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Impact of non-linear SUVR transformations on the statistical power of tau PET longitudinal studies

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Background

- **Tau PET radiotracers** are increasingly used in Alzheimer's disease (AD) clinical trials, necessitating **harmonization** of quantitative results across tracers.
- **Harmonization techniques**, such as the CenTauR scale, differ in their mathematical approaches — linear (e.g., CenTauR) versus non-linear transformations.
- Non-linear methods may better capture inter-tracer relationships **but can also alter the statistical properties of the data**.

Aim

- **To examine how a non-linear transformation impacts statistical power to detect treatment effects on tau accumulation in longitudinal tau-PET studies.**

Methods

- We analyzed two distinct cohorts to derive empirical parameters for power calculations. **The first cohort included 71 amyloid-β–positive (Centiloid >24), cognitively impaired participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI)**, with baseline and 1-year [^{18}F]flortaucipir tau-PET scans. **The second cohort consisted of 342 cognitively unimpaired, amyloid-β–positive participants from the A4 Study** — a clinical trial targeting preclinical Alzheimer's disease — with baseline and 72- or 84-week follow-up tau-PET scans.
- From these cohorts, we estimated baseline SUVR distributions, mean longitudinal SUVR change, and the correlation between baseline and change to inform statistical power calculations (**Figure 1**).
- Using these empirical estimates, **we performed simulations of 10,000 hypothetical trials to assess power to detect varying levels of treatment effect** (50%, 75%, and 100% slowing of tau accumulation).
- Finally, we compared statistical power using raw SUVR values versus SUVR values transformed with a **previously proposed non-linear function** (**Figure 2**):

$$SUVR_{transformed} = 67.83 \times (SUVR - 1.34) + 24.85 \times (SUVR - 1.34) \times \tanh\left(4.03 \times (SUVR - 1.34)\right) + 10.99$$

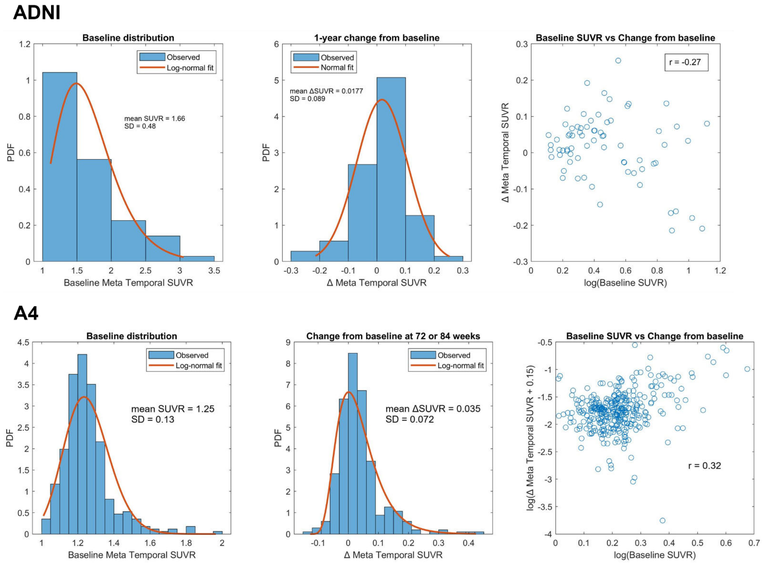

Figure 1. Empirical estimation of the baseline SUVR distributions, change from baseline SUVR distributions, and correlation between baseline SUVR and SUVR change, in ADNI (upper row) and A4 (lower row).

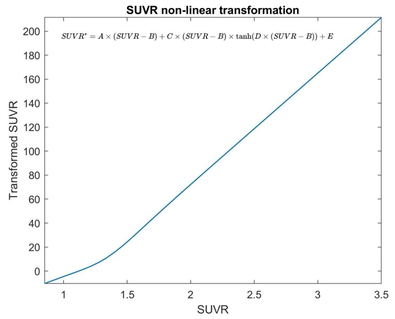

Figure 2. Previously proposed non-linear SUVR transformation function for between-tracer harmonization. The insert represents the transformation's functional form, which is dependent on 5 parameters: A = 67.83; B = 1.338; C = 24.85; D = 4.03; E = 10.99.

Results

- Across both cohorts, **applying the non-linear SUVR transformation consistently reduced statistical power compared to using raw SUVR values** (**Figure 3**).
- In the ADNI cohort, the impact was modest, with power decreasing by up to ~2% (**Figure 3A**) and estimated effect sizes slightly lower when using the transformation (d = 0.0996 vs. 0.0979 for 50% slowing; d = 0.1995 vs. 0.1956 for 100% slowing).
- In the A4 study, the reduction in power was more pronounced, reaching up to ~25% (**Figure 3B**) , with a more substantial drop in effect sizes (d = 0.2518 vs. 0.2032 for 50% slowing; d = 0.5010 vs. 0.4066 for 100% slowing).

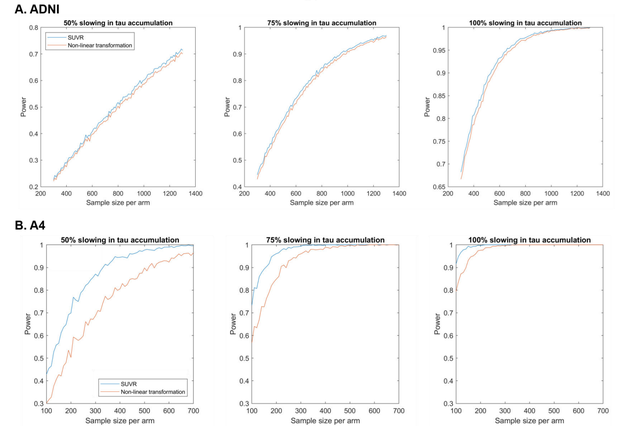

Figure 3. Sample size estimates required to detect a 50% (left), 75% (middle), and 100% (right) slowing in tau accumulation, estimated based on A) ADNI and B) A4 study populations. Results are presented for raw SUVR values (blue lines) as well as for the transformed SUVR (orange lines).

Conclusions

- **Non-linear transformations of tau-PET SUVR data for harmonization may reduce the statistical power to detect treatment effects, especially in trials targeting preclinical AD.**

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