

^{18}F -FD4 PET Visualizes α -syn Pathology and Enables AI-derived Staging in Multiple System Atrophy



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Core Take-Home Message: ^{18}F -FD4 PET is a pioneering in vivo biomarker for MSA that directly visualizes α -synuclein pathology, enabling earlier diagnosis, biological subtyping and staging, and longitudinal disease tracking.

Introduction

Direct in vivo measurement of α -synuclein pathology remains a major unmet need in multiple system atrophy (MSA), constraining biologically informed diagnosis, disease staging and therapeutic development.

Method

Subjects with ^{18}F -FD4 PET imaging at Huashan Hospital:

- 45 patients with clinically diagnosed MSA
- 9 healthy controls (HCs)
- 8 MSA patients with one-year follow-up scans

^{18}F -FD4 PET imaging analysis:

- Visual assessment
- Semi-quantitation (SUVR)
- Spatiotemporal progression patterns (subtypes and stages)

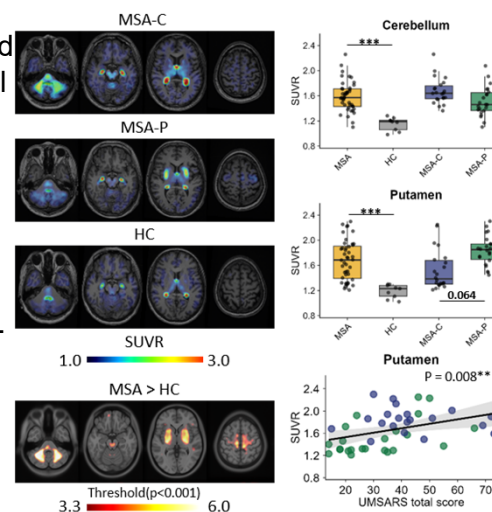
Conclusion

^{18}F -FD4 PET can visualize pathology, model progression and track disease severity in vivo, positioning it as a promising biomarker for patient stratification and therapeutic monitoring in MSA clinical trials.

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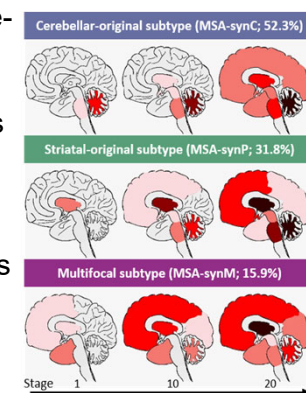
Results

(1) ^{18}F -FD4 recapitulated the expected anatomical distribution of pathology and showed 97.8% concordance between tracer topography and clinical syndrome, supporting its ability to map disease-relevant α -syn burden in vivo.



(2) In around one-third patients, tracer-positive regions were detected before the emergence of the corresponding overt motor syndrome, suggesting that ^{18}F -FD4 PET can reveal clinically silent pathology.

(3) Unsupervised machine-learning-based progression modeling identified three trajectories of regional involvement—cerebellar-origin, striatal-origin and a previously unrecognized synchronous multi-regional pattern—thereby extending beyond the conventional MSA-C/MSA-P classification.



(4) Integration of ^{18}F -FD4 PET with dopaminergic and metabolic imaging enabled a biologically grounded staging framework that refined patient stratification.

(5) Longitudinal increases in regional ^{18}F -FD4 uptake correlated with clinical worsening, supporting its potential as a progression biomarker.

