

RESEARCH ARTICLE

Magnetic Resonance Imaging Measures to Track Atrophy Progression in Progressive Supranuclear Palsy in Clinical Trials

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ABSTRACT: Background: Several magnetic resonance imaging (MRI) measures have been suggested as progression biomarkers in progressive supranuclear palsy (PSP), and some PSP staging systems have been recently proposed.

Objective: Comparing structural MRI measures and staging systems in tracking atrophy progression in PSP and estimating the sample size to use them as endpoints in clinical trials.

Methods: Progressive supranuclear palsy-Richardson's syndrome (PSP-RS) patients with one-year-follow-up longitudinal brain MRI were selected from the placebo arms of international trials (NCT03068468, NCT01110720, NCT01049399) and the DescribePSP cohort. The discovery cohort included patients from the NCT03068468 trial; the validation cohort included patients from other sources. Multisite age-matched healthy controls (HC) were included for comparison. Several MRI measures were compared: automated atlas-based volumetry (44 regions), automated planimetric measures of brainstem regions, and four previously described staging systems, applied to volumetric data.

Results: Of 508 participants, 226 PSP patients including discovery (n = 121) and validation (n = 105) cohorts, and

251 HC were included. In PSP patients, the annualized percentage change of brainstem and midbrain volume, and a combined index including midbrain, frontal lobe, and third ventricle volume change, were the progression biomarkers with the highest effect size in both cohorts (discovery: >1.6; validation cohort: >1.3). These measures required the lowest sample sizes (n < 100) to detect 30% atrophy progression, compared with other volumetric/planimetric measures and staging systems.

Conclusions: This evidence may inform the selection of imaging endpoints to assess the treatment efficacy in reducing brain atrophy rate in PSP clinical trials, with automated atlas-based volumetry requiring smaller sample size than staging systems and planimetry to observe significant treatment effects. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: progressive supranuclear palsy; atlas-based volumetry; staging system; progression; clinical trials

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Introduction

Progressive supranuclear palsy-Richardson's syndrome (PSP-RS) is a rapidly-progressive neurodegenerative 4R-tauopathy, yet effective treatments are lacking.^{1,2} To date, most clinical trials have employed clinical progression markers as primary endpoints to determine treatment efficacy.³⁻⁷ However, there is a strong rationale for using neuroimaging-based progression markers as additional endpoints since: (i) they are not affected by day-to-day variability and (ii) because they allow direct assessment of treatment-related attenuation of neurodegeneration, by measuring longitudinal cerebral tau accumulation or brain atrophy.⁸

While positron emission tomography (PET) tracers have been developed to assess cerebral tau accumulation in vivo,⁹⁻¹¹ tau-PET imaging is an expensive procedure restricted to specialized centres, not yet established to monitor longitudinal 4R tau accumulation in PSP-RS.^{9,12} In contrast, MRI has become widely available and recent trials have already incorporated structural MRI-based measures as secondary endpoints.⁴⁻⁷ The main knowledge gap in this field is which MRI measure to optimally use to effectively monitor disease progression in clinical trials.

Previous studies suggested midbrain, pons, third ventricle, or lateral ventricle volumes to provide the smallest sample size estimates for detecting treatment effects over 1 year.¹³⁻²⁰ Other studies found that planimetric measures such as midbrain area and Magnetic Resonance Parkinsonism Index (MRPI), which are diagnostic markers to distinguish PSP from Parkinson's disease,²¹⁻²³ also showed potential as PSP progression biomarkers.²³⁻²⁵ Finally, recent studies have developed PSP staging systems (SS) based on the concept that the neurodegenerative process emerges in subcortical regions and subsequently spreads to other connected structures, defining sequential progression patterns of tau deposition and atrophy.²⁶⁻²⁸ Kovacs and colleagues²⁶ developed a neuropathologic staging approach in PSP based on the sequential spread of tau aggregates in specific cell populations. Scotton et al.²⁸ proposed a probabilistic, data-driven PSP staging system based on the sequence of MRI-assessed atrophy progression across brain regions. The breadth of different MRI measures and SS proposed to quantify PSP progression renders it difficult to a priori select the best measure as an endpoint to capture treatment effects in clinical trials.

Therefore, we leveraged the large-scale longitudinal MRI data of two independent cohorts of PSP-RS patients from existing observational studies or placebo arms of trials, with the main objective of evaluating systematically volumetric and planimetric MRI measures in comparison with the more recent SS to detect atrophy progression in PSP-RS. This study

represents the first attempt to apply neuropathologically-derived PSP SS to volumetric MRI data in vivo, thus we first evaluated whether patients fitted the described spatial-temporal sequences of regional involvement of the SS, and then investigated the performances of these SS as progression markers by looking at longitudinal atrophy spread to new regions. For each MRI-based measure (planimetric/volumetric measures and SS), we determined and validated the sensitivity to track PSP-related brain atrophy progression, reporting effect sizes and sample size required to detect potential treatment effects in clinical trials.

Methods

Study Participants

We included two independent multisite cohorts of PSP-RS patients² from the placebo arms of three randomized controlled trials (PASSPORT [NCT03068468],⁶ AL-108-231 [NCT01110720],⁷ TAUROS [NCT01049399])⁵ and from the DescribePSP network cohort.²⁹ Detailed information and inclusion criteria are provided in the Supplementary Materials. PSP-RS patients from the NCT03068468⁶ trial were used as a discovery cohort ($n = 132$), while patients from other sources^{5,7,29} were used as an independent validation cohort ($n = 117$) (Fig. S1). A multicohort group of healthy controls (HC) aged >45 years was included for baseline and longitudinal comparison with PSP-RS patients. HC were selected from the Alzheimer's-Disease-Neuroimaging-Initiative (ADNI, $n = 116$), the Degeneration-Controls-and-Relatives (DANCER) cohort ($n = 70$), and a previously published multicentre German HC cohort ($n = 73$).³⁰ HC from ADNI had 52-week longitudinal brain MRI, while individuals from the other cohorts had baseline MRI only (Supplementary Materials). Demographics, longitudinal clinical data, and T1-weighted MRI were obtained. Ethics approval was obtained at each site from the local ethics committee, and all participants gave written informed consent.

MRI Processing and Application of Staging Systems

The DICOM 3D T1-weighted MR images were pseudonymized, visually inspected for quality control (six PSP and one HC were excluded because of poor MRI quality) and processed through an automated pipeline of atlas-based volumetry^{17,30} as described in the Supplementary Materials. In view of the longitudinal design of the current study, the T1-weighted images at baseline and follow-up of each subject were co-registered prior to volumetric analysis. This approach creates a within-subject average image to reduce

measurement variability for longitudinal evaluations which may occur with cross-sectional processing pipelines.³¹ Volumes were summed for bilateral regions and normalized to intracranial volume (ICV). Subjects with ICV variation $\geq 2\%$ between baseline and follow-up were excluded (PSP, $n = 17$; HC, $n = 7$). Automated planimetric measurements (midbrain and pons area, superior and middle cerebellar peduncle width, third ventricle and frontal horns width, MRPI, and MRPI 2.0) were performed using a previously described automated algorithm.^{21,32-34} The methodology description and information on algorithm success rate (92.4%) and failures are provided in the Supplementary Materials and Table S1.

Five staging systems were investigated: one previously described data-driven MRI SS (MRI-ss)²⁸ reflecting the sequence of atrophy progression across brain regions, and four neuropathologic SS²⁶ describing the sequential involvement of brain structures in terms of tau pathology (1) in neurons (Neuronal-ss), (2) in astroglia (Astroglial-ss) (3) in oligodendroglia (Oligodendroglial-ss), and (4) considering these cell populations together (Pathological-ss). Each SS included six distinct stages,^{26,28} each characterized by the involvement of different brain regions (Table S2). For SS application to volumetric data, volumes were transformed into w-scores (age- and sex-adjusted z-scores) using regional mean and standard deviation from HC. A threshold ($w\text{-score} \leq -2$) was used to define the presence/absence of atrophy in each region, consistent with previous PET studies adopting similar methods.^{35,36} Each participant was assigned to a stage, both at baseline and follow-up (rules in Table S3).

Statistics

Comparisons among groups were performed with Fisher's exact test, Wilcoxon rank-sum test, and ANCOVA (covariates: age and sex). *P*-values of all between-group comparisons were corrected for multiple testing according to Bonferroni's method. Differences in volumetric/planimetric measures between baseline and follow-up were transformed into annualized percentage change rates. A previously described index obtained by summing the midbrain, third ventricle, and frontal lobe annualized volumetric change was calculated.¹⁷ The standardized effect size with 95% confidence intervals was calculated for each measure/score, based on the mean and standard deviation of its annualized percentage change rate in each PSP-RS cohort, consistent with previous reports.^{17,20,37} The sample size was estimated based on a two-sample *t*-test with 5% significance level and 80% power, to detect 20%, 30%, or 50% changes in atrophy progression rate in the intervention arm.¹⁷ Associations between clinical and imaging longitudinal changes were assessed using Pearson product-moment correlation and linear regression. To investigate the

effectiveness of imaging SS in detecting atrophy progression, we used two alternative methods. The first simpler method consisted of assessing the stage change over time in each patient. The latter method consisted of stratifying patients into stages at baseline and then measuring volume changes in the regions included in the subsequent stage (indicative of atrophy spread), enabling effect size and sample size estimation, which were compared for the different SS and volumetric/planimetric measures. Figure 1 shows a flowchart of the study design and main analyses.

Results

The final study cohort included 226 PSP-RS patients with longitudinal clinical and MRI assessment, split into a discovery cohort ($n = 121$; 68 [56.2%] male; mean [SD] age 69.8 [5.8] years) and an independent validation cohort ($n = 105$; 49 [46.7%] male; mean [SD] age 67.8 [6.9] years), and 251 age- and sex-matched HC (131 [52.2%] male; mean [SD] age 68.1 [8.3] years), 109 of whom had longitudinal MRI (Fig. S1). Group demographics are shown in Table S4.

Baseline Evaluation

At baseline, PSP-RS patients showed diffuse brain atrophy compared with HC, detected by MR volumetry and planimetry (Tables S4 and S5). Volume loss was found both in grey (GM) and white matter (WM) regions; the most striking atrophy involved brainstem regions, ventral diencephalon, superior cerebellar peduncles and globus pallidus, coupled with ventricular enlargement (Table S5). The highest mean percentage difference and z-scores from HC were detected by planimetric indexes as MRPI (+85.8% to HC; mean PSP z-score: +3.97) and MRPI 2.0 (+182.7% to HC; mean PSP z-score: +4.05), which were superior to the midbrain-to-pons area ratio and volumes (Table S5). All results were consistent across the two independent PSP-RS cohorts.

Longitudinal Evaluation

PSP-RS patients were slightly younger than HC with longitudinal MRI, thus the analyses included age as covariate (Tables 1 and S6). Progression over one-year time was observed in most planimetric and volumetric measures, in all groups (Table S7). GM volumes showed more severe longitudinal loss in PSP-RS patients than in HC, while WM volumes showed similar slight reduction in all groups (Tables 1 and S6). The highest annualized percentage change rate in PSP-RS patients was observed in clinical scores, followed by MR planimetry (MRPI 2.0) and ventricular volumes. On the contrary, the highest effect size and smallest sample size was obtained by automated volumetry

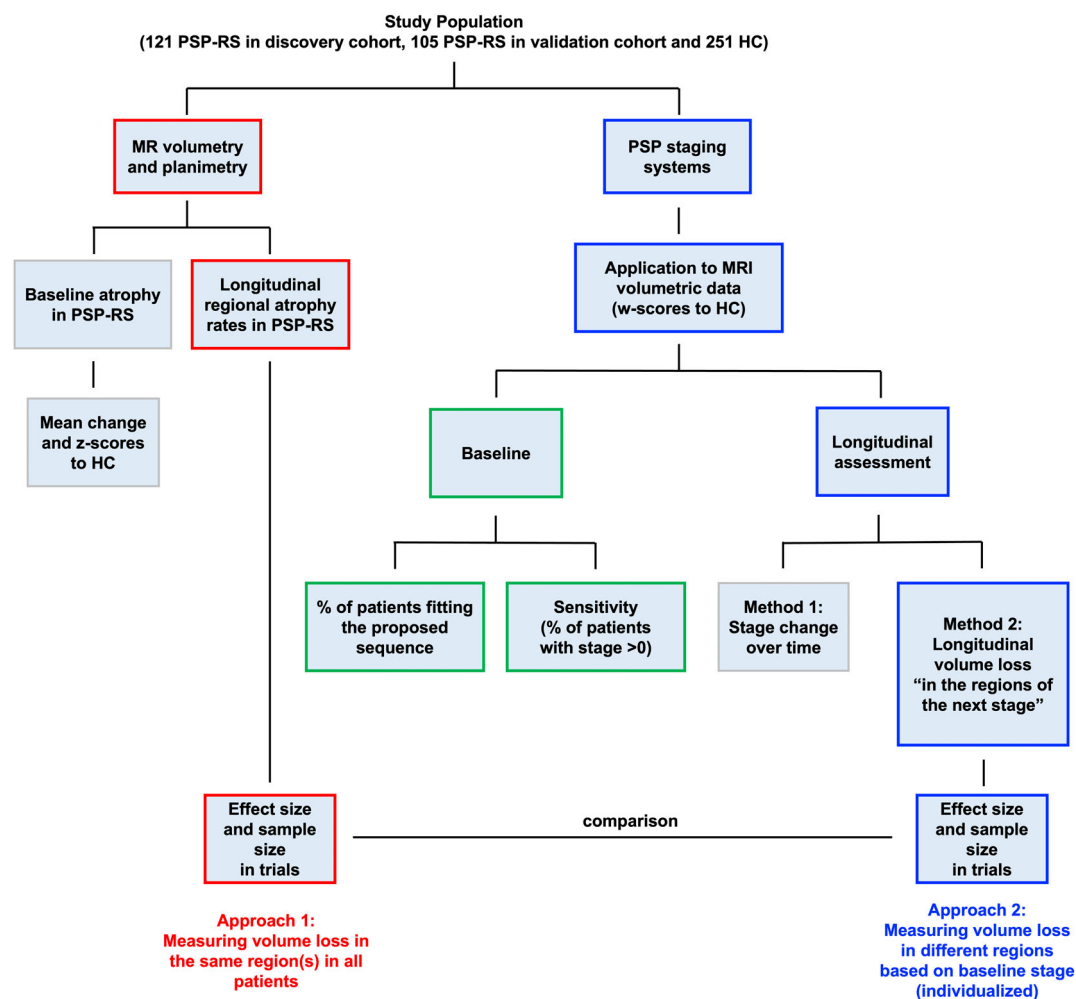


FIG. 1. A flowchart of the study design with the main analyses. Boxes highlighted in red refer to the assessment of magnetic resonance (MR) planimetric and volumetric measures as progression biomarkers in progressive supranuclear palsy-Richardson's syndrome (PSP-RS). Boxes highlighted in blue refer to the assessment of staging systems as progression biomarkers in comparison with automated volumetry and planimetry. Boxes highlighted in green refer to the application of staging systems to MR volumetric data in our patients, to evaluate whether they fitted the described spatial-temporal sequences of the staging systems. HC, healthy controls. [Color figure can be viewed at wileyonlinelibrary.com]

(brainstem, midbrain, red nucleus, lateral ventricles) (Fig. 2, Table S8). An index combining the midbrain, third ventricle, and frontal lobe volume changes performed slightly worse than the midbrain alone. The lower effect sizes of clinical scores and planimetry compared with volumetry were explained by larger inter-individual variability (SD). Further details can be found in the Supplementary Materials. All results were consistent across the two cohorts (Fig. 2, Table S9).

Correlations Between Imaging and Clinical Progression

The proposed imaging progression biomarkers (brainstem and midbrain volumes) were associated with the clinical progression. A linear model including PSP-RS score and brainstem atrophy at baseline as covariates revealed a significant association ($\beta = -0.21$;

$P = 0.0016$) between the brainstem volume annualized percentage change rate and the PSPRS score annualized percentage change rate; similar results were obtained for midbrain volume ($\beta = -0.19$; $P = 0.00413$). Further details are included in the Supplementary Materials and Figure S2.

Application of the Staging Systems to Volumetric Data

For each SS, participants were assigned to a stage based on their atrophy pattern (Tables S2 and S3). First, we investigated the percentage of patients fitting the described sequences of regional involvement, and we found that the Neuronal-ss and the Oligodendroglial-ss showed the highest percentage of patients fitting the described sequence, in both cohorts (Fig. 3, Table S9). The Neuronal-ss also showed the highest sensitivity

TABLE 1 Longitudinal evaluation of clinical and imaging measures in patients with progressive supranuclear palsy and in control subjects

Data	Longitudinal PSP discovery cohort (N = 121)	Longitudinal PSP validation cohort (N = 105)	Longitudinal HC cohort (N = 109)	P-value among all groups
Sex (M/F)	68/53	59/56	63/46	0.219 ^a
Age at baseline (years)	69.8 (5.8)	67.8 (6.9)	72.2 (6.4)	<0.001 ^{b,f,g,h}
Age at follow-up (years)	70.9 (5.8)	68.8 (6.4)	73.3 (6.4)	<0.001 ^{b,f,g,h}
Inter-scan interval (years)	1.07 (0.05)	1.10 (0.23)	1.09 (0.12)	0.340 ^b
Data	PSP discovery annualized change rate, %	PSP validation annualized change rate, %	HC annualized change rate, %	P-value
PSPRS total	+26.5% (24.7)	+26.7% (26.6)	–	0.535 ^c
MR volumetry				
Brainstem	–2.65% (1.57)	–2.72% (1.89)	–0.30% (1.51)	<0.001 ^{d,f,g}
Midbrain	–2.51% (1.57)	–2.60% (1.82)	–0.23% (1.44)	<0.001 ^{d,f,g}
Pons	–2.52% (1.72)	–2.53% (1.99)	–0.18% (1.38)	<0.001 ^{d,f,g}
Medulla	–3.40% (2.40)	–3.67% (2.80)	–0.86% (2.84)	<0.001 ^{d,f,g}
Lateral ventricles	+8.70% (5.64)	+8.37% (6.39)	+3.46% (3.62)	<0.001 ^{d,f,g}
Inferior lateral ventricles	+11.91% (14.09)	+10.87% (13.68)	+4.81% (8.94)	<0.001 ^{d,f,g}
Third ventricle	+6.56% (5.13)	+5.93% (5.14)	+2.57% (3.86)	<0.001 ^{d,f,g}
Fourth ventricle	+4.35% (3.54)	+4.10% (4.52)	+0.55% (3.59)	<0.001 ^{d,f,g}
SCP	–3.27% (2.65)	–2.79% (2.38)	+0.12% (2.77)	<0.001 ^{d,f,g}
Striatum	–3.36% (5.91)	–3.55% (5.15)	+0.19% (2.98)	<0.001 ^{d,f,g}
Caudate nucleus	–4.55% (7.30)	–4.30% (6.36)	–0.04% (2.07)	<0.001 ^{d,f,g}
Putamen	–2.67% (6.44)	–3.00% (5.39)	+0.40% (4.07)	<0.001 ^{d,f,g}
Red nucleus	–2.97% (1.84)	–2.59% (1.92)	–0.44% (1.27)	<0.001 ^{d,f,g}
Midbrain + frontal lobe – third ventricle ^e	–10.67% (6.62)	–10.38% (7.75)	–3.19% (5.03)	<0.001 ^{d,f,g}
MR–PSP staging system				
MRI–ss	–2.78% (2.12)	–2.72% (2.31)	/	0.871 ^d
Neuronal–ss	–2.13% (1.81)	–2.47% (1.95)	/	0.383 ^c
Astroglial–ss	–3.80% (5.76)	–3.03% (4.59)	/	0.695 ^c
Oligodendroglial–ss	–1.87% (1.45%)	–1.45% (1.26%)	/	0.013 ^c
MR planimetry				
Third ventricle width	+6.4% (5.9)	+7.4% (7.4)	+2.69% (8.16)	0.002 ^d
Midbrain area	–7.9% (7.8)	–7.3% (9.3)	–1.2% (5.5)	<0.001 ^{d,f,g}
M/P area ratio	–6.0% (8.4)	–5.5% (10.2)	–0.6% (7.0)	<0.001 ^{d,f,g}
MRPI	+5.7% (15.9)	+8.0% (17.4)	+3.7% (11.3)	0.405 ^d
MRPI 2.0	+10.9% (18.2)	+15.0% (21.9)	+5.9% (14.1)	0.069 ^d

Notes: The annualized percentage change rates of MR measures are shown as mean (standard deviation). For the staging systems, the mean annualized percentage change rates of the regions included into the 'next stage' were considered (ie, for a patient in stage I at baseline, the annualized volumetric change in the structures corresponding to the stage II was considered; etc.). Patients who did not fit the considered staging system at baseline were not included in this analysis. Significant *P*-values after Bonferroni correction are highlighted in bold type. Patients with values of 0 in clinical scores at baseline or follow-up were not considered in this analysis to avoid 'infinite' values. A selection of the best clinical, volumetric, and planimetric measures is shown in this table. The full list of all volumetric and planimetric measures is included in the Supplementary Materials.

Abbreviations: Astroglial–ss, neuropathologically-derived staging system in astroglial cells; CSF, cerebrospinal fluid; GM, grey matter; HC, healthy control subjects; ICP, inferior cerebellar peduncle; MCP, middle cerebellar peduncle; M/P, midbrain/pons; MRI, magnetic resonance imaging; MRI–ss, MRI-derived staging system; MRPI, Magnetic Resonance Parkinsonism Index; Neuronal–ss, neuropathologically-derived staging system in neurons; NS, not significant; Oligodendroglial–ss, neuropathologically-derived staging system in oligodendroglial cells; PSP, progressive supranuclear palsy; PSPRS, PSP rating scale; SCP, superior cerebellar peduncle; WM, white matter.

^aFisher's exact test.

^bANOVA followed by post-hoc test.

^cTwo-sample *t*-test or Wilcoxon rank-sum test, with Bonferroni correction ($P < 0.05/12$; $P < 0.00417$).

^dANCOVA with age and sex as covariates, with Bonferroni correction ($P < 0.05/64$; $P < 0.00078$), followed by post-hoc test.

^eThe annualized percentage change rate after dividing it by the number of the regions ($n = 3$) was: –3.56% (2.21) in the discovery PSP cohort, –3.46% (2.58) in the validation PSP cohort, and –1.06% (1.67) in the HC cohort.

^fPSP-RS in the discovery cohort vs. HC, $P < 0.05$ in the post-hoc analysis.

^gPSP-RS in the validation cohort vs. HC, $P < 0.05$ in the post-hoc analysis.

^hPSP-RS in the discovery cohort vs. PSP-RS in the validation cohort, $P < 0.05$ in the post-hoc analysis.

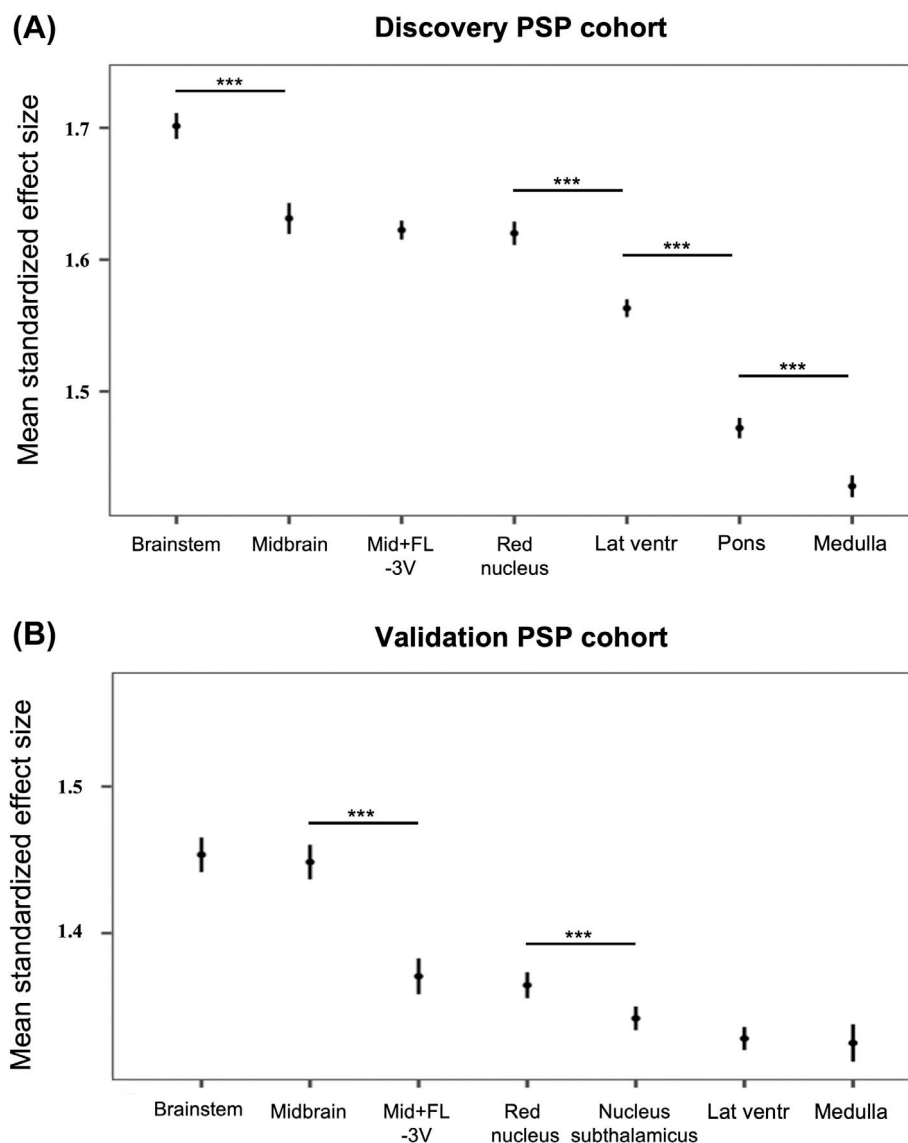


FIG. 2. Mean standardized effect size value with 95% confidence intervals of the best regions/scores, in the discovery (A) and validation (B) progressive supranuclear palsy (PSP) cohorts. The standardized effect size for each magnetic resonance (MR) measure was calculated as the mean annualized percentage change rate divided by its standard deviation in PSP patients. The brainstem volume, the midbrain volume, the combined volumetric index (midbrain + frontal lobe – third ventricle volume changes), and the red nucleus volume showed the highest effect size values in both cohorts. Planimetric measures and staging systems are not shown in the figure since their effect size values were lower than those of the measures shown here. The performances of different regions/scores were compared using Wilcoxon rank-sum test. *** $P < 0.001$.

(percentage of PSP patients in stage >0), while other systems had more patients in stage 0 (Fig. 3, Table S9), in both cohorts. Further data are available in the Supplementary Materials and Tables S10–S12. Overall, the Neuronal-ss was the most reliable SS in our cohorts.

Longitudinal Staging Systems' Assessment

We first investigated whether PSP-RS patients changed stage over time (Method 1), but >75% patients remained on the same stage between baseline and follow-up, for all SS (Fig. 4, Table S13). By stratifying patients by stage at baseline and measuring the volume change rates of the regions in the next stage (Method

2, see Supplementary Materials) we obtained lower effect size and sample size estimation for all SS than those obtained by using the brainstem or midbrain volume in all patients (Table S8). All results were consistent across the two cohorts.

Discussion

In this study including two independent large cohorts of PSP-RS patients, the automated atlas-based volumetry of brainstem regions showed the highest effect size and required the lowest sample size ($n < 100$) to evaluate atrophy progression over a one-year time

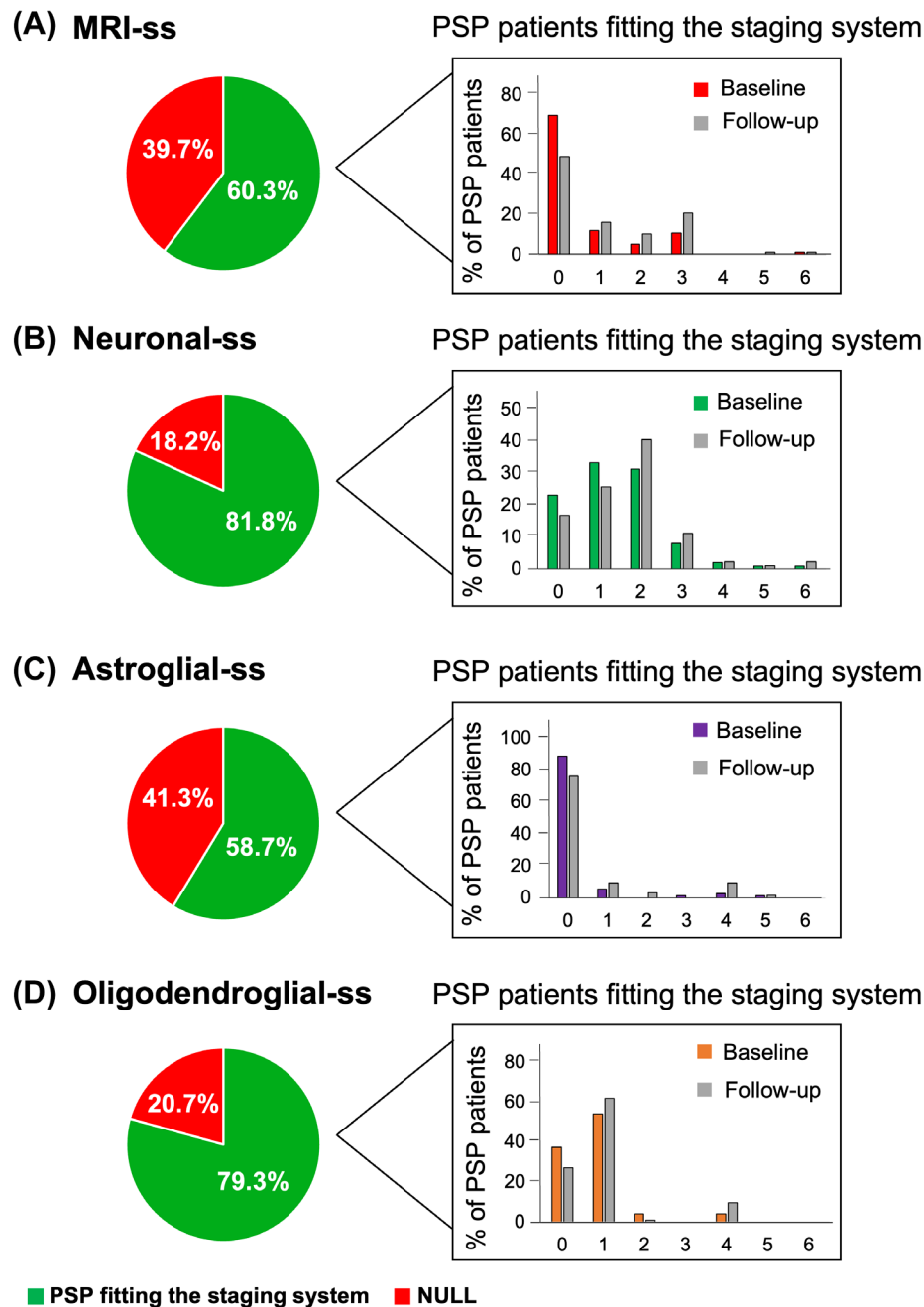


FIG. 3. For each of the considered staging systems, the left half of the figure shows a pie chart with the percentage of progressive supranuclear palsy (PSP) patients fitting the sequential regional involvement described by the staging system at baseline (in green). The right part of the figure shows the distribution across stages 0–6 of PSP patients fitting the staging system. The Neuronal-ss and the Oligodendroglial-ss showed the highest percentage of PSP patients fitting the staging system, and the Neuronal-ss had the highest sensitivity (percentage of patients assigned to stages above zero). Data shown in the figure are from the discovery PSP cohort; detailed data for both cohorts can be found in the Supplementary Materials. **(A)** MRI-ss = MRI-derived staging system; **(B)** Neuronal-ss = neuropathologically-derived staging system in neurons; **(C)** Astroglial-ss = neuropathologically-derived staging system in astroglial cells; **(D)** Oligodendroglial-ss = neuropathologically-derived staging system in oligodendroglial cells. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/terms-and-conditions)]

period in PSP-RS, outperforming other volumetric/planimetric measures and the PSP staging systems described to date.

About 20 interventional trials have been conducted in PSP over the last two decades, six are ongoing and others are planned for future years.³⁸ Half of these trials included among their endpoints structural MRI,

making it the most used objective progression biomarker in PSP (clinicaltrials.gov). These data highlight a very urgent need for robust evidence guiding the selection of MR measurements as endpoints in upcoming trials.⁸ Existing studies investigated longitudinal brain atrophy in PSP measuring the progressive volume change of crucially involved regions.^{13–20} The recent

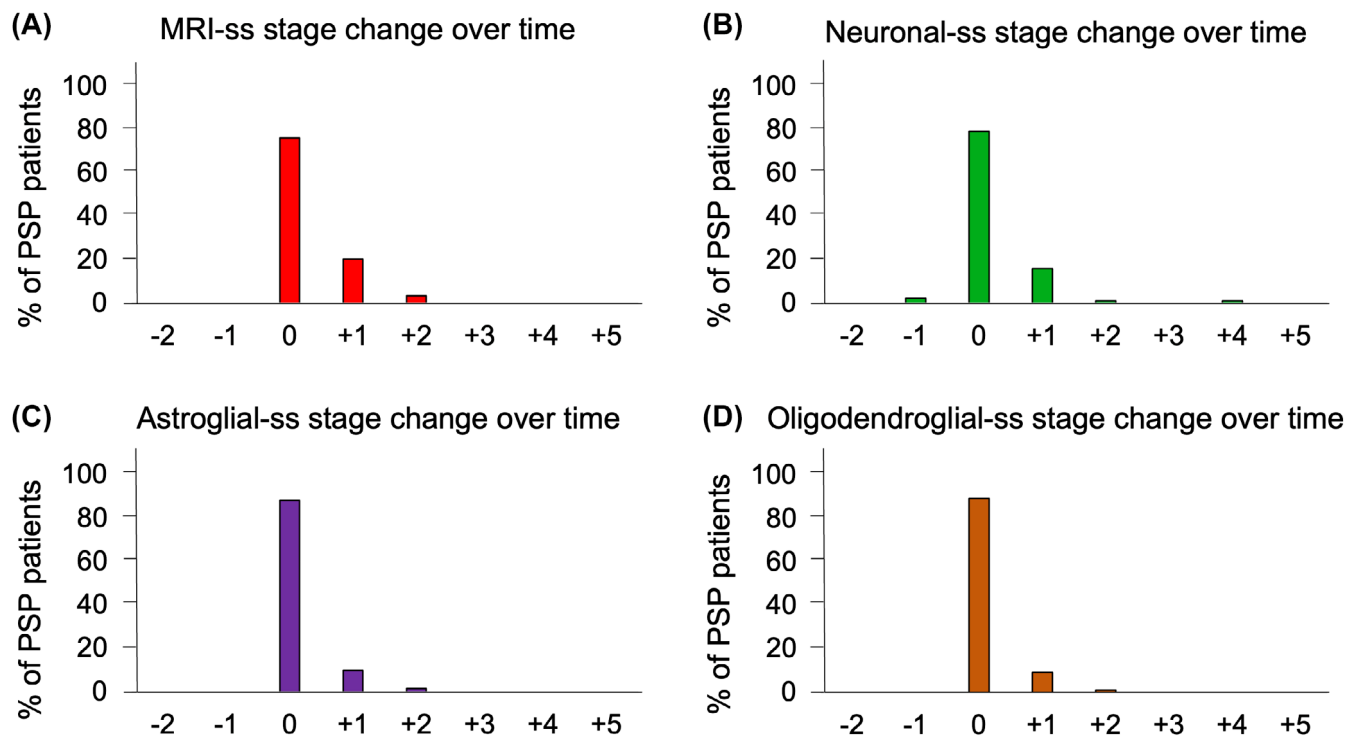


FIG. 4. Stage change over time between baseline and follow-up examination in progressive supranuclear palsy (PSP) patients, for each staging system. (A) MRI-ss = MRI-derived staging system; (B) Neuronal-ss = neuropathologically-derived staging system in neurons; (C) Astroglial-ss = neuropathologically-derived staging system in astroglial cells; (D) Oligodendroglial-ss = neuropathologically-derived staging system in oligodendroglial cells. On the x-axis of each graph, negative values reflect a stage decrease while positive values reflect a stage increase over time; 0 means no stage change over a one-year time period. Patients with non-null stage both at baseline and follow-up examinations were included in this analysis (MRI-ss, PSP = 59; Neuronal-ss, PSP = 87; Astroglial-ss, PSP = 60; Oligodendroglial-ss, PSP = 86). Data shown in the figure are from the discovery PSP cohort; detailed data for both cohorts can be found in the Supplementary Materials. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/mds.29866)]

description of distinct stages in the neurodegenerative PSP process,²⁶⁻²⁸ however, allows for a potential paradigm shift in how to measure brain atrophy progression. Indeed, the understanding of the temporal sequence of brain regions' involvement allows assessment of atrophy spread, rather than simply measuring progressive volume loss in a target region. In this study, we compared these two different methods of measuring atrophy progression, by calculating longitudinal volume change in the same regions in all patients on one hand (approach-1) and by assessing the atrophy spread to 'new' regions starting from the baseline atrophy pattern (stage) on the other hand (approach-2).

By looking at the same regions in all patients, we performed a head-to-head comparison of many planimetric and volumetric measures. Automated planimetric measures (MRPI, MRPI 2.0)^{21,34} showed greater potential than volumetry in detecting atrophy at baseline, and the MRPI 2.0 showed a remarkable mean annualized percentage increase (10–15%), higher than other measures, but a large standard deviation was observed, due to high interindividual variability. Conversely, volumetric measures had lower percentage change over time (2–5% in most regions), but showed a very consistent change across subjects, with minimal standard

deviations. These discrepancies, which may well be explained by the different nature of these imaging measures (planimetry focusing exclusively on specific parts of the brain structures, and volumetry considering the entire structures), may make these two MR techniques potentially useful in different scenarios. Indeed, planimetric measures may be more sensitive tools to study individual trajectories of atrophy progression in PSP patients, and further studies are needed to clarify their biological relevance; conversely, MR volumetry, which had lower variability across subjects, may be more sensitive (fewer patients are required) to detect deviations from the expected atrophy progression rates, which is crucial in clinical trials. Among volumetric measures, the top three in terms of effect size and sample size estimation were the brainstem volume, the midbrain volume, and a combined index obtained by summing midbrain, frontal lobe, and third ventricle volume changes.¹⁷ These robust volumetric measures were also more powerful than clinical scores as progression markers (in terms of effect size and sample size estimations), in line with previous reports,^{17,20} supporting their use as endpoints in clinical trials.

The second approach, consisting of an individualized assessment of atrophy spread to new regions depending

on the baseline atrophy pattern, was performed through the application of previously described staging systems^{26,28} to MR volumetric data. These included: three SS derived from neuropathologic data describing the sequential involvement of brain regions in terms of tau pathology in the three main cell populations (neurons, astroglia, oligodendroglia),²⁶ and a probabilistic data-driven SS reflecting the sequence of brain atrophy based on MRI volumes.²⁸

The current study represents the first attempt to apply neuropathologic SS to volumetric MRI data *in vivo*, and to validate the MRI-derived SS described by Scotton et al²⁸ in independent cohorts. For this reason, prior to longitudinal analysis, we conducted a preliminary analysis to evaluate whether our patients fitted the described spatial-temporal sequences of the various SS. More than 70% of patients showed a brain atrophy pattern fitting the sequence described by the neuronal and oligodendroglial neuropathologic SS,²⁶ while lower percentages of patients showed an atrophy pattern consistent with the sequence of tau pathology regional involvement in astroglia²⁶ or with the previously described MRI-derived SS.²⁸ This result provides insights into the association between MR volumes and tau pathological burden,³⁹ suggesting that brain atrophy selectively matches tau pathology in neurons and oligodendroglia. Indeed, Tau accumulation starts in the neurons of the globus pallidus and brainstem regions,²⁶ and in the oligodendroglia of the globus pallidus,²⁶ which were among the most atrophic regions in our PSP patients, in both cohorts. On the contrary, astroglial tau accumulation starts in the striatum, spreading to the globus pallidus and midbrain only in the latest stages,²⁶ not matching the spatial-temporal sequence of atrophy. The relatively low percentage of patients fitting the previously described MRI-derived staging system²⁸ may be explained by the different methodology, since the other researchers employed event-based modeling²⁸ while we used w-scores from HC to establish the presence of atrophy and apply the described SS. The rationale of our approach is a higher feasibility in clinical trial settings, where complex mathematical algorithms for staging might not be available.

Subsequently, we investigated the usefulness of imaging SS in tracking PSP-related atrophy progression. We first assessed the progression through different stages over time, and then measured volume changes in the regions which were the next to be involved according to the SS spatial-temporal sequence. Both methods investigated atrophy spread to new regions; the former was simpler and straightforward, while the latter was complex but allowed effect size and sample size estimations. Unfortunately, the direct evaluation of stage increase over time was not a suitable method, since >75% of patients remained on the same stage between baseline and 52-week follow-up. The second method detected

longitudinal volumetric changes, but showed smaller effect size and required larger sample sizes in trials than measuring the midbrain or brainstem volume in all patients.

This study has great novelty in the application of neuropathologically derived SS²⁶ to MRI data, also assessing their usefulness in tracking disease progression, and has several strengths. First, this is the largest longitudinal study comparing structural MRI progression biomarkers in PSP-RS, validating the results in two large, international cohorts. Second, all MRI measures were obtained using automated pre-established operator-independent methods, avoiding subjective evaluations. Third, the study population included patients fulfilling the inclusion/exclusion criteria employed in previous clinical trials to provide a reliable evidence-based guide for selecting imaging endpoints in trial settings. Finally, the longitudinal change of the proposed measures was significantly larger in PSP-RS than in HC, demonstrating that the observed changes were due to the neurodegenerative process rather than just aging.

There are some limitations to the study. First, we selectively investigated progressive brain atrophy in PSP, and other disease control groups were missing; thus, it was not possible to establish whether the observed atrophy rates were specific for PSP or shared across other neurodegenerative diseases. Second, PSP variants were not included due to the very limited sample size, thus restricting our conclusions to PSP-RS. This study design, however, allowed the achievement of robust evidence in PSP-RS (the phenotype most commonly enrolled in trials),^{38,40} reducing the potential heterogeneity due to different clinical and imaging trajectories in PSP variants.^{38,41-43} Third, we investigated atrophy progression at the group level, but several factors such as age at onset, duration, clinical severity, or atrophy at baseline may influence individual clinical and imaging progression.⁴⁴⁻⁴⁶ Future studies to develop powerful models for predicting individual trajectories in PSP patients are needed. Fourth, this was a multicohort study and imaging data were acquired with different MRI protocols, potentially introducing some bias; the two PSP cohorts, however, showed very similar atrophy pattern and progression rates despite the MRI protocol discrepancies, suggesting no major impact on the reliability of our findings. A final limitation was the lack of post-mortem diagnostic confirmation; however, the mismatch between clinical and pathological diagnoses is usually low in patients with a PSP-RS phenotype.^{1,47}

In conclusion, this large, longitudinal study performed a comprehensive head-to-head comparison of several structural MRI measures and identified the automated volumetry of brainstem regions as the most suitable progression biomarker for trials in PSP-RS. These findings provide robust evidence to inform the

selection of imaging endpoints in PSP-RS, supporting the design and execution of upcoming disease-modifying clinical trials.

Funding Sources and Conflicts of Interest

H.J.H. has used atlas-based volumetric MRI analysis in industry-sponsored research projects. M.K. serves as a consultant for AbbVie and Stada; received honoraria for scientific presentations from AbbVie, Ever, and Licher, and was funded by the German Parkinson's Disease Association, Pitzer Foundation, Petermax-Müller Foundation, and MHH Plus Foundation. J.L. reports speaker fees from Bayer Vital, Biogen, Eisai, Merck, Roche, TEVA, and Zambon; consulting fees from Axon Neuroscience, Eisai, and Biogen; author fees from Thieme medical publishers, and W. Kohlhammer GmbH medical publishers; and is inventor of a patent 'Oral Phenylbutyrate for Treatment of Human 4-Repeat Tauopathies' (EP 23156122.6) filed by LMU Munich. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH; is beneficiary of the phantom share program of MODAG GmbH; and is inventor of a patent 'Pharmaceutical Composition and Methods of Use' (EP 22159408.8) filed by MODAG GmbH. A.L.B. has served as a paid consultant to AGTC, Alchemab, Alector, Alzprotect, Amylyx, Arkuda, Arrowhead, Arvinas, Aviado, Eli Lilly, GSK, Humana, Merck, Modalis, Muna, Oligomerix, Oscotec, Pfizer, Roche, Switch, Transposon, and UnlearnAI. His institution received research support from Biogen and Eisai for him serving as a site investigator for clinical trials, as well as from Regeneron. He has received research support from the National Institutes on Aging: NIH U19AG063911, R01AG078457, R01AG073482, R56AG075744, R01AG038791, RF1A G077557, P01AG019724, R01AG071756, U24AG057437; Rainwater Charitable Foundation, Bluefield Project to Cure FTD, GHR Foundation, Alzheimer's Association, Association for Frontotemporal Degeneration, Gates Ventures, Alzheimer's Drug Discovery Foundation, UCSF Parkinson's Spectrum Disorders Center, and the University of California Cures AD Program. G.H. participated in industry-sponsored research projects from AbbVie, Biogen, Biohaven, Novartis, Roche, Sanofi, and UCB; has ongoing research collaborations with Roche, UCB, and AbbVie; serves as a consultant for AbbVie, Alzprotect, Amylyx, Aprineua, Asceneuron, Bayer, Bial, Biogen, Biohaven, Epidarex, Ferrer, Kyowa Kirin, Lundbeck, Novartis, Retrotope, Roche, Sanofi, Servier, Takeda, Teva, and UCB; received honoraria for scientific presentations from AbbVie, Bayer, Bial, Biogen, Bristol Myers Squibb, Kyowa Kirin, Pfizer, Roche, Teva, UCB, and Zambon. G.H. was funded by the Deutsche

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Data Availability Statement

The data were collected within the context of clinical trials or observational studies and can be requested from the respective owners of the data.

References

1. Stamelou M, Respondek G, Giagkou N, Whitwell JL, Kovacs GG, Hoglinger GU. Evolving concepts in progressive supranuclear palsy and other 4-repeat tauopathies. *Nat Rev Neurol* 2021;17(10):601–620.
2. Hoglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord* 2017;32(6):853–864.
3. Coughlin DG, Litvan I. Progressive supranuclear palsy: advances in diagnosis and management. *Parkinsonism Relat Disord* 2020;73:105–116.
4. Hoglinger GU, Litvan I, Mendonca N, et al. Safety and efficacy of tilavonemab in progressive supranuclear palsy: a phase 2, randomised, placebo-controlled trial. *Lancet Neurol* 2021;20(3):182–192.
5. Hoglinger GU, Huppertz HJ, Wagenpfeil S, et al. Tideglusib reduces progression of brain atrophy in progressive supranuclear palsy in a randomized trial. *Mov Disord* 2014;29(4):479–487.
6. Dam T, Boxer AL, Golbe LI, et al. Safety and efficacy of anti-tau monoclonal antibody gosuranemab in progressive supranuclear palsy: a phase 2, randomized, placebo-controlled trial. *Nat Med* 2021;27(8):1451–1457.
7. Boxer AL, Lang AE, Grossman M, et al. Davunetide in patients with progressive supranuclear palsy: a randomised, double-blind, placebo-controlled phase 2/3 trial. *Lancet Neurol* 2014;13(7):676–685.
8. van Eimeren T, Antonini A, Berg D, et al. Neuroimaging biomarkers for clinical trials in atypical parkinsonian disorders: proposal for a neuroimaging biomarker utility system. *Alzheimers Dement (Amst)* 2019;11:301–309.
9. Brendel M, Barthel H, van Eimeren T, et al. Assessment of 18F-PI-2620 as a biomarker in progressive supranuclear palsy. *JAMA Neurol* 2020;77(11):1408–1419.
10. Tezuka T, Takahata K, Seki M, et al. Evaluation of [¹⁸F]PI-2620, a second-generation selective tau tracer, for assessing four-repeat tauopathies. *Brain Commun* 2021;3(4):fcab190.
11. Jin J, Su D, Zhang J, Li X, Feng T. Tau PET imaging in progressive supranuclear palsy: a systematic review and meta-analysis. *J Neurol* 2023;270(5):2451–2467.

12. Leuzy A, Chiotis K, Lemoine L, et al. Tau PET imaging in neurodegenerative tauopathies-still a challenge. *Mol Psychiatry* 2019;24(8):1112–1134.
13. Dutt S, Binney RJ, Heuer HW, et al. Progression of brain atrophy in PSP and CBS over 6 months and 1 year. *Neurology* 2016;87(19):2016–2025.
14. Tsai RM, Lobach I, Bang J, et al. Clinical correlates of longitudinal brain atrophy in progressive supranuclear palsy. *Parkinsonism Relat Disord* 2016;28:29–35.
15. Agosta F, Caso F, Jecmenica-Lukic M, et al. Tracking brain damage in progressive supranuclear palsy: a longitudinal MRI study. *J Neurol Neurosurg Psychiatry* 2018;89(7):696–701.
16. Paviour DC, Price SL, Lees AJ, Fox NC. MRI derived brain atrophy in PSP and MSA-P. Determining sample size to detect treatment effects. *J Neurol* 2007;254(4):478–481.
17. Hoglinger GU, Schope J, Stamelou M, et al. Longitudinal magnetic resonance imaging in progressive supranuclear palsy: a new combined score for clinical trials. *Mov Disord* 2017;32(6):842–852.
18. Whitwell JL, Xu J, Mandrekar JN, Gunter JL, Jack CR Jr, Josephs KA. Rates of brain atrophy and clinical decline over 6 and 12-month intervals in PSP: determining sample size for treatment trials. *Parkinsonism Relat Disord* 2012;18(3):252–256.
19. Whitwell JL, Tosakulwong N, Schwarz CG, et al. MRI outperforms [18F]AV-1451 PET as a longitudinal biomarker in progressive supranuclear palsy. *Mov Disord* 2019;34(1):105–113.
20. Street D, Jabbari E, Costantini A, et al. Progression of atypical parkinsonian syndromes: PROSPECT-M-UK study implications for clinical trials. *Brain* 2023;146(8):3232–3242.
21. Nigro S, Antonini A, Vaillancourt DE, et al. Automated MRI classification in progressive supranuclear palsy: a large international cohort study. *Mov Disord* 2020;35(6):976–983.
22. Whitwell JL, Hoglinger GU, Antonini A, et al. Radiological biomarkers for diagnosis in PSP: where are we and where do we need to be? *Mov Disord* 2017;32(7):955–971.
23. Hwang M, Yang H, Kim Y, et al. Differential progression of midbrain atrophy in parkinsonism: longitudinal MRI study. *Neurodegener Dis* 2017;17(1):31–37.
24. Kannenberg S, Caspers J, Dinkelbach L, et al. Investigating the 1-year decline in midbrain-to-pons ratio in the differential diagnosis of PSP and IPD. *J Neurol* 2021;268(4):1526–1532.
25. Quattrone A, Morelli M, Quattrone A, et al. Magnetic Resonance Parkinsonism Index for evaluating disease progression rate in progressive supranuclear palsy: a longitudinal 2-year study. *Parkinsonism Relat Disord* 2020;72:1–6.
26. Kovacs GG, Lukic MJ, Irwin DJ, et al. Distribution patterns of tau pathology in progressive supranuclear palsy. *Acta Neuropathol* 2020;140(2):99–119.
27. Briggs M, Allinson KSJ, Malpetti M, Spillantini MG, Rowe JB, Kaalund SS. Validation of the new pathology staging system for progressive supranuclear palsy. *Acta Neuropathol* 2021;141(5):787–789.
28. Scotton WJ, Bocchetta M, Todd E, et al. A data-driven model of brain volume changes in progressive supranuclear palsy. *Brain Commun* 2022;4(3):fcac098.
29. Respondek G, Hoglinger GU. DescribePSP and ProPSP: German multicenter networks for standardized prospective collection of clinical data, imaging data, and biomaterials of patients with progressive supranuclear palsy. *Front Neurol* 2021;12:644064.
30. Huppertz HJ, Moller L, Sudmeyer M, et al. Differentiation of neurodegenerative parkinsonian syndromes by volumetric magnetic resonance imaging analysis and support vector machine classification. *Mov Disord* 2016;31(10):1506–1517.
31. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage* 2012;61(4):1402–1418.
32. Nigro S, Arabia G, Antonini A, et al. Magnetic resonance parkinsonism index: diagnostic accuracy of a fully automated algorithm in comparison with the manual measurement in a large Italian multicentre study in patients with progressive supranuclear palsy. *Eur Radiol* 2017;27(6):2665–2675.
33. Nigro S, Cerasa A, Zito G, et al. Fully automated segmentation of the pons and midbrain using human T1 MR brain images. *PLoS One* 2014;9(1):e85618.
34. Quattrone A, Bianco MG, Antonini A, et al. Development and validation of automated Magnetic Resonance Parkinsonism Index 2.0 to distinguish progressive Supranuclear palsy-parkinsonism from Parkinson's disease. *Mov Disord* 2022;37(6):1272–1281.
35. Malpetti M, Kaalund SS, Tsvetanov KA, et al. In vivo ¹⁸F-flortaucipir PET does not accurately support the staging of progressive supranuclear palsy. *J Nucl Med* 2022;63(7):1052–1057.
36. Liu FT, Lu JY, Li XY, et al. (18F)-Florizotol PET imaging captures the distribution patterns and regional vulnerability of tau pathology in progressive supranuclear palsy. *Eur J Nucl Med Mol Imaging* 2023;50(5):1395–1405.
37. Stamelou M, Schope J, Wagenpfeil S, et al. Power calculations and placebo effect for future clinical trials in progressive supranuclear palsy. *Mov Disord* 2016;31(5):742–747.
38. Street D, Malpetti M, Rittman T, et al. Clinical progression of progressive supranuclear palsy: impact of trials bias and phenotype variants. *Brain Commun* 2021;3(3):fcab206.
39. Spina S, Brown JA, Deng J, et al. Neuropathological correlates of structural and functional imaging biomarkers in 4-repeat tauopathies. *Brain* 2019;142(7):2068–2081.
40. Mariani LL, Guimaraes-Costa R, Grabli D, et al. Are PSP patients included in clinical trials representative of the general PSP population? *Parkinsonism Relat Disord* 2019;66:202–206.
41. Pavone C, Weigand SW, Ali F, et al. Longitudinal clinical decline and baseline predictors in progressive supranuclear palsy. *Parkinsonism Relat Disord* 2023;107:105290.
42. Scotton WJ, Shand C, Todd E, et al. Uncovering spatiotemporal patterns of atrophy in progressive supranuclear palsy using unsupervised machine learning. *Brain Commun* 2023;5(2):fcad048.
43. Shoeibi A, Litvan I, Tolosa E, Ser TD, Lee E, TAUROS Investigators. Progression of two progressive supranuclear palsy phenotypes with comparable initial disability. *Parkinsonism Relat Disord* 2019;66:87–93.
44. AlWazan BA, Garcia-Cordero I, Couto B, et al. Investigating differences in young- and late-onset progressive supranuclear palsy. *J Neurol* 2023;270(12):6103–6112.
45. Whitwell JL, Xu J, Mandrekar J, Gunter JL, Jack CR Jr, Josephs KA. Imaging measures predict progression in progressive supranuclear palsy. *Mov Disord* 2012;27(14):1801–1804.
46. Bang J, Lobach IV, Lang AE, et al. Predicting disease progression in progressive supranuclear palsy in multicenter clinical trials. *Parkinsonism Relat Disord* 2016;28:41–48.
47. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol* 2009;8(3):270–279.

APPENDIX

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.