Alternative nonparametric binding potentials and their test-retest reproducibility

As the non-displaceable distribution volume (V_{ND}) is ultimately estimated in order to calculate the tracer binding potentials to the target of interest, we considered two available test-retest datasets with [^{11}C]DASB [1] (10 subjects, 20 scans) and [^{11}C]CUMI-101 [2] (6 subjects, 12 scans) and checked the reproducibility characteristics of binding potentials derived using HYDECA versus using the purported reference region. While the results related to the binding potentials $BP_{P\text{-}HYBRID}$ and $BP_{ND\text{-}HYBRID}$ [3] are reported in the main manuscript, here we report results related to alternative binding potentials that can be derived when performing nonparametric quantification of the Positron Emission Tomography (PET) data [4, 5].

Specifically, in all scans and regions, we also calculated:

$$BP_{P\text{-}END} = V_{T\text{-}END} - V_{ND}\ (\text{HYDECA}) \qquad \text{(S1 Equation)}$$

where V_{ND} (HYDECA) is the V_{ND} estimated using HYDECA, and $V_{T\text{-}END}$ is the tracer total distribution volume (V_T) obtained in each region using numerical deconvolution (singular value decomposition) and calculated as [4, 5]:

$$V_{T-END} = K_i \int_0^{T_{END}} R_i(\tau) d\tau \qquad \text{(S2 Equation)}$$

with T_{END} the scan end time; and

$$BP_{P\text{-}NP2} = V_{T\text{-}NP2} - V_{ND}\ (\text{HYDECA}) \qquad \text{(S3 Equation)}$$

where $V_{T\text{-}NP2}$ is the V_T obtained in each region using singular value decomposition and calculated as [4]:

$$V_{T-NP2} = \frac{K_i}{N} \sum_{n=N_1}^{n=N_Q} \frac{R_i^{-1}(n)}{log(1/n)} \qquad \text{(S4 Equation)}$$

where $R_i^{-1}(n)$ indicates the n^{th} quantile of the residence density, which is the time at which $R_i(t)$ reaches a n^{th} of its initial value, with $n = N_1, ..., N_Q$; Q is the number of considered quantiles; and the factor log(1/n) ensures that, if the residence density is exponential as in the case of a one-tissue compartment model, $R_i^{-1}(n)/\log(1/n)$ is equal to the mean of the residence distribution.

For each of the test-retest pair and region, we calculated the percent difference PD_{BPP} as $PD_{BPP} = 100 \frac{|BP_{P-T} - BP_{P-RT}|}{(BP_{P-T} + BP_{P-RT})/2}$, where $BP_{P\text{-}T}$ indicates the test estimate, and $BP_{P\text{-}RT}$ the re-test estimate. We computed average and standard deviation (SD) (across subjects within the same tracer) of the PD_{BPP} values in each region, and compared them to those obtained for: $BP_{P\text{-}RR,LEGA} = V_T\ (\text{LEGA}) - V_{T\text{-}RR,LEGA}$, which is based on the distribution volume in the purported reference region ($V_{T\text{-}RR,LEGA}$), estimated using Likelihood Estimation in Graphical Analysis (LEGA) [6]; $BP_{P\text{-}RR,2TCM} = V_T\ (\text{2TCM}) - V_{T\text{-}RR,2TCM}$, with V_T (2TCM) and $V_{T\text{-}RR,2TCM}$ the V_T obtained in each target region and reference region, respectively, using the two-tissue compartment model (2TCM); $BP_{P\text{-}\alpha} = V_T(\text{LEGA}) - \alpha V_{T\text{-}RR,LEGA}$ and $BP_{P\text{-}d} = V_T(\text{LEGA}) - (V_{T\text{-}RR,LEGA} - d)$, with α and d derived from the blocking data as described in the manuscript.

Similarly, we also calculated alternative nonparametric binding potentials:

$$BP_{ND\text{-}END} = BP_{P\text{-}END}/V_{ND}\ (\text{HYDECA}) \qquad \text{(S5 Equation)}$$

and

$$BP_{ND\text{-}NP2} = BP_{P\text{-}NP2}/V_{ND} \text{ (HYDECA)} \qquad \text{(S6 Equation)}$$

and compared their test-retest percent difference (PD_{BPND}; average and SD values computed in each region as with BP_P above) to that of: $BP_{ND\text{-}RR,LEGA} = BP_{P\text{-}RR,LEGA}/V_{T\text{-}RR,LEGA}$; $BP_{ND\text{-}RR,2TCM} = BP_{P\text{-}RR,2TCM}/V_{T\text{-}RR,2TCM}$; $BP_{ND\text{-}\alpha} = BP_{P\text{-}\alpha}/\alpha V_{T\text{-}RR,LEGA}$; and $BP_{ND\text{-}d} = BP_{P\text{-}d}/(V_{T\text{-}RR,LEGA} - d)$.

S1 and **S2 Figs** summarize the reproducibility of alternative nonparametric binding potentials that can be derived using HYDECA, with β and γ optimized using either strategies, and the reproducibility obtained for all the other binding potentials. PD_{BPP} values obtained using HYDECA with either sets of optimized tuning parameters are close to each other (**S1 Fig**). Overall, average PD_{BPP} values obtained for binding potentials based on HYDECA are better or comparable to values obtained using $V_{T\text{-}RR,LEGA}$. Average percent difference values for $BP_{P\text{-}RR,2TCM}$ are consistently the worst in the case of [^{11}C]DASB, and overall in the case of [^{11}C]CUMI-101. Average percent difference values based on the scaled $\alpha V_{T\text{-}RR,LEGA}$ or corrected $V_{T\text{-}RR,LEGA} - d$ are better than corresponding values based on $V_{T\text{-}RR,LEGA}$ alone, with both tracers, and are comparable or, in some regions, better than values obtained for estimates based on HYDECA. With [^{11}C]DASB, PD_{BPP} values obtained for estimates based on HYDECA are the best in amygdala (AMY), temporal lobe (TEM) (HYDECA using $\beta_{opt\text{-}S}$, $\gamma_{opt\text{-}S}$) and ventral striatum (VST) considering $BP_{P\text{-}END}$. With [^{11}C]CUMI-101, PD_{BPP} values obtained for estimates based on HYDECA are the best in hippocampus (HIP), TEM and cingulate (CIN) considering $BP_{P\text{-}END}$; and HIP (for HYDECA using $\beta_{opt\text{-}S}$, $\gamma_{opt\text{-}S}$) considering $BP_{P\text{-}NP2}$.

For both tracers PD_{BPND} values for BP_{ND} estimates obtained using $V_{T\text{-}RR,LEGA}$ are in general, on average, better than PD_{BPND} values obtained based on HYDECA, with the exception of $BP_{ND\text{-}END}$ in AMY and TEM with [^{11}C]DASB; and $BP_{ND\text{-}END}$ in HIP (for HYDECA using $\beta_{opt\text{-}B}$ and $\gamma_{opt\text{-}B}$), and $BP_{ND\text{-}NP2}$ in TEM and occipital lobe (OCC), with [^{11}C]CUMI-101 (**S2 Fig**). Average percent difference values for $BP_{ND\text{-}RR,2TCM}$ are the worst in the case of [^{11}C]DASB, with few exceptions, but overall comparable to $BP_{ND\text{-}RR,LEGA}$ in the case of [^{11}C]CUMI-101. Average percent difference values based on the scaled $\alpha V_{T\text{-}RR,LEGA}$ or corrected $V_{T\text{-}RR,LEGA} - d$ are overall the best with both tracers. The SD values for the PD_{BPND} are comparable across methods, with exclusion of $BP_{ND\text{-}RR,2TCM}$ in the case of [^{11}C]DASB.

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