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NEUROIMAGING

Developing a Novel Reference Region for PI-2620-PET Imaging to Facilitate Assessment of 4-Repeat Tauopathies

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Abstract

Background: Neurodegenerative 4-repeat (4R) tauopathies commonly manifest as progressive supranuclear palsy (PSP). PSP patients show elevated PI-2620-PET in subcortical 4R tau predilection sites (e.g., globus pallidus), suggesting PI-2620-PET as a promising 4R tau neuroimaging candidate. However, optimal quantification of PI-2620-PET in 4R tauopathies remains challenging, as conventional cerebellar tau-PET reference regions also accumulate 4R tau. We aimed to use unbiased image-derived input function (IDIF) PET data to determine an optimized PET reference region for in vivo quantification of 4R tau.

Methods: We obtained 60-minute dynamic PI-2620-PET in 54 PSP Richardson Syndrome (PSP-RS) patients and 19 healthy controls (HC), applying IDIF-modeling using carotid timeseries to assess unbiased PI-2620-PET binding and determine total distribution volume (VT). Through an iterative approach, we intensity-normalized VT-images against white-matter regions in the Hammers brain atlas, identifying regions where intensity-normalized pallidum PET values showed the largest PSP-RS vs. HC differences. White-matter regions with strongest PSP-RS vs. HC differences surviving multiple-comparison correction were summarized into a single reference region spanning bilateral temporo-orbital white-matter. This ROI was then used to determine SUVRs using conventional 20-40 minute PI-2620-PET data in PSP-RS, a PSP-non-RS validation sample (n = 63), as well as non-tau disease controls (i.e., alpha-synucleinopathies, n = 20; Alzheimer's disease, n = 23).

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Results: Using PI-2620 SUVRs obtained with the temporo-orbital white-matter reference, we detected strong PSP-RS vs. HC group differences in basal ganglia SUVRs using voxel-wise comparisons (p <0.001, FWE-cluster corrected). Similar basal ganglia differences were detected for PSP-non-RS vs. HC, but not for alpha-syn (no group differences) or AD vs. HC (cortical AD-like group differences). In contrast, minimal group differences were found using a conventional inferior cerebellar grey matter reference region.

Conclusions: Our findings strongly suggest temporo-orbital white-matter is superior to inferior cerebellum as a reference region for PI-2620-PET imaging in 4R tauopathies, due to increased sensitivity and purported specificity for 4R tau.

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