Analysis of Overestimation of DVR in SUVR Using the Logan Plot with Plasma Input

In ligand-receptor dynamic PET studies, tracer kinetic modeling including compartmental modeling and graphical analysis using the Logan plot (*1, 2*) with a plasma input function is regarded as the gold standard method for quantification of ROI kinetics, where the noise in ROI time activity curves (TACs) is usually low and negligible. As it is simple and independent of model configuration, the Logan plot with plasma input is commonly used as a standard method for estimating distribution volumes from ROI TACs. Since the overestimation of DVR in the SUVR is not dependent on the noise levels in tissue kinetics, it is safe to assume that the tissue TACs are noise free for the analysis of overestimation of DVR in SUVR using the Logan plot with plasma input. Let C(t) and $C_{REF}(t)$ be the tracer concentrations in target and reference tissues, respectively, and $C_P(t)$ is the tracer concentration in plasma at time t. In this study, we assume that there is a time t* such that 1) the tissue kinetics attain equilibrium relative to the reference tissue input, i.e., $C(t)/C_{REF}(t)$ is a constant for $t \geq t^*$; 2) reference tissue input $C_{REF}(t)$ can be approximated by one exponential as $C_{REF}(t) = \alpha e^{\beta t}$ for $t \geq t^*$. Based on the above assumptions, the tissue total distribution volume V_T (*6*) can be determined by the Logan plot using Eq. 1, where "$\int_0^t$" represents mathematical integration operation from time 0 to t, V_T and δ are the slope and the intercept of linear regression line for $t \geq t^*$, respectively.

$$\frac{\int_0^t C(s)ds}{C(t)} = V_T \frac{\int_0^t C_P(s)ds}{C(t)} + \delta \qquad \text{Eq. 1}$$

Eq. 1 can be rewritten in a bilinear form as Eq. 2 below:

$$\int_0^t C(s)ds = V_T \int_0^t C_P(s)ds + \delta C(t) \qquad \text{Eq. 2}$$

Let V_{T_REF} and δ_{REF} be the distribution volume and intercept for reference tissue in Eq. 1, and take the mathematical derivatives of Eq. 2 for C(t) and $C_{REF}(t)$, we have $C(t) = V_T C_P(t) + \delta C'(t)$ and $C_{REF}(t) = V_{T\_REF} C_P(t) + \delta_{REF} C_{REF}'(t)$ where $C'(t)$ and $C_{REF}'(t)$ are the derivatives of C(t) and $C_{REF}(t)$, respectively. By simple algebraic operations with $C(t)=SUVR C_{REF}(t)$, and $C'(t)= SUVR C_{REF}'(t)$, we have

$$SUVR = \frac{(1-\delta_{REF}\beta)}{(1-\delta\beta)} DVR \qquad \text{Eq. 3}$$

where $DVR = V_T/V_{T\_REF}$. Note that β is one exponential clearance rate of the reference tissue for $t \geq t^*$ which is usually non-positive, i.e., $\beta \leq 0$, and δ (δ_{REF}) is the y-intercept of linear regression of the Logan plot. δ is negative and its absolute value increases with steeper slope of the linear regression (i.e., as V_T increases). Both δβ and 1-δβ are nonnegative for practical situations when analyzing [^{11}C]PiB PET data. Based on Eq. 3, we have Bias% = 100(SUVR-DVR)/DVR = $100(\delta-\delta_{REF})\beta/(1-\delta\beta)$, the overestimation of DVR in SUVR increases as V_T increases. Since increase in V_T is equivalent to increase in DVR, we can conclude that the overestimation of DVR in SUVR increases as DVR increases. This theoretically explains why the overestimation of DVR in SUVR is higher in the patient groups, either MCI or AD, than in controls in those ROIs where patient group has higher DVR than the control group.

The Logan Plot with Reference Tissue Input

The Logan plot with reference tissue input (hereafter the Logan plot) described by Eq. 10 below is used to estimate DVR for the tracer kinetics that attain equilibrium relative to reference tissue (*3, 4, 5*):

$$\frac{\int_0^t C(s)ds}{C(t)} = DVR\frac{\int_0^t C_{REF}(s)ds}{C(t)} + \delta$$

The Logan plot is commonly used in ligand receptor PET studies without arterial blood sampling. There are two purposes to implement the Logan plot in this study: 1) the estimates of DVR from the low noise levels of ROI TACs are used as a reference in this study; and 2) to evaluate the noise-induced underestimation in the DVR images generated by the Logan plot.

SUVR Calculation

$$SUVR = \frac{\sum_{i=30}^{37} w_i C(t_i)}{\sum_{i=30}^{37} w_i C_{REF}(t_i)}$$

In the equation above, w_i represents the duration of frame i while t_{30} = t* = 52.5 min, and t_{37} = 87.5 min is the mid time point of the last frame of 90-min dynamic PET scan.

Evaluation of the RE Plot

Methods

The presence of relative equilibrium conditions for [^{11}C]PiB was evaluated using low noise level of ROI kinetics in both control and MCI groups. Single t* value used in the RE and Logan plots, and SUVR for all subjects was determined at 52.5 min post tracer injection corresponding to the last 8 time frames from 50 to 90 minutes of dynamic scans.

Results

The relative equilibrium state of [^{11}C]PiB kinetics was examined first by plotting time t versus mean ± SD of SUVR calculated from ROI TACs as $C(t)/C_{REF}(t)$ (Supplemental Figure 1). The plot shows that SUVR(t) becomes constant at t ≥ 52.5 min in both control and MCI groups when two typical ROIs, the lateral temporal cortex and the posterior cingulate cortex, were selected. The statistical analysis of the relative equilibrium of tissue kinetics for all ROIs is summarized in Supplemental Table 1. In both control and MCI groups, the slope of the linear regression of time t versus SUVR(t) for t ≥ = 52.5 min in all 14 ROIs was small, and not significantly different from zero (Supplemental Table 1). Zero slope of linear regression for SUVR(t) means that ROI TACs attain a constant level relative to cerebellum TACs at t ≥ 52.5 min.

Due to the relative equilibrium of [^{11}C]PiB ROI kinetics, the RE plot attains linearity in the last 8 points, corresponding to t ≥ 52.5 min (Supplemental Figure 2). The DVRs estimated from the slope of linear regressions of the RE plots were almost the same as DVRs from the Logan plots using the ROI kinetic analysis:

DVR (RE plot) = 1.00DVR (Logan plot) – 0.00, $R^2 = 0.98$

with slope not significantly different from 1 ($p = 0.61$).

Cross-validation for the Bias-corrected SUVR

Methods

A sample of 66 scans from healthy controls and 12 scans from the MCI (CDR = 0.5) group was randomly divided to 2 sub-datasets of 33 scans from healthy controls and 6 scans from MCI. One sub-dataset was used as a training dataset to estimate λ and μ using full dynamic PET data with RE plot, and the other sub-dataset was used to estimate DVRs using the bcSUVR method applied only to 50 to 90 min dynamic PET data. To obtain statistics of estimates, the above random sampling process and corresponding parameter estimation were repeated 100 hundred times. Based on the DVRs estimated using the RE plot and the Logan plot from ROI TACs, Bias% for bcSUVR was calculated relative to each method.

Results

The population based SUVR correction method has been validated in samples that included both healthy controls and MCI subjects. This cross-validation study shows that the Bias% of bcSUVR relative to the DVRs from the Logan plot with ROI TACs is less than 5% (Supplemental Figure 4). In addition, the Bias% of bcSUVR relative to the DVRs from the reference RE plot was less than 1% for striatum and cortical ROIs, and about 2% for pons and white matter. More importantly, the % bias was not different between MCI and control groups (T test, p values ranged from 0.14 to 0.89).

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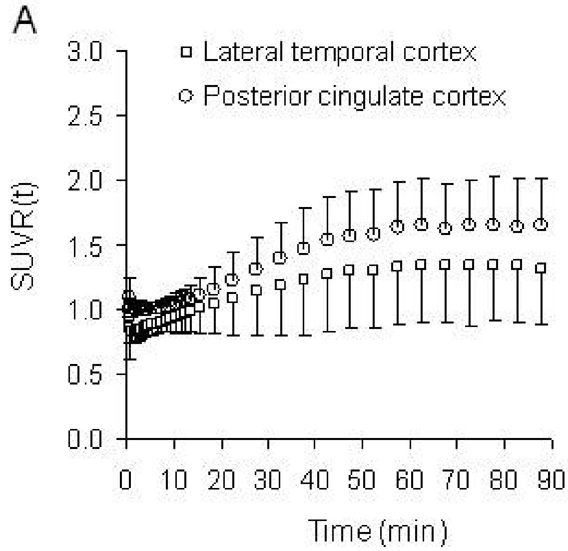
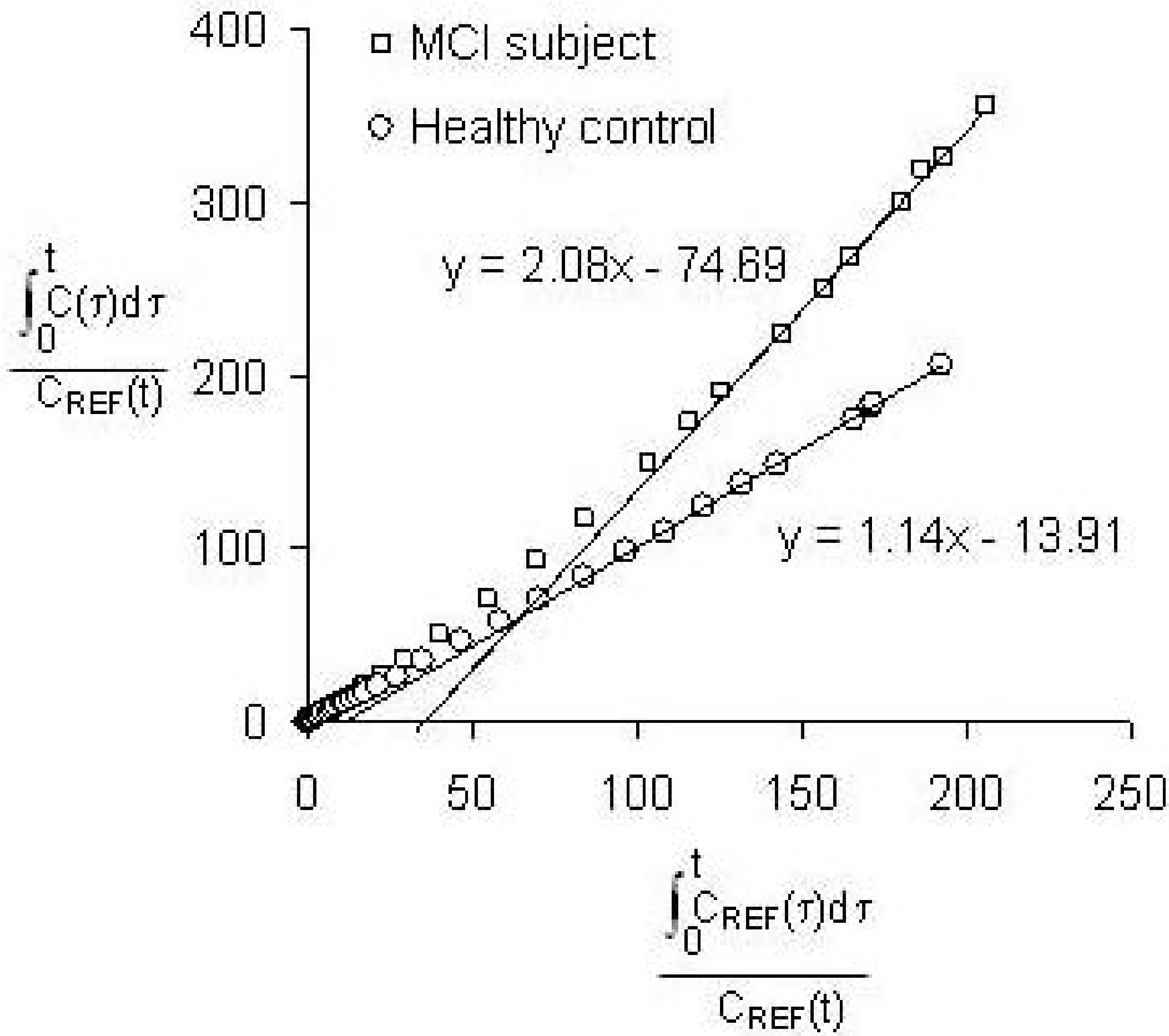
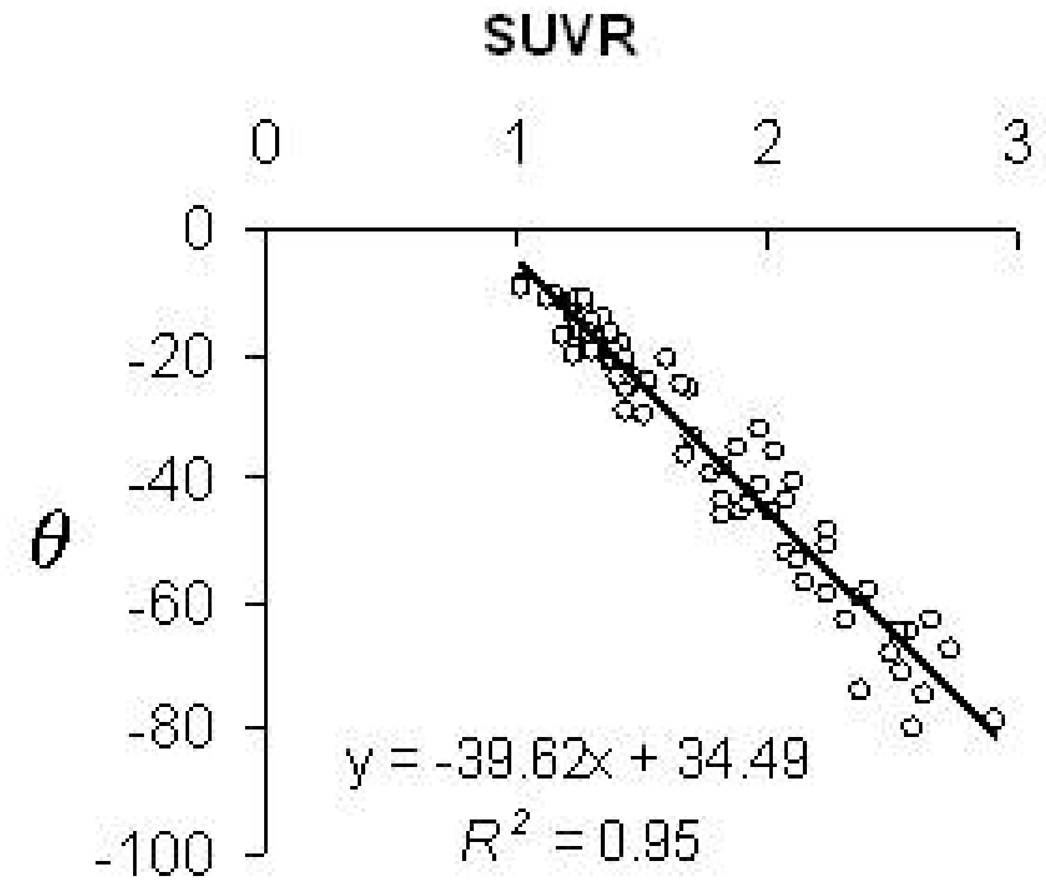


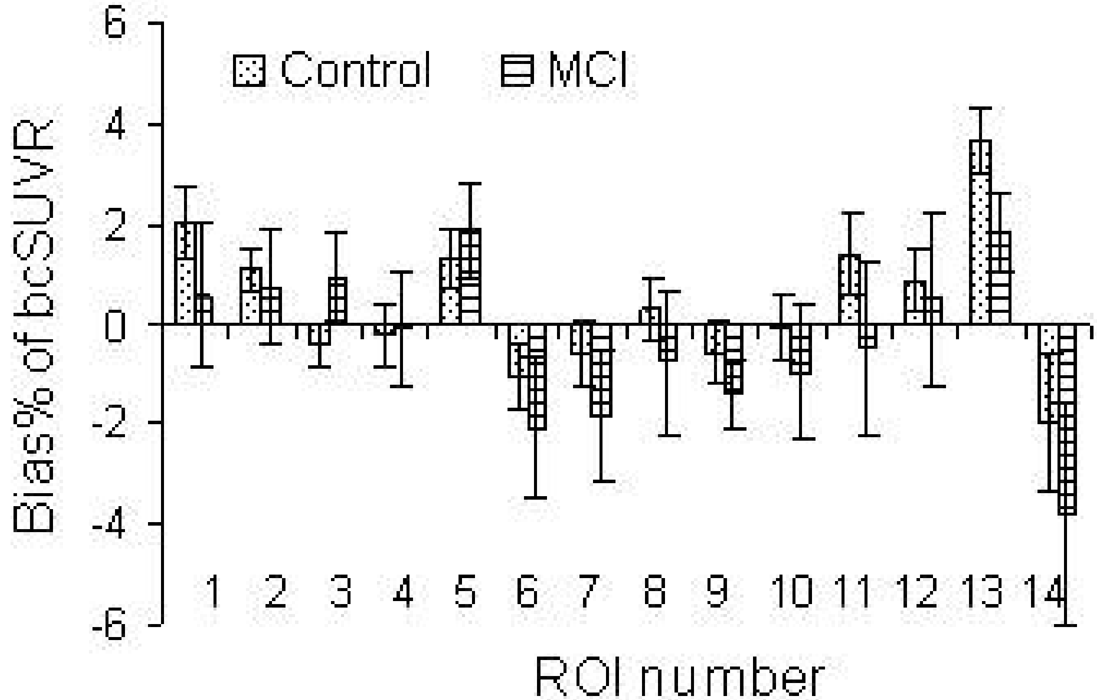
SUPPLEMENTAL **FIGURE 1.** The Mean ± standard deviation of standardized uptake value ratio (SUVR) as a function of time t post tracer injection for the two representative ROI kinetics. The SUVR(t) achieved a stable values for t ≥ 52.5 min equilibrium in [^{11}C]PiB studies of both (A) healthy controls (n = 66) and (B) individuals with mild cognitive impairment (MCI) (n = 12) .



SUPPLEMENTAL **FIGURE 2.** The RE plot generated from a posterior cingulate time activity curves (TACs) in $[^{11}C]$PiB studies with cerebellum reference tissue input. MCI: mild cognitive impairment.



SUPPLEMENTAL **FIGURE 3.** Linear relationship between θ and SUVR in the posterior cingulate cortex. The estimates of θ and SUVR were estimated from 66 healthy controls and 12 mild cognitive impairment (MCI) subjects.



SUPPLEMENTAL **FIGURE 4.** Mean ± standard error of percent bias of DVR estimates (Bias%) in bias-corrected SUVR (bcSUVR) calculated from the cross-validation study with ROI TACs using the Logan plot. There was no significant difference between mild cognitive impairment (MCI) and control groups in Bias% of bcSUVR (T test, p values: 0.14 to 0.89).

Supplemental Table 1. Linear regression of ROI SUVR(t) for t ≥ t* (=52.5 min).

Estimates	Group	ROI	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Slope (1/min)	Control	Mean	-0.001	-0.001	-0.005	0.001	-0.001	0.002	0.002	0.000	0.002	0.000	0.000	0.001	-0.006	0.003
		SD	0.005	0.005	0.004	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.004	0.004	0.004	0.005
	MCI	Mean	0.000	-0.001	-0.005	0.001	0.002	0.003	0.002	0.001	0.002	0.001	0.001	0.000	-0.006	0.004
		SD	0.007	0.005	0.003	0.003	0.004	0.004	0.003	0.004	0.003	0.004	0.005	0.007	0.005	0.004
Statistical p value for H_0: slope = 0	Control	Mean	0.501	0.477	0.302	0.409	0.413	0.307	0.341	0.364	0.425	0.344	0.478	0.465	0.228	0.316
		SD	0.297	0.302	0.283	0.329	0.298	0.293	0.296	0.307	0.302	0.276	0.296	0.318	0.303	0.308
	MCI	Mean	0.427	0.418	0.287	0.392	0.387	0.351	0.287	0.387	0.421	0.297	0.360	0.389	0.218	0.283
		SD	0.344	0.339	0.242	0.310	0.319	0.276	0.275	0.333	0.345	0.307	0.307	0.378	0.321	0.251

Regions of interests (ROIs) are numbered as: 1: caudate, 2: putamen, 3: thalamus, 4: lateral temporal, 5: mesial temporal, 6: orbital frontal, 7: prefrontal, 8: superior frontal, 9: occipital, 10: parietal, 11: anterior cingulate, 12: posterior cingulate, 13: pons, 14: white matter. The SUVR(t) was calculated as the tissue concentration ratio of ROI to cerebellum at time t. The *p* and t values were obtained from the two-sided *t* test for two-sample unequal variance.

Table 2. The statistics of ROI estimates from conventional and improved quantification methods for [^{11}C]PIB specific binding.

Estimates	Group	ROI	1	2	3	4	5	6	7	8	9	10	11	12	13	14
SUVR	Control	Mean	1.390	1.462	1.306	1.325	1.151	1.345	1.298	1.396	1.383	1.408	1.578	1.629	1.896	1.935
		SD	0.405	0.328	0.191	0.360	0.116	0.381	0.402	0.454	0.209	0.331	0.448	0.434	0.163	0.181
	MCI	Mean	1.890	1.924	1.527	1.704	1.250	1.930	1.930	2.050	1.445	1.796	2.263	2.237	1.864	1.870
		SD	0.535	0.359	0.258	0.421	0.280	0.213	0.321	0.423	0.262	0.330	0.475	0.500	0.168	0.251
	T test	p	0.009	0.001	0.014	0.011	0.250	0.000	0.000	0.000	0.448	0.002	0.000	0.001	0.546	0.408
bcSUVR from ROI TACs	Control	Mean	1.274	1.376	1.325	1.183	1.059	1.182	1.157	1.241	1.236	1.235	1.353	1.425	1.665	1.468
		SD	0.308	0.248	0.146	0.265	0.088	0.289	0.307	0.351	0.184	0.259	0.338	0.340	0.107	0.170
	MCI	Mean	1.613	1.693	1.484	1.427	1.124	1.568	1.582	1.681	1.262	1.483	1.800	1.824	1.625	1.382
		SD	0.402	0.274	0.183	0.310	0.210	0.164	0.247	0.330	0.198	0.256	0.375	0.390	0.115	0.259
	T test	p	0.015	0.002	0.014	0.023	0.316	0.000	0.000	0.001	0.676	0.008	0.002	0.005	0.278	0.292
DVR by RE plot from ROI TACS	Control	Mean	1.271	1.371	1.323	1.177	1.055	1.172	1.150	1.232	1.226	1.226	1.339	1.410	1.645	1.435
		SD	0.301	0.243	0.136	0.258	0.089	0.278	0.299	0.343	0.167	0.252	0.326	0.332	0.087	0.107
	MCI	Mean	1.609	1.692	1.477	1.418	1.105	1.562	1.578	1.679	1.259	1.475	1.800	1.813	1.628	1.376
		SD	0.389	0.264	0.194	0.308	0.209	0.153	0.240	0.311	0.203	0.243	0.354	0.387	0.119	0.234
	T test	p	0.013	0.001	0.021	0.023	0.427	0.000	0.000	0.000	0.610	0.005	0.001	0.004	0.656	0.405
DVR by Logan plot from ROI TACS	Control	Mean	1.246	1.359	1.330	1.187	1.045	1.195	1.165	1.238	1.244	1.237	1.336	1.412	1.607	1.498
		SD	0.281	0.234	0.124	0.264	0.088	0.286	0.305	0.344	0.180	0.256	0.331	0.330	0.085	0.105
	MCI	Mean	1.608	1.676	1.471	1.426	1.104	1.599	1.609	1.688	1.279	1.494	1.805	1.811	1.595	1.433
		SD	0.418	0.244	0.186	0.295	0.211	0.145	0.230	0.292	0.201	0.235	0.344	0.362	0.111	0.204
	T test	p	0.013	0.001	0.025	0.019	0.359	0.000	0.000	0.000	0.578	0.003	0.001	0.003	0.712	0.300
DVR by Logan plot from DVR images	Control	Mean	1.172	1.298	1.338	1.061	0.979	1.034	1.031	1.103	1.099	1.082	1.154	1.239	1.469	1.067
		SD	0.207	0.177	0.092	0.173	0.067	0.192	0.211	0.245	0.111	0.178	0.225	0.236	0.062	0.070
	MCI	Mean	1.415	1.537	1.447	1.222	0.995	1.315	1.349	1.438	1.122	1.260	1.486	1.530	1.474	1.028
		SD	0.277	0.193	0.164	0.227	0.145	0.120	0.191	0.235	0.151	0.176	0.255	0.292	0.097	0.166
	T test	p	0.012	0.001	0.044	0.036	0.711	0.000	0.000	0.000	0.627	0.006	0.001	0.006	0.856	0.439
bcSUVR images	Control	Mean	1.236	1.288	1.174	1.189	1.062	1.204	1.171	1.243	1.234	1.252	1.372	1.413	1.592	1.619
		SD	0.309	0.252	0.155	0.269	0.090	0.284	0.301	0.347	0.187	0.256	0.338	0.341	0.122	0.136
	MCI	Mean	1.568	1.588	1.314	1.439	1.128	1.586	1.589	1.677	1.261	1.499	1.824	1.809	1.541	1.552
		SD	0.403	0.280	0.196	0.314	0.214	0.160	0.242	0.326	0.203	0.253	0.373	0.391	0.134	0.220

	T test	p	0.018	0.004	0.035	0.021	0.312	0.000	0.000	0.001	0.671	0.007	0.001	0.005	0.248	0.327

Regions of interest (ROIs) are numbered as: 1: caudate, 2: putamen, 3: thalamus, 4: lateral temporal, 5: mesial temporal, 6: orbital frontal, 7: prefrontal, 8: superior frontal, 9: occipital, 10: parietal, 11: anterior cingulate, 12: posterior cingulate, 13: pons, 14: white matter. The *p* and t values were obtained from the two-sided *t* test for two-sample unequal variance.