

Optimization of [¹⁸F]MK6240 reference regions for tau-PET quantification reliability

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INTRODUCTION

- [¹⁸F]MK6240 tau-PET presents meningeal off-target binding that encroaches in the cerebellum, the seat of tau-PET reference regions.
- Consequently, tau-PET quantification is highly dependent on the characteristics of the chosen reference region.
- Eroding the outer edge of the cerebellum grey matter (GM) reduces the effect of meningeal off-target binding, but results in a smaller, putatively less stable reference region.
- Including cerebellar white matter (WM), which features the lowest PET signal, should also be considered.
- We aimed to compare different reference regions to identify the one offering the most reliable quantification.

METHOD

- 537 [¹⁸F]MK6240 tau-PET images from 408 participants aged 50+ or 18–25 from the TRIAD cohort with 6 mm FWHM blurring
- Clinical Groups: Young adults (CU(Y)), cognitively unimpaired (CU A– or CU A+), and amyloid-PET positive with mild cognitive impairment (MCI) or AD dementia.
- Reference Regions Evaluated (**Figure 1**):
 1. Eroded inferior cerebellar GM;
 2. Eroded whole cerebellum;
 3. Cerebellar WM;
 4. Cerebellar peduncles

ANALYSES

- Methods were compared on reference region variance, temporal meta-ROI reliability, and tau-PET Braak staging using cross-sectional and longitudinal (~2 years follow-up) data.

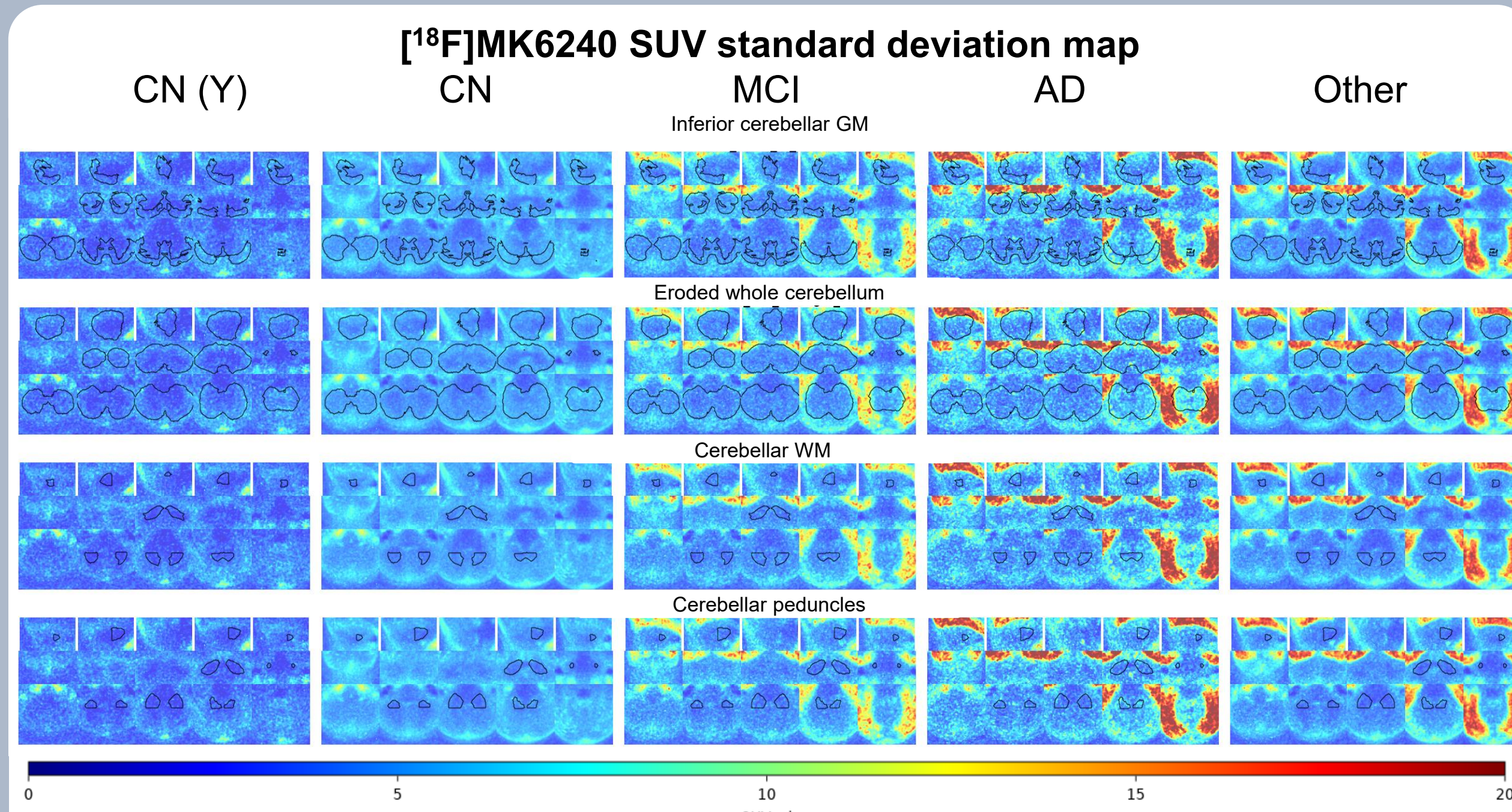


Figure 1: All four reference regions outlined over SUV standard deviation maps across clinical subgroups



Figure 2: Eroded whole cerebellum and eroded inferior cerebellar grey matter (GM) reference regions tended to have larger variances than Cerebellar white matter (WM) and cerebellar peduncles reference ROIs. However, the latter two also had lower uptake, negating the variance differences.

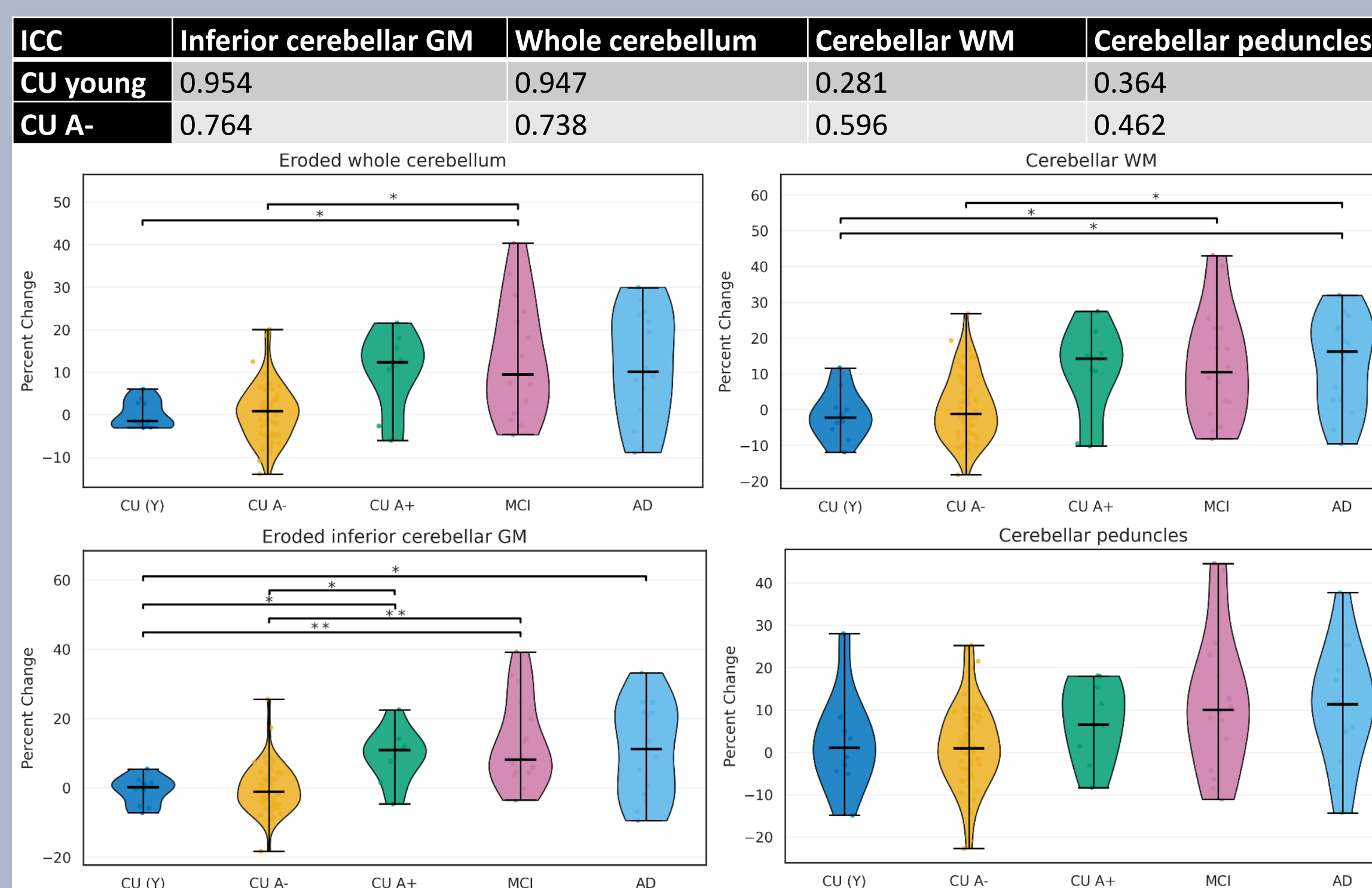


Figure 3: Intraclass correlations for tau-PET in the temporal meta-ROI signal in control participants (CU young and CU A–) are highest when using inferior cerebellar grey matter or whole cerebellum as a reference region. Inferior cerebellar GM, however, was the only reference region enabling a detection of a significant signal increase in the CU A+ compared to the CU A–.

RESULTS

- The GM reference regions (inferior cerebellar GM and whole cerebellum) tended to have a higher uptake compared to the WM reference regions (cerebellar WM and peduncle; **Figure 2**).
 - This resulted in higher variance, although clinical groups did not differ significantly from one another ($p > 0.05$).
- GM reference regions showed superior test-retest reliability in control populations (CU(Y) and CU A–; **Figure 3**);
 - The inferior cerebellar GM offered the strongest detection of longitudinal tau-PET signal increase. It was the only reference region enabling detection of a significant signal increase in CU A+ compared to CU A–.

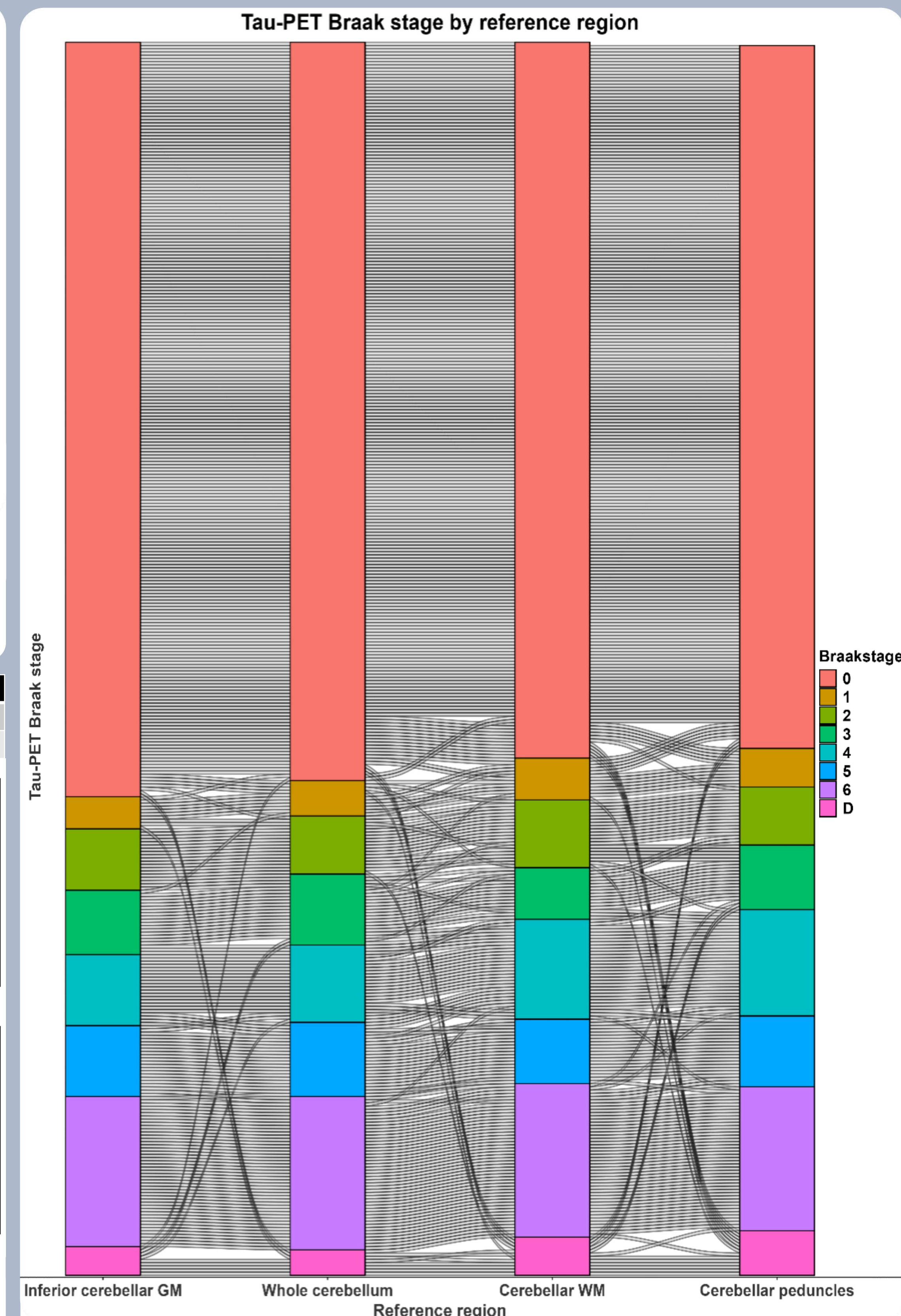


Figure 4: Tau-PET Braak stages tended to be overestimated by the cerebellar WM and cerebellar peduncle reference regions, as shown by the greater number of discordant classifications.

- Using tau-PET Braak stages, the inferior cerebellar GM and whole cerebellum regions had the highest number of stage 0 (**Figure 4**);
 - Conversely, tau-PET Braak stages tended to be overestimated by the cerebellar WM and cerebellar peduncle reference regions, as demonstrated by a greater number of discordant classifications.

DISCUSSION

- The inclusion of white matter (WM) within reference regions did not improve tau-PET quantification, despite the WM tissue offering the lowest interindividual variability.
- Grey matter-dominant (GM) reference regions, and inferior cerebellar GM in particular, offer the best longitudinal stability, quantification accuracy, and lowest risk of false-positive results.

FUNDING