)	21.1(3.1)	0.612	29.0(4.0)	28.4(4.3)	0.794	5.3(0.5)	5.1(0.7)	0.506
precuneus	21.2(1.9)	20.5(3.2)	0.660	28.9(2.4)	28.3(4.5)	0.763	16.1(1.7)	16.2(2.1)	0.911
	BP_{ND}			BP_{ND} PVC					
	HC	AD		HC	AD				
	Mean(SD)	Mean(SD)	*p*	Mean(SD)	Mean(SD)	*p*			
hippocampus	1.8(0.2)	1.2(0.4)	**0.002**	2.2(0.2)	1.3(0.5)	**0.001**			
amygdala	2.6(0.3)	2.2(0.5)	0.083	3.2(0.4)	2.8(0.6)	0.124			
cerebellum	2.0(2.0)	2.1(0.4)	0.772	2.2(0.2)	2.3(0.4)	0.858			
entorhinal	2.3(0.2)	1.7(0.5)	**0.023**	2.8(0.3)	2.1(0.7)	**0.038**			
ant- cingulate	3.5(0.2)	3.4(0.6)	0.736	5.0(0.4)	4.9(0.9)	0.706			
post- cingulate	3.6(0.2)	3.5(0.6)	0.662	5.1(0.3)	5.0(0.8)	0.857			
precuneus	3.4(0.1)	3.4(0.7)	0.808	5.1(0.2)	5.0(1.0)	0.866			

Conclusions: ^{11}C-UCB-J binding is significantly reduced in hippocampus for AD patients. Significant volume reduction was seen for hippocampus, amygdala and entorhinal. With PVC, the statistical significance and the magnitude of this difference increased. Hippocampus, amygdala and entorhinal were mildly impacted while cortical regions were largely impacted by the PVE, and the size of the Gaussian PSF had a mild effect on PVC.

References: [1] Finnema *et al*., *Sci Transl Med* 2016; [2] Erlandsson *et al*., *PMB* 2012.



V_T images before and after PVC.
Arrows pointed at hippocampus regions.