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Clinical Correlates of Cognitive Impairment in Progressive Supranuclear Palsy and Multiple System Atrophy: A Comparative Neuropsychological Study

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Abstract

Background

Atypical Parkinsonian Syndromes (AP), such as Progressive Supranuclear Palsy (PSP), Multiple System atrophy (MSA), are characterized by motor and non-motor symptoms. Although cognitive impairment is a core feature of AP, its differential profile across AP syndromes has been inadequately understood, particularly in underrepresented populations like in India.

Aim

To compare cognitive and neuropsychological profiles in PSP and MSA and examine their clinical correlates.

Methods

In this cross-sectional study, AP patients underwent cognitive assessment using the Frontal Assessment Battery (FAB), the Montreal Cognitive Assessment (MoCA), the Addenbrooke's Cognitive Examination-III (ACE-III), and selected neuropsychological tests from the NIMHANS Neuropsychology Battery for the elderly (NNBE). Between-group comparisons were conducted using age-adjusted ANCOVA. Partial correlations examined associations between cognition and clinical variables within each group.

Results

A total of 159 patients were included in which PSP (n = 98, mean age 62.5 ± 7.4 years) was older than MSA (n = 61, 58.6 ± 7.8 years). Groups were gender-matched (p = 0.48). After age adjustment and FDR correction, PSP showed significantly lower scores than MSA on FAB, MoCA, and ACE-III Total, as well as on fluency, attention, visuospatial construction, and visuospatial working memory measures (all corrected $p < 0.05$). In PSP, cognitive performance correlated with education, motor severity (UPDRS-III, PSPRS), and mood (all $p < 0.05$), whereas in MSA, cognition correlated only with education and multilingualism, with no significant association with motor or symptom severity.

Conclusion

PSP demonstrates greater global and domain-specific cognitive impairment than MSA, particularly in fluency and working memory, with cognition more closely tied to motor and mood burden. In MSA, cognition is more reserve-driven. Routine cognitive screening may aid early differentiation and clinical management of AP.

Introduction

Atypical Parkinsonian syndromes (AP), including Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA), are progressive neurodegenerative disorders marked by a combination of motor and non-motor features that complicate diagnosis and management. They share Parkinsonian motor manifestations with idiopathic Parkinson's disease (PD), but differ in neuropathology, progression, responsiveness to dopaminergic therapy, and the profile of cognitive and behavioral impairments(McFarland and Hess 2017; Jellinger 2025). Cognitive dysfunction is increasingly recognized as a clinical "red flag" in these syndromes(McFarland and Hess 2017), affecting executive function, attention, verbal fluency, memory, language, and visuospatial abilities, though assessment is often confounded by bradyphrenia, speech impairment, and motor slowing(Jellinger 2025). Early and accurate cognitive evaluation is nevertheless important for differential diagnosis, prognostication, and understanding functional outcomes(Raimo et al. 2023).

Cognitive impairment in AP is heterogeneous across syndromes and phenotypic subtypes(Raimo et al. 2023), and cognitive dysfunction in PSP and MSA remains relatively understudied(Jellinger 2025). Prior work suggests(Raimo et al. 2023) a gradient of cognitive severity across AP, with MSA typically showing milder impairment and PSP exhibiting more prominent executive and global cognitive deficits, including impairments in set shifting, inhibitory control, verbal fluency, working memory, and aspects of memory with relatively preserved early episodic memory(Litvan et al. 1989; Gerstenecker et al. 2013). In contrast, global cognitive decline in MSA is less consistently reported and is not considered a defining feature(Stankovic et al. 2014). Verbal fluency and memory deficits are generally more pronounced in PSP than in MSA(Miki et al. 2021), though findings are not entirely uniform across studies(Bak et al. 2005). Whether this gradient reflects a genuine difference in disease-driven cognitive burden, or is instead shaped by demographic factors such as age and cognitive reserve, has not been systematically examined.

Neuropsychiatric symptoms such as apathy, depression, anxiety, and sleep behavior disorder significantly contribute to functional disability(Santangelo et al. 2018). However, most available data derive from Western cohorts and are limited by modest sample sizes and restricted neuropsychological assessment. Data from South Asian populations remains scarce, despite indications of a relatively higher frequency of sporadic AP with early cognitive dysfunction among individuals of Indian origin(Chaudhuri et al. 2000).

To address this gap, there is a need for multidomain cognitive and neuropsychiatric characterization of PSP and MSA in well-phenotyped, underrepresented cohorts, and for a clearer understanding of how demographic, linguistic, and disease-related factors shape cognitive outcomes. The present cross-sectional study, conducted within an ongoing multicentre prospective atypical Parkinsonism project (ATPARK)(Yadav et al. 2025) In India, systematically compares global and domain-specific cognitive performance and neuropsychiatric profiles in PSP and MSA using a standardized test battery. In addition, we examined how education, multilingualism, motor severity, and affective symptoms relate to cognition

within each syndrome, to assess whether the pattern of cognitive correlates, disease-driven versus reserve-driven, differs between PSP and MSA.

Materials and methods

Study setting and study participants

This cross-sectional study was conducted at the National Institute of Mental Health and Neuro Sciences (NIMHANS) and MS Ramaiah Medical College and Hospital, Bengaluru, India. Between July 2024 and November 2025, movement disorder specialists recruited 159 patients. Eligible participants had a possible diagnosis of atypical parkinsonism (AP), specifically progressive supranuclear palsy (PSP; n = 98) or multiple system atrophy (MSA; n = 61), based on Movement Disorder Society criteria for PSP(Höglinger et al. 2017) & MSA(Wenning et al. 2022). We excluded patients with a history of traumatic brain injury, intellectual developmental disorder, or other psychiatric comorbidities.

Clinical assessments

Socio-demographic variables (age, gender, years of education, etc.) and clinical variables (age of onset and illness duration) were recorded. The most commonly spoken languages in the cohort included Hindi (n = 112), English (n = 81), Kannada (n = 66), Bengali (n = 40), Tamil (n = 25), and Telugu (n = 18). Family history of PD, history of alcohol use, smoking, and presence of health conditions such as diabetes mellitus and hypertension were noted. The motor/disease severity was assessed using the Unified Parkinson's Disease Rating Scale part-III (UPDRS-III)(Goetz et al. 2008), PSP rating scale (PSPRS) (Grötsch et al. 2021), and Unified MSA rating scale Part I and II (UMSARS-I & II)(Wenning et al. 2004), respectively, for PSP and MSA. Depression and anxiety were measured by the Hamilton Depression Rating Scale (HAM-D)(Hamilton 1960) and the Hamilton Anxiety Rating Scale (HAM-A)(Thompson 2015), respectively.

Neuropsychological and cognitive assessments

Cognitive function was evaluated using the Frontal Assessment Battery (FAB)(Dubois et al. 2000), Addenbrooke's Cognitive Examination-III (ACE-III)(Mekala et al. 2020), the Montreal Cognitive Assessment (MoCA)(Nasreddine et al. 2005), and selected subtests (digit span, Corsi block, fluency, Word list, Stick construction test) from the NIMHANS Neuropsychological Battery for Elderly (NNBE) (Tripathi et al. 2013) (**Supplementary file**). Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI)(Cummings et al. 1994).

Statistical Analysis

The collected data were entered into the Research Electronic Data Capture (REDCap) database and analyzed using Jamovi (version 2.6.26). The normality of the data was evaluated using the Shapiro-Wilk. Continuous variables were expressed as mean ± SD or median (Q1-Q3) as appropriate and categorical variables as frequencies (%). Between-group comparisons were conducted using age-adjusted ANCOVA, and associations between cognitive performance and clinical variables were examined using partial correlations controlling for age; for both analyses, the Benjamini-Hochberg false discovery rate (FDR) procedure was applied to correct for multiple comparisons (corrected $p < 0.05$ considered significant). Categorical variables were compared using the chi-square test, with significance set at $p < 0.05$.

Results

Clinical and socio-demographic characteristics

A total of 159 patients with AP were included, comprising 98 PSP (61.6%) and 61 with MSA (38.4%). PSP patients had a significantly later age of onset and had a higher prevalence of hypertension than MSA patients. Disease duration, education, sex, family history, diabetes, smoking, and alcohol use did not differ significantly between groups. Given the significant age difference between groups, all subsequent cognitive and behavioral comparisons were adjusted for age using ANCOVA (Table 1).

Table 1
Demographics and clinical characteristics

Variable	PSP (n = 98)	MSA (n = 61)	p value
Age (years)	62.5 ± 7.4	58.6 ± 7.8	**0.002**
Age of onset (years)	59.9 ± 7.9	55.8 ± 7.9	**0.002**
Sex (M: F)	71:27	41:20	0.482
Duration of Illness	24 (12, 48)	24 (12,37.25)	0.611
Years of education	10 (6.25, 15)	10 (7, 15)	0.614
No. of Languages known	2 (1, 3)	2 (1, 3)	0.683
Family history of PD (%)	7 (7.14)	2 (3.28)	0.483
Consanguinity in family (%)	6 (6.12)	7 (11.48)	0.248
Hypertension (%)	50.0	29.5	**0.013**
Diabetic (%)	29.5	24.5	0.585
Alcohol drinking (%)	22 (22.49)	7 (15.22)	0.133
Smoking (%)	18 (18.37)	6 (9.84)	0.247
UPDRS Part-III	34 (22, 49)	29 (18, 46)	0.265
PSPRS	32 (25, 46)	NA	NA
UMSARS-I	NA	16 (10, 20)	NA
UMSARS-II	NA	17 (11.5,24)	NA
HAM-A	11.3 ± 5.8	11.5 ± 5.5	0.828
HAM-D	12 (9, 15.5)	13.5 (10, 17)	0.137
NPI Total	5 (2, 9)	4 (1, 7)	0.335

Independent sample t-test, values are given in mean ± SD; Mann-Whitney U test, values are given in median (Q1, Q3); Chi-square test (categorical).

Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Neuropsychiatric Inventory (NPI), PSP rating scale (PSPRS), Unified MSA rating scale Part I and II (UMSARS-I & II), Unified Parkinson's Disease Rating Scale part-III (UPDRS-III)

Cognitive and Behavioral Comparison (Age-Adjusted ANCOVA)

After age adjustment and false discovery rate (FDR) correction across 29 comparisons (Benjamini-Hochberg procedure), PSP patients showed significantly lower scores than MSA patients on multiple cognitive domains (Table 2).

Table 2
Cognitive and Behavioral comparison - PSP vs MSA (age-adjusted, FDR-corrected)

Cognitive Measure	PSP (n = 98)	MSA (n = 61)	p (FDR)
Global Cognitive Screening			
MoCA Total	17.0 (11.8–22.2)	21.0 (15.0–24.0)	**0.047**
FAB Total	9.3 ± 3.7	11.3 ± 4.3	**0.040**
ACE-III Total	68.5 (54.0–82.0)	77.0 (62.0–87.0)	**0.049**
ACE-III Sub-domains			
ACE-III Attention	13.0 (10.0–17.0)	15.0 (13.0–18.0)	**0.049**
ACE-III Memory	18.0 (13.0–23.0)	20.0 (15.0–24.0)	0.114
ACE-III Fluency	6.0 ± 2.7	7.7 ± 2.4	**0.003**
ACE-III Language	22.0 (19.0–23.0)	23.0 (20.0–25.0)	0.278
ACE-III Visuospatial	10.0 (7.0–13.0)	13.0 (8.0–15.0)	0.092
Attention & Working Memory (NNBE)			
Digit Span Forward	4.0 (2.0–5.0)	4.0 (3.0–5.0)	**0.049**
Digit Span Backward	2.0 (2.0–4.0)	3.0 (2.0–5.0)	0.102
Corsi Block Forward	3.0 (1.0–5.0)	5.0 (3.2–6.0)	**0.002**
Corsi Block Backward	3.0 (2.0–4.0)	4.0 (3.0–5.0)	**0.008**
Verbal Learning & Memory (NNBE)			
Word List Trial 1	3.0 (2.0–4.0)	4.0 (2.0–4.0)	0.077
Word List Trial 3	5.0 (4.0–7.0)	6.0 (5.0–8.0)	0.065
Word List Delayed Recall	4.0 (2.0–5.0)	4.0 (3.0–6.0)	0.126
Recognition	9.0 (7.0–10.0)	9.0 (7.0–9.0)	0.784
Fluency			
Fruits Fluency	7.5 ± 3.7	9.2 ± 3.0	0.054
Vegetable Fluency	7.9 ± 4.0	10.1 ± 3.9	**0.035**

Values are medians (Mann-Whitney U test) or means (t-test for FAB/fluency measures), adjusted for age via ANCOVA. p-values FDR-corrected (Benjamini-Hochberg) across 29 comparisons. "Yes" = corrected p < 0.05.

Addenbrooke's Cognitive Examination-III (ACE-III), Frontal Assessment Battery (FAB), Montreal Cognitive Assessment (MoCA)

Cognitive Measure	PSP (n = 98)	MSA (n = 61)	p (FDR)
Animal Fluency	8.3 ± 3.7	10.5 ± 4.6	**0.024**
Phonemic Fluency (COWA-P)	3.3 ± 3.1	5.0 ± 3.3	**0.019**
Visuospatial Construction & Memory (NNBE)			
Stick Construction Total	24.0 (17.0–24.0)	24.0 (22.2–24.0)	**0.046**
Stick Construction IR	21.0 (14.0–24.0)	23.0 (20.0–24.0)	0.055
Stick Construction DR	8.0 (5.2–13.0)	13.0 (5.2–15.0)	0.120
Values are medians (Mann-Whitney U test) or means (t-test for FAB/fluency measures), adjusted for age via ANCOVA. p-values FDR-corrected (Benjamini-Hochberg) across 29 comparisons. "Yes" = corrected p < 0.05.			
Addenbrooke's Cognitive Examination-III (ACE-III), Frontal Assessment Battery (FAB), Montreal Cognitive Assessment (MoCA)			

Global cognitive performance was poorer in PSP across all screening measures: FAB Total (p = 0.040), ACE-III Total (p = 0.049), and MoCA (p = 0.047).

ACE-III Subdomains

Within ACE-III sub-domains, significant group differences were observed for Attention (p = 0.049) and Fluency (p = 0.003), while Memory (p = 0.114), Language (p = 0.278), and Visuospatial subscores (p = 0.092) did not survive FDR correction.

NNBE- subtests

Visuospatial attention and working memory, as assessed by the Corsi Block task, were significantly lower in PSP on both forward (p = 0.002) and backward (p = 0.008) conditions. Verbal attention (Digit Span Forward) also differed between groups (p = 0.049). Semantic fluency was reduced in PSP for both vegetable (p = 0.035) and animal naming (p = 0.024), as was phonemic fluency (p = 0.019). Visuo-spatial construction (Stick Construction total score) was significantly lower in PSP (p = 0.046), though immediate and delayed recall variants did not reach significance after correction.

Summary of significant correlations in PSP

Education was the single most pervasive positive predictor of cognitive performance in PSP, with significant associations surviving FDR correction across nearly every domain tested-global cognition (ACE-III Total, MoCA, FAB), all ACE-III subdomains including memory, attention, language, fluency, and visuospatial function, both digit span and Corsi block tasks, all three word list trials and delayed recall, stick construction immediate and delayed, and recognition memory. Effect sizes were moderate to strong, with the highest correlations observed for Digit Span Backward (ρ = +0.60) and MoCA (ρ =

+0.54), suggesting that verbal working memory and global screening performance are most strongly reserve-dependent, even within PSP. **(Figure-1)**

PSPRS showed the broadest and strongest negative correlations with cognition among all clinical variables. Higher disease severity was associated with worse performance across visuospatial construction, memory (both immediate and delayed, ρ= -0.52 to -0.55), FAB and global screening (ρ= -0.40 to -0.53), all three semantic fluency tasks and phonemic fluency (ρ= -0.27 to -0.43), all ACE-III subdomains including memory, attention, language, fluency, and visuospatial, Corsi block tasks, and word list learning and delayed recall. The visuospatial-constructional domain showed the strongest coupling to PSPRS severity, followed closely by executive/fluency measures. **(Figure-1)**

UPDRS-III showed a very similar pattern to PSPRS, with significant negative correlations across visuospatial construction (ρ= -0.51 to -0.52), FAB (ρ= -0.46), ACE-III Total and all subdomains, Corsi block tasks, semantic and phonemic fluency, word list learning, and digit span backward. The overlap between UPDRS-III and PSPRS correlations was substantial, indicating that both motor severity measures independently and redundantly capture the same severity-cognition relationship in PSP. PSPRS showed slightly stronger and more consistent effects, consistent with it being a PSP-specific scale that captures oculomotor and postural instability dimensions closer to the fronto-subcortical circuits driving cognitive decline.

HAM-A had a significant negative association with global cognition, attention, memory, visuospatial function, and MoCA - five domains in total - indicating that anxiety is not merely a parallel comorbidity in PSP but is independently linked to broader cognitive performance, at least at a correlational level. HAM-D showed a narrower but still significant negative association with verbal delayed recall and FAB - suggesting that depression in PSP may have particular relevance for retrieval-based memory and executive function specifically, rather than cognition globally. **(Figure-1)**

Number of languages showed only one significant correlation in PSP - stick construction delayed recall (ρ=+0.30) making multilingualism a comparatively weak predictor in this group, in contrast to its much broader role in MSA. **(Figure-1)**

Summary of significant correlations - MSA

The pattern in MSA was strikingly different and considerably simpler. After FDR correction across 198 comparisons, only two variables showed any significant association with cognition: education and number of languages spoken. **(Figure-2)**

Education was the dominant predictor across virtually every cognitive domain in MSA. It showed strong positive correlations with global cognition (ACE-III Total ρ=+0.59, MoCA ρ =+0.47, FAB ρ=+0.43), all ACE-III subdomains without exception- including attention (ρ =+0.52), memory (ρ=+0.53), language (ρ=+0.49), fluency (ρ=+0.41), and visuospatial (ρ =+0.47) phonemic fluency (ρ=+0.50), both digit span tasks (forward ρ=+0.66, backward ρ =+0.49), and Corsi block backward (ρ=+0.40). The Digit Span Forward correlation of (ρ =+0.66) was the single strongest individual correlation in the entire MSA dataset,

underscoring how powerfully premorbid education predicts immediate auditory attention span in this population.

Number of languages spoken showed a comparably broad pattern, with significant positive associations across global cognition (ACE-III Total ρ=+0.46, MoCA ρ =+0.44, FAB ρ=+0.45), ACE-III subdomains including visuospatial (ρ=+0.45), fluency (ρ=+0.44), language (ρ =+0.39), and attention (ρ=+0.36), phonemic fluency (ρ=+0.51), both digit span tasks, and Corsi block backward. The strength and breadth of the multilingualism effect in MSA are notable, with many languages performing almost as strongly as education across nearly the same set of domains, suggesting that multilingualism contributes cognitive reserve in MSA independently of formal educational attainment.

No measure of disease severity or mood survived correction in MSA. UPDRS-III, UMSARS-I, UMSARS-II, HAM-A, and HAM-D all failed to reach FDR-corrected significance for any cognitive domain. This was not for lack of signal in the raw, uncorrected data; several of these variables showed moderate uncorrected correlations (ρ in the 0.25–0.35 range) - but none withstood correction in a group of 61 patients tested across multiple comparisons. Whether this reflects a true biological decoupling of motor/autonomic severity from cognition in MSA, or a power limitation of this sample size, cannot be resolved from the current data alone.

Discussion

This study examined cognitive and neuropsychological profiles in PSP and MSA, using age-adjusted group comparisons and FDR-corrected correlation analyses to characterize disease-specific patterns of cognitive involvement and their relationship to clinical and sociodemographic variables. The findings reveal not merely a quantitative difference in cognitive burden between the two syndromes, but qualitatively distinct clinical architectures characterized by disease-specific domain profiles, divergent correlate structures, and fundamentally different relationships between cognition and disease severity.

PSP carries a disproportionate burden on across frontal and subcortical cognitive domains

PSP patients performed significantly worse than MSA patients on executive functions (FAB), global cognitive screening (ACE-III Total, MoCA), attention, semantic and phonemic fluency, visuospatial working memory (Corsi block backward), and visuospatial constructional praxis (stick construction), independent of age (Jellinger 2025). Episodic memory, language, and visuospatial memory (both IR and DR) did not differ significantly between groups.

This domain-specific pattern maps onto the known distribution of four-repeat tau pathology in PSP(Stamelou et al. 2021), which preferentially targets the basal ganglia (globus pallidus, subthalamic nucleus, substantia nigra), brainstem, and frontal cortex(Kovacs et al. 2020), with comparatively less

involvement of medial temporal structures central to episodic memory consolidation compared to Alzheimer’s Disease. (Macedo et al. 2022)

This anatomical asymmetry would predict precisely the pattern observed: prominent impairment in domains served by fronto-striato-pallidal and fronto-cerebellar loops (attention, set-shifting, fluency, visuospatial construction), alongside relative preservation of hippocampally-dependent memory encoding. The marked fluency deficit in particular is consistent with disruption of dorsolateral prefrontal-basal ganglia circuitry supporting self-generated word retrieval under time pressure a circuit especially vulnerable to subcortical tau burden. Our findings are concordant with those of Hu et al. (2025), who analyzed a multicentre cohort of 1,138 individuals with PSP, CBS, MSA, and Parkinson's disease and found that frontal executive dysfunction was most pronounced in PSP, whereas cognitive deficits in MSA were comparatively milder. These findings extend this pattern to an Indian clinical cohort.(Hu et al. 2025)

The attentional deficit may also have a partly oculomotor origin: the same brainstem and superior colliculus pathology producing PSP's hallmark vertical gaze palsy could plausibly degrade visual search and attentional scanning on paper-and-pencil or screen-based tasks, independent of "higher-order" executive impairment. Whether this attentional deficit in PSP is primarily executive, primarily oculomotor, or genuinely composite remains a tractable empirical question that this dataset is not positioned to resolve, but it cautions against interpreting attention scores in PSP as a pure index of prefrontal integrity.

In PSP, cognition, motor severity, and mood move together

Cognitive performance in PSP correlated robustly with both UPDRS-III and PSPRS across nearly every domain tested, and independently with anxiety and depression scores in several domains (global cognition, attention, memory, visuospatial function), even after FDR correction across multiple comparisons. This indicates that cognitive decline in PSP does not progress independently of overall disease severity or affective state - the three move together.

A plausible circuit-level explanation is that the same fronto-striato-limbic loops implicated in executive dysfunction also subserve mood regulation, particularly anterior cingulate and orbitofrontal-striatal circuits affected by PSP's basal ganglia and frontal tau burden(Jellinger 2025). Under this account, depression and anxiety in PSP would not be a purely reactive psychological response to motor disability but a direct consequence of the same degenerative process producing the cognitive and motor phenotype apathy, executive impairment, and Parkinsonism as co-emergent outputs of damage to overlapping cortico-striato-pallido-thalamic loops, rather than three independent symptom domains. This has a direct clinical implication: a single cognitive assessment in a PSP patient reflects, at least in part, where that patient sits on the motor-severity and mood spectrum at the time of testing, rather than purely an independent cognitive trajectory.

Notably, this coupling between motor function and cognition in PSP is now supported by independent multicentre evidence: Hu et al. (2025) found that motor function predicted cognition in PSP but not in

MSA, specifically characterizing the motor-cognitive relationship in MSA as decoupled - a pattern that directly mirrors our own findings.(Hu et al. 2025)

In MSA, cognitive performance is determined by reserve, not by disease severity

In sharp contrast, cognitive performance in MSA showed no significant association with motor severity (UPDRS-III), autonomic/historical staging (UMSARS-I), motor examination severity (UMSARS-II), or affective symptoms (HAM-A, HAM-D) once corrected for multiple comparisons. The only variables associated with cognitive performance across nearly every domain were years of education and the number of languages spoken- both established proxies for cognitive reserve. (Stern 2009, 2012).

This dissociation is consistent with the topography of alpha-synuclein pathology in MSA, which is concentrated in olivopontocerebellar and striatonigral systems- cerebellum, pons, putamen, substantia nigra - with comparatively limited primary involvement of the frontal and parietal association cortex (Poewe et al. 2022; Hu et al. 2025). If the cortical substrates underlying the cognitive battery tests (AE III, MoCA) are relatively spared by MSA's core pathological process, cognitive performance would be expected to depend more heavily on factors external to disease severity - precisely as observed.

An additional mechanistic explanation involves cerebellar contributions to cognition. Beyond its established role in motor coordination, the cerebellum participates in higher-order cognitive processing through reciprocal cerebello-thalamo-cortical and cortico-ponto-cerebellar networks. This concept forms the basis of the Cerebellar Cognitive Affective Syndrome (CCAS), in which cerebellar lesions are associated with impairments in executive functioning, attention, verbal fluency, and visuospatial processing, whereas primary amnestic deficits are generally less prominent(Schmahmann and Sherman 1998; Buckner 2013).

In the present study, the cognitive domains that showed relative impairment in the MSA group, namely attention, verbal fluency, and visuospatial-executive functioning, are broadly consistent with the cognitive profile described in CCAS(Schmahmann and Sherman 1998). Although executive dysfunction in MSA is multifactorial and may arise from both cerebellar and striatonigral degeneration, the prominent involvement of the olivopontocerebellar system in MSA provides a biologically plausible substrate for these deficits(Stankovic et al. 2014; Jellinger 2023, 2025).

One possible interpretation is that PSP and MSA produce partially overlapping cognitive profiles through disruption of different large-scale neural circuits. In PSP, four-repeat tau pathology preferentially affects the pallido-nigro-luysian axis and frontal-subcortical networks, leading to prominent executive dysfunction and verbal fluency impairment(Kovacs et al. 2020; Stamelou et al. 2021). In contrast, cognitive impairment in MSA may reflect disruption of cerebello-cortical and striatonigral networks associated with the predominant involvement of the olivopontocerebellar and striatonigral systems by α-synuclein pathology that predominantly affects the olivopontocerebellar and striatonigral

systems(Fanciulli and Wenning 2015; Poewe et al. 2022), resulting in a qualitatively similar but generally less severe pattern of cognitive impairment than that observed in PSP(Hu et al. 2025).

This interpretation is also consistent with our finding that cognitive impairment in PSP demonstrated stronger associations with disease severity than in MSA. Although this hypothesis requires confirmation through multimodal neuroimaging and longitudinal neuropathological studies, it provides a plausible neurobiological framework for understanding how distinct neurodegenerative pathologies may converge on overlapping cognitive domains while differing in the magnitude and progression of cognitive impairment.

The absence of a severity correlation may also reflect a measurement-substrate mismatch rather than true cognitive sparing: UMSARS captures motor and autonomic dysfunction (orthostatic hypotension, bladder dysfunction, gait, bradykinesia) that may not load onto the same neural systems as cognition in MSA(Wenning et al. 2004), whereas PSPRS incorporates oculomotor, bulbar, and axial motor features(Golbe and Ohman-Strickland 2007), several of which arise from brainstem and basal ganglia structures anatomically linked with frontal-subcortical circuits subserving executive function(Kovacs et al. 2020). In other words, UMSARS and standard cognitive tests may simply be probing largely separate neural systems in MSA -not that cognition is broadly spared from the disease process.

Practically speaking, this suggests that in MSA, a patient's educational and linguistic background is a stronger determinant of measured cognitive performance than the current disease stage. Low scores in an MSA patient with limited education may reflect baseline reserve more than disease progression, and serial within-patient tracking may be more informative than cross-sectional comparison against severity scales in this population.

A divergent cognitive architecture between the two atypical Parkinsonism

Together, these findings suggest distinct cognitive–clinical architectures rather than a single continuum in which PSP simply represents a more severe form of cognitive impairment than MSA. In PSP, cognitive impairment was closely associated with disease severity, supporting the concept that cognitive dysfunction constitutes a core clinical manifestation of the disease. This observation is consistent with the preferential involvement of frontal-subcortical networks by four-repeat tau pathology, particularly within the pallido–nigro–luysian axis and its cortical connections(Kovacs et al. 2020; Stamelou et al. 2021), which are central to executive functioning and verbal fluency (Cummings 1993; Hu et al. 2025).

In contrast, cognitive performance in MSA showed weaker associations with disease severity, suggesting that cognitive variability may be influenced by factors beyond motor progression. Given the predominant involvement of the olivopontocerebellar and striatonigral systems in MSA(Stefanova and Wenning 2023), together with evidence for cerebellar contributions to executive, attentional and visuospatial processing, cerebello-cortical dysfunction represents one plausible mechanism underlying these cognitive features(Schmahmann and Sherman 1998).

These observations also raise an important methodological consideration. Conventional neuropsychological batteries, including screening measures that primarily emphasize executive and cortical cognitive functions, may be more sensitive to cognitive impairment arising from frontal-subcortical network degeneration than to the subtler cognitive consequences of cerebellar dysfunction. Consequently, future studies of cognitive impairment in MSA may benefit from incorporating assessments specifically designed to detect Cerebellar Cognitive Affective Syndrome and related cerebellar cognitive deficits alongside conventional neuropsychological measures.

Limitations

The MSA group (n = 61) is smaller than the PSP group (n = 98), and the absence of a significant severity-cognition association in MSA after correction should be interpreted as "not detected at the corrected threshold," not as definitive evidence that no such relationship exists biologically - a larger MSA cohort might reveal smaller but real severity effects. Severity was measured with different, disease-specific instruments in each group (PSPRS/UPDRS-III vs. UMSARS-I/II) that were not designed to be cross-comparable, limiting direct inference about the relative strength of the severity-cognition relationship between diseases. The cross-sectional design precludes any conclusion about the temporal or causal relationship between mood and cognition in PSP, or between reserve and cognitive trajectory in MSA - longitudinal data would be needed to determine, for example, whether reserve in MSA delays the onset of detectable decline or simply masks decline of similar underlying magnitude to PSP. Education and disease severity were also examined as separate univariate correlates in MSA rather than modeled jointly, so their relative and possibly overlapping contributions to cognitive variance were not formally partitioned. We did not stratify participants by clinical subtype due to the limited sample size within individual subgroups, which would have reduced statistical power and the reliability of subgroup comparisons. Future studies with larger cohorts should investigate subtype-specific cognitive profiles and clinical correlates. Finally, oculomotor function was not directly assessed alongside attention measures in PSP, so the proposed oculomotor contribution to the attentional deficit remains a hypothesis rather than a tested finding in this dataset.

Declarations

Acknowledgment: We thank our patients and family members for their willingness to participate in the ATPARK study.

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Disclosures

Ethical Compliance Statement: - The study was approved by the Institute Ethics Committee (NIMHANS/44th IEC (BS&NS)/2023 dated 25th September 2023), and written informed consent was obtained from all the study participants.

Author Contribution

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We thank our patients and family members for their willingness to participate in the ATPARK study.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and privacy considerations but are available from the corresponding author on reasonable request.

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Figures

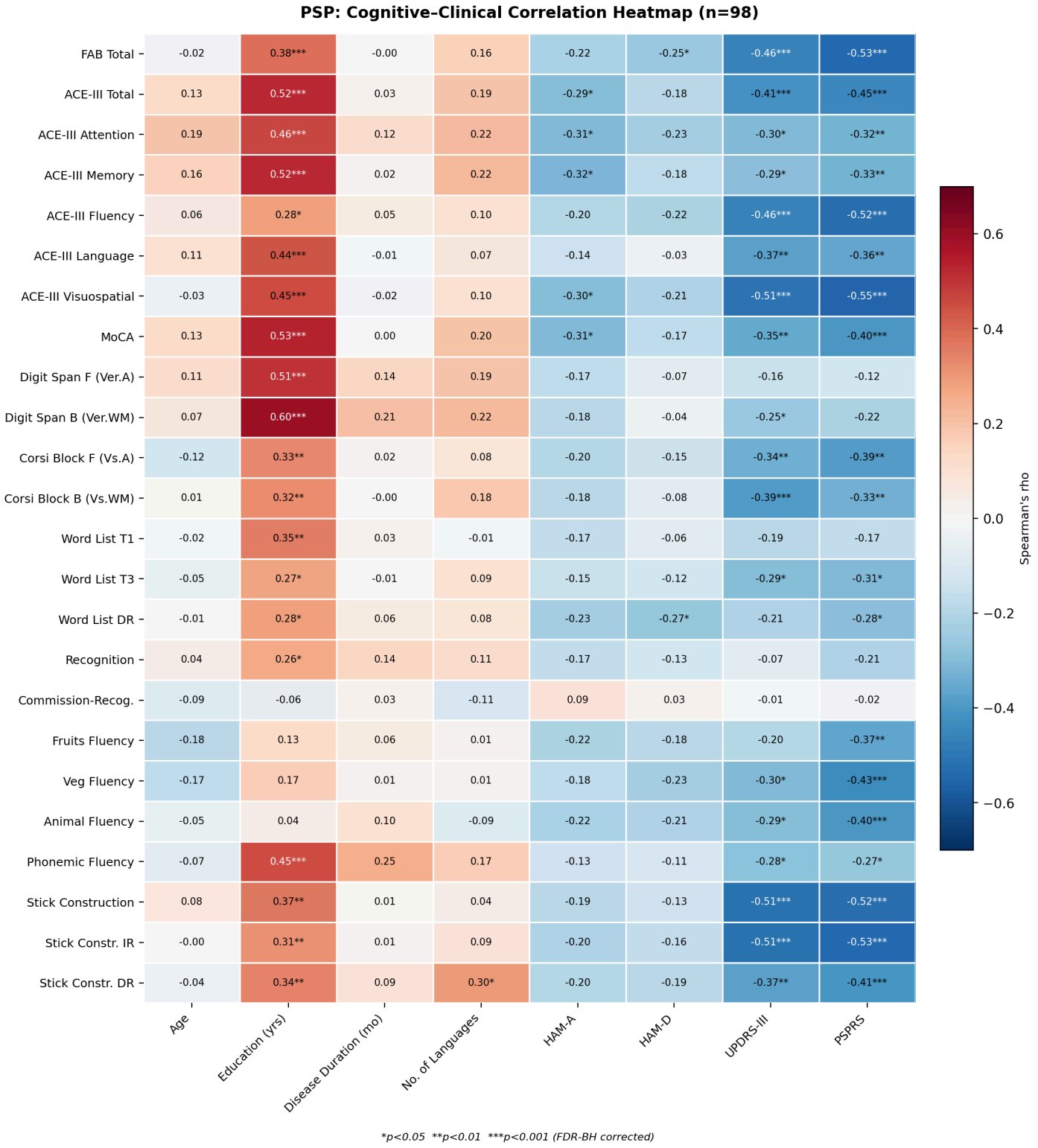


Figure 1

Spearman correlation heatmap showing the associations between demographic and clinical variables and neuropsychological measures in patients with progressive supranuclear palsy (PSP;*n*=98). Rows (Y Axis) represent global cognitive measures and individual neuropsychological test scores, while columns (X Axis) represent demographic and clinical variables. Each cell displays the Spearman correlation coefficient (ρ), with color intensity indicating the strength and direction of the association (red, positive

correlation; blue, negative correlation). Asterisks denote statistically significant correlations after Benjamini-Hochberg false discovery rate (FDR) correction ($p < 0.05$, **p**< 0.01, ***p*** < 0.001).

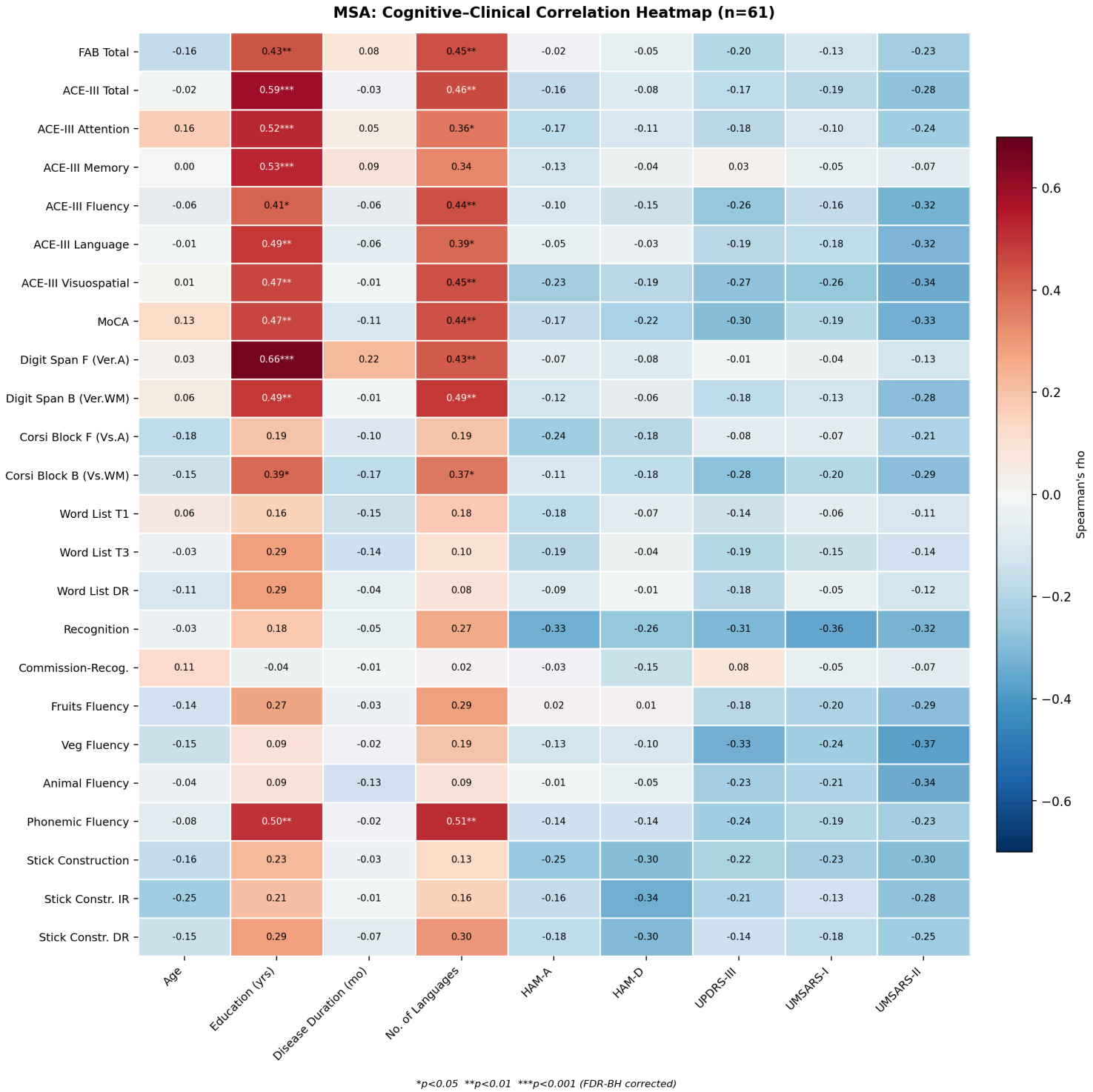


Figure 2

Spearman correlation heatmap showing the associations between demographic and clinical variables and neuropsychological measures in patients with multiple system atrophy (MSA;*n*=61). Rows (Y-axis) represent global cognitive measures and individual neuropsychological test scores, while columns (X-axis) represent demographic and clinical variables. Each cell displays the Spearman correlation

coefficient (ρ), with color intensity indicating the strength and direction of the association (red, positive correlation; blue, negative correlation). Asterisks denote statistically significant correlations after Benjamini-Hochberg false discovery rate (FDR) correction ($p < 0.05$, **p** < 0.01, ***p***< 0.001).

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