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Cognitive impairment in multiple system atrophy:

A position statement by the Neuropsychology Task Force of the MDS multiple system atrophy (MODIMSA) Study Group

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Abstract

Consensus diagnostic criteria for multiple system atrophy consider dementia as a non-supporting feature, despite emerging evidence demonstrating that cognitive impairments are an integral part of the disease. Cognitive disturbances in multiple system atrophy occur across a wide spectrum from mild single domain deficits to impairments in multiple domains and even to frank dementia in some cases. Frontal-executive dysfunction is the most common presentation, while memory and

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visuospatial functions may also be impaired. Imaging and neuropathological findings support the concept that cognitive impairments in MSA originate from striatofrontal deafferentation with additional contributions from intrinsic cortical degeneration and cerebellar pathology. Based on a comprehensive evidence-based review we here propose future avenues of research that may ultimately lead to diagnostic criteria for cognitive impairment and dementia associated with multiple system atrophy.

Keywords

cognition; multiple system atrophy; neuropsychology

Introduction

Historically, multiple system atrophy (MSA) has been considered a rapidly progressive movement disorder for which the future occurrence of cognitive impairment leads to re-appraisal of the primary diagnosis.[1] MSA can be divided into two motor phenotypes: a parkinsonian variant with prominent akinetic-rigid parkinsonism (MSA-P) and a cerebellar variant (MSA-C) characterized by progressive ataxia. Increasing evidence suggests that cognitive impairment is common in both MSA subtypes. However, cognitive deficits in MSA remain poorly characterized and are still considered non-supporting diagnostic features by current consensus diagnostic criteria.[2] Recent prospective neuropsychological studies estimate dementia prevalence rates in MSA of up to 31%[3-8] and reveal widely overlapping patterns of cognitive deficits compared with other parkinsonian disorders. Progressive frontotemporal degeneration on neuroimaging[9-13] and postmortem findings of neuronal loss, astrogliosis and glial cytoplasmic inclusion (GCI) accumulation in frontal and temporal regions of demented MSA patients further point towards cognitive decline as a characteristic feature in some MSA patients. The prevalence rates of mild, moderate and severe cognitive impairment in autopsy-confirmed MSA are 22%, 2% and 0.5%, respectively.[1] The disparity in frequencies with clinical series may relate to ascertainment bias in neuroepidemiological studies, with demented MSA cases being excluded ante-mortem, in line with prevailing diagnostic criteria.

Time interval from MSA diagnosis to clinically significant cognitive symptoms is estimated to be 7 years on average.[8] However, cases with early cognitive impairment have been described,[7, 14, 15] and in some cases cognitive decline has preceded motor impairment.[7] Among patients surviving more than 8 years, almost 50% are reported to be cognitively impaired,[3] suggesting that if the disease did not have such a rapid course the cumulative prevalence of dementia in MSA would be similar to Parkinson's disease (PD) based on long-term, longitudinal studies.[16,17] Furthermore, 14% of MSA patients were found to be demented in the last year prior to death[8] and exceptionally long term MSA survivors showed dementia onset after 13.5 and 17 years.[18] While the influence of disease duration is still unclear,[3, 5, 6, 19, 20] motor impairment is established as a predictor for the severity of cognitive impairment in MSA.[3, 5, 6]

Research on MSA-related cognitive deficits is hampered by existing consensus criteria classifying dementia as a non-supportive criterion.[2] However, several investigators have attempted to circumvent this obstacle by either (1) omitting the dementia criterion of the consensus statement or (2) by utilizing other clinical MSA criteria which only define "signs of severe dementia" as an exclusion criterion. In such instances, dementia in MSA patients was diagnosed using PD dementia criteria,[6] DSM-IV criteria[7] or cut-off values of the Clinical Dementia Rating Scale [7, 20] or Mattis Dementia Rating Scale[3].

In view of the increasing recognition of cognitive deficits in MSA, we systematically reviewed the existing literature on cognitive dysfunction in MSA. We searched PubMed with the following search term: *("multiple system atrophy" OR MSA OR "olivopontocerebellar atrophy" OR OPCA OR "striatonigral degeneration" OR SND OR "Shy-Drager syndrome") AND (neuropsychology OR neuropsychological OR dementia OR cognition OR cognitive OR frontal-executive OR memory)* for reports published between August 15, 1988 and August 15, 2013. Only peer-reviewed, English language reports were considered. Based on this systematic review, we attempted to propose future avenues of research that may ultimately lead to operational criteria for cognitive impairment and dementia associated with MSA.

Cognitive impairment in MSA

The majority of existing studies addressing cognitive function in MSA exclude demented patients following current consensus diagnostic criteria[2], which may influence conclusions. Although global cognitive impairment is not a consistent feature of MSA,[21, 22] a recent study revealed reduced Mini-Mental State Examination[23] scores in 26% of MSA patients[3] Evidence from neuropsychological studies suggests executive dysfunction as a prominent cognitive disturbance in MSA, affecting up to 49% of patients (Table 1).[3, 12, 24] This includes problems with semantic and phonemic word list generation,[25, 26] perseverative behavior,[27] and diverse impairments of problem solving, flexibility, response inhibition, attention and working memory (Table 2).[25, 27]

Regarding other cognitive domains, around 20% of MSA patients have frontal lobe release signs[4] and apraxia is present in 8%-10% of MSA of both motor subtypes.[4, 28] There is conflicting evidence on whether MSA-related attention deficits occur.[3, 24, 26] Impairments of working memory are similar to other parkinsonian disorders.[3, 27] Memory disturbances, observed in up to 66% of MSA patients, commonly present with impaired verbal learning,[24] immediate[6] and delayed recall[3, 12, 24], and less often recognition[3], although this finding is not universal.[26] MSA patients may experience visuospatial and constructional difficulties compared with controls,[6, 12, 26] despite inconsistent reports.[3, 29] Language functions like spontaneous speech, syntax, repetition or lexico-semantic functions seem to be mostly preserved,[12, 27] but have not been studied thoroughly. Nevertheless, impaired naming was reported in one study comparing demented with non-demented MSA patients.[6]

Cognitive impairment in the motor subtypes: MSA-P

Most neuropsychological studies in MSA have investigated MSA-P patients. Executive dysfunction, reported in 40% of MSA-P patients (Table 1),[24] includes impairment in a range

of abilities, such as decreased speed of thinking and problem solving difficulties,[21, 30] impaired attentional set shifting, mental flexibility,[21, 26] abstract reasoning[28] and perseverative tendencies,[26, 28] while impaired conceptual thinking and response inhibition[20, 28, 31] are not reported widely.[19, 22, 26] Prospective studies reveal impaired verbal fluency in MSA-P patients compared with controls (Table 2).[22, 26, 28, 30]

Impaired spontaneous immediate verbal recall is a robust feature of MSA-P [19, 24, 31], while recognition is less impaired.[19, 20, 22, 26, 30, 31] Visuospatial and visuoconstructional functions are also diminished in MSA-P patients. It remains unclear, whether memory and visuospatial deficits are also caused by executive impairment.[21, 22, 28, 30, 31] Attention and working memory are variably impaired in MSA-P.[20, 24]

Cognitive impairment in the motor subtypes: MSA-C

Abnormal performance on the Frontal Assessment Battery,[32] a screening test for executive dysfunction, has been reported in almost half of patients with MSA of the cerebellar subtype (MSA-C),[24] accompanied by prolonged time to complete Trail Making Test.[20] In addition, there are conflicting reports concerning the Wisconsin Card Sorting Test[33] and Stroop Tests[34] yielding both impaired[19, 20] and normal performances.[26, 35, 36] Other executive functions seem to be preserved (Table 1).[20] Verbal fluency is moderately decreased in MSA-C as compared with controls,[20, 35, 36] albeit not after accounting for depression and anxiety[19] and not in all cohorts.[26] However, there has been a relative lack of detailed neuropsychological evaluations in the MSA-C subgroup, possibly accounting for inconsistent findings (Table 2).

A deficit of learning is the most prominent memory dysfunction in MSA-C,[19, 35] while variable results have been reported regarding recall[19, 20, 24, 35, 36] and recognition disturbances.[19, 20, 35] There are also controversial reports concerning attention[20, 24, 36] and visuospatial functions in MSA-C.[20, 26, 36] Impaired encoding and disturbed maintenance of verbal information[19] as reported in MSA-C has been referred to as “cerebellar cognitive affective syndrome”.[37]

Cognitive impairment in the motor subtypes: MSA-P vs. MSA-C

Comparative studies of cognitive impairment in MSA-P and MSA-C revealed controversial results (Table 2).[20, 24, 26] Kawai and colleagues reported that multiple domains were affected in MSA-P as opposed to MSA-C where only visuospatial deficits were observed.[26] Others reported more pronounced executive and verbal memory decline in MSA-C as compared with MSA-P[20] or comparable neuropsychological performance in both MSA motor subtypes.[24] However, difficulties in immediate recall in MSA-P and impaired learning and long-term memory in MSA-C likely reflect different subcortical degeneration patterns.[19]

Cognitive impairment in MSA vs. Lewy body disease

A similar pattern of cognitive impairment in MSA and PD with prominent executive dysfunction is widely reported (Table 2).[22, 25, 30, 38-40]. For example, MSA-P and PD

patients share the same pattern of impaired spontaneous retrieval of newly learned information that improves with cueing.[19] Further, similar[38, 39] or even more pronounced visuospatial disturbances have been observed in MSA compared with PD patients.[27, 28] Notably, all comparative studies have included only non-demented PD patients.

The cognitive profile of demented MSA patients appears to differ from that of PD dementia (PDD) patients. PDD patients experience cognitive decline at around 70 years of age irrespective of time of PD onset[41], contrary to MSA patients who develop dementia later into the disease[8]. While 45-65% of PDD patients[42] experience hallucinations, they are infrequent in MSA patients.[43] Information processing speed is severely affected in PDD[41], however, it remains to be determined whether similar deficits occur in MSA.

A comparative study of cognitive impairment in dementia with Lewy bodies (DLB), MSA and PD disclosed the most profound deficits in DLB, intermediate performance in MSA, and PD being least impaired across all cognitive domains.[27, 44] Strikingly, multi domain cognitive deficits emerge within the first year from parkinsonism onset in DLB[45] compared with later onset of cognitive decline in MSA. Recurrent and well-formed visual hallucinations[45] are strongly related to cognitive deterioration and Lewy body pathology in DLB in contrast with their very rare occurrence in MSA (9%).[43] Further, fluctuating cognition, a cardinal feature of DLB dementia, appears to be absent in MSA.[45] It is possible, however, that this feature may have been overlooked as it has never been systemically studied to date in MSA.

Cognitive impairment in MSA vs. PSP

Compared with MSA, global cognitive performance is worse in PSP,[3, 22, 28, 40] with more conspicuous executive disturbance declining rapidly in the latter patients[22, 28, 30, 38] as well as more pronounced deterioration in memory,[3, 22] attention and visuospatial ability (Table 2).[3, 28, 29, 38] In the largest prospective study to date[3], selective impairment in frontal lobe functions affected 62% and 32% of PSP and MSA patients, respectively. This supports a common core pattern of frontal dysexecutive impairment in parkinsonian syndromes independent of underlying pathology.[3]

Imaging correlates of cognitive impairment in MSA

The majority of MRI studies (Table 3) reveal a characteristic pattern of prefrontal, frontal, temporal and parietal cortical atrophy in MSA-P[9, 46-48] and MSA-C,[49-52] although some qualitative differences between subgroups have been reported.[49] The distribution of cortical atrophy is supported by hypometabolism on fluorodeoxyglucose (FDG) positron emission tomography (PET) in prefrontal and frontal,[53, 54] temporal and parietal regions in MSA-P,[54] and in frontal and inferior parietal regions in MSA-C.[55, 56] Cortical thinning in cognitively impaired MSA patients has been reported in the same regions as in AD and PDD[6].

A longitudinal volumetric MR study found a marked progression of brain atrophy in patients with MSA-P including striatum, mesencephalon, thalamus and cerebellum, but also cortical regions such as the primary sensorimotor cortex, supplementary motor area, lateral premotor cortex, medial frontal gyrus, middle frontal gyrus, orbito-frontal cortex, insula, posterior

parietal cortex and hippocampus[9]. Interestingly, short disease duration was correlated with progression of atrophy in the striatum whereas longer disease duration was correlated with increasing atrophy in the cortical areas and cerebellar hemispheres, thus suggesting that early degeneration of the basal ganglia drives late onset cortical atrophy[9]. Favoring this hypothesis of primary subcortical deafferentation of cortical regions, Paviour and colleagues reported a correlation between pontine, midbrain and cerebellar atrophy and impairment in different cognitive domains as well as global cognition in MSA patients,[13] which is supported by the observation of cerebellar hypoperfusion associated with visuospatial decline in MSA-C.[26] On the other hand, prefrontal atrophy correlated with overall memory scores in MSA as a group[20] and correlation between dorsolateral prefrontal hypoperfusion and visuospatial impairment in both motor MSA subtypes and executive dysfunction in MSA-P argue for primary cortical affection.[26] Decreased FDG uptake in the frontal lobes of early MSA-C, spreading to other cortical regions in advanced disease[12], contrary to steady cerebellar hypometabolism, further supports the hypothesis of intrinsic cortical pathology in MSA.[55] Cholinergic denervation in MSA affecting all cerebral cortex regions highlights degeneration of all major cholinergic pathways important for attention, learning and memory.[57]

In MSA patients, the mean cortical amyloid burden using Pittsburgh Compound B PET was comparable to that of controls.[6] However, the role of amyloid pathology should not be completely rejected because substantial amyloid burden was reported in some demented MSA cases.[6]

Neuropathological considerations

Post-mortem studies have shown widespread subcortical degenerative changes in MSA brains. Both basal ganglia and cerebellar circuits are affected in MSA and therefore the grading scale classifies predominant striatonigral (SND) and olivopontocerebellar (OPCA) type of degeneration.[58] Substantia nigra and putamen are mostly affected, while caudate nucleus and globus pallidus are also involved but to a lesser degree.[1, 59] Cerebellar degeneration in MSA comprises severe loss of Purkinje cells and to lesser extent neurons in the dentate nucleus.[1]

With prominent nigral and putaminal degeneration[1] and secondary disruption of striato–pallido–thalamocortical circuits[60], it is assumed that the concept of “subcortical dementia” may, at least partially, explain cognitive features of MSA. Despite the lack of detailed neuropsychological studies in patients with pathologically proven MSA, the similarity of widespread subcortical pathology in basal ganglia disorders, indirectly suggests that the disruption of subcortico-cortical pathways is likely to mediate some of the cognitive disorders in MSA. Furthermore, executive, memory, visuospatial and language impairment present within the group of patients with different types of cerebellar disorders indicate that the cerebellum participates in the organization of higher order functions through its cortical inputs,[37] also favoring the concept of subcortical deafferentation.

On the other hand, post-mortem evidence of frontal, temporal and parietal cortical degeneration argue for additional primary cortical involvement in the cognitive deficits

reported.[14, 15, 61-64] Neuronal loss, astrogliosis and loss of myelinated fibers in deeper cortical layers of frontal lobes[14, 15] and insula,[15] abundant GCIs found in deep cortical gray mater and white matter of frontal and parietal lobe,[14, 15] vacuolation of glial cells in frontal cortex[62] and ubiquitinated neuronal inclusions and dots-like structures in prefrontal areas[61] point toward prominent frontal degeneration in MSA. Temporal lobe atrophy with GCIs and neuronal cytoplasmic inclusions are confined to hippocampus, amygdala, insula, temporal, cingulate and entorhinal regions of exceptionally long-term duration MSA case.[63, 64] Evidence for cortical degeneration in MSA recently led to the proposal of the term "cortical MSA" as a distinct clinicopathological variant of MSA.[65] It has also been suggested that cases with severe temporal atrophy should be classified as a different subgroup.[66]

Degeneration of pedunculopontine tegmentum and dorsolateral tegmental nucleus[67, 68] with abundant GCIs is in accordance with diminished cortical and subcortical acetylcholinesterase activity also observed in MSA based on PET results.[57, 69]

Behavioral and neuropsychiatric symptoms in MSA

The influence of mood disturbances and anxiety on executive,[19, 24] memory[6, 19] and visuospatial decline[6] is usually recognized as substantial in MSA, although not reported across all cohorts.[3] Approximately 40-85% MSA patients report at least mild depression,[24, 70-72] while a third are moderately to severely depressed.[70, 71, 73]

Anxiety is reported to affect 37% of MSA patients.[74] Although high levels of depression and anxiety are present in both MSA motor subtypes,[19, 20, 24, 26, 73] a dissociation has been reported, with MSA-P patients being more depressed and MSA-C subjects more anxious.[19, 20]

MSA patients appear to suffer from apathy more frequently than PD patients,[44, 75] with a mean rate of 65% in MSA.[44] Excessive daytime sleepiness affects more than 25% of MSA patients regardless of motor subtype, but contrary to PD it is unrelated to depression.[76, 77]

Discussion and outlook

In view of increasing awareness of cognitive impairments in PD and atypical parkinsonism, we aimed to emphasize the importance of paying more attention to cognitive and behavioral features in MSA. Based on existing evidence, we suggest that cognitive impairment is present in MSA more frequently than previously considered. Executive functions and fluency are the most commonly affected, while attention, memory and visuospatial domains are sometimes impaired, and language mostly spared. While visuospatial impairment may be one of the major difficulties in MSA-C patients[26], MSA-P patients seem to exhibit more executive problems. In addition, MSA-P patients show more recall deficits improving with cueing while learning disturbances appear more typically in MSA-C patients, suggesting that distinctive subcortical degeneration patterns (SND or OPCA) may differently influence cognition via cortical inputs in MSA. Generally, impaired attention and executive functions in both motor subtypes impact on all cognitive functions as well as behavioral features and severity of motor impairment. Both imaging and morphological data allow us to conclude that both deafferentation from subcortical structures and intrinsic cortical pathology play a

role in cognitive decline, with the former being a feature of early disease, while the cortical contribution becomes apparent later in the disease course. However, among a considerable number of comparative studies, only one[3] provides neuropsychological data from a large number of MSA patients (Table 2). Further, except for one small cohort of prospectively followed MSA patients,[38] evidence is mostly obtained from cross-sectional studies. A further shortcoming is the lack of a detailed assessment of cognitive functions in pathologically proven MSA cases.

Although the pattern of cognitive disturbances in MSA largely overlaps with cognitive impairment in other basal ganglia disorders, the quantitative difference may provide an important clue in clinically discriminating MSA from other synucleinopathies and PSP. Onset of clinically significant cognitive decline 5-6 years after disease onset or subtle problems even earlier, absence of hallucinations, prominent executive deficit and gradual progression towards dementia in some cases contribute to the profile of cognitive decline in MSA patient. Hence, the MODIMSA neuropsychology group has launched efforts to examine the issue of cognitive impairment and dementia in MSA in greater detail, ultimately aiming to revise the current consensus criteria by including operational guidelines for MSA dementia. The latter will serve to better recognize and characterize cognitively impaired MSA patients, a prerequisite for further research and therapeutic trials.

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Table 1
Impaired cognitive functions in MSA, MSA-P and MSA-C

	Often impaired	Sometimes impaired	Reference
MSA P+C	• Executive cognition	• Attention and working memory • Spontaneous recall (immediate and delayed) • Recognition • Visuospatial functions	3, 25, 27, 29, 40
MSA-P	• Executive cognition	• Attention and working memory • Spontaneous immediate recall • Visuospatial	6, 12, 13, 19-22, 24, 26, 28, 30, 31, 38, 39
MSA-C	• Executive cognition	• Attention and working memory • Spontaneous delayed recall • Recognition • Visuospatial functions	6, 12, 19, 20, 24, 26, 35, 36

MSA … Multiple system atrophy
MSA-P … Multiple system atrophy, parkinsonian variant
MSA-C … Multiple system atrophy, cerebellar variant

Table 2

Summary of the methods and results of the neuropsychological studies assessing cognitive functions in MSA

Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
Robbins 1992[21]	MSA/ normal controls	15	-	55.2±7.7	6.1±2.7	NART, Vocabulary, Similarities, Arithmetic, Digit span, Picture Completion, Block Design, Picture Arrangement from WAIS-R; Recognition memory test; Unconventional views and Incomplete letters tests; McKenna naming test; Spatial short term span, Spatial working memory, modified Tower of London task, ID/ED attention set shifting from CANTAB; pattern and spatial recognition, simultaneous and delayed matching-to-sample, conditional visuospatial associative learning test	MSA patients performed worse on Spatial working memory task (increased 'between search errors'), Tower of London (slower in the subsequent thinking time with task difficulty effect), ID/ED set shifting, simultaneous matching to sample and conditional visuospatial associative learning tests compared to controls.
Testa 1993[39]	MSA/ PD/ normal controls	19	-	56.2±7.8	4.5±2.3	Vocabulary, Similarities and Block design from WAIS; Categorical verbal fluency test; Visuospatial Orientation Line Test of Benton; Zazzo's test; Short Tale test; crew and nut test; choice reaction times-CTRs and movement times- MTs	MSA and PD patients were impaired on similarities, block design, Benton's test, Zazzo's test, short tale, CRTs, MTs and screw test compared to controls. MSA patients had prolonged MTs compared to PD patients.
Robbins 1994[40]	MSA/ PSP/ PD/ normal controls	16 MSA not classified		51.1±1.99	6.2±0.7	Spatial short term memory task, Spatial working memory task, planning task and attention set shifting from CANTAB	Increased 'between search errors' on Spatial working memory task in MSA patient compared to controls and different strategy for dealing with the task compared to PSP and PD patients. MSA patients were slower in the subsequent thinking time on planning task compared to PSP and PD patients who had slower initial thinking time. MSA patients were impaired on extradimensional shifting stage, but to a lesser degree than PSP patients.
Pillon 1995[22]	MSA/ PSP/ PD	14	-	-	4.8±0.5	MMSE; Mattis DRS; verbal subtests from WAIS-R; CMP Raven, WMS; WCST; verbal fluency; graphic series; Stroop; TMT A and B; CVLT; GB test; 'frontal score'	MSA patients showed impairment in category and phonemic fluency, global 'frontal score', trial making test A and B, but normal Stroop and WCST compared

Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
							to controls. Compared to PD, MSA patients scored b to controls. Compared to PD, MSA patients scored b to controls. Compared to PD, MSA patients scored b to controls. Compared to PD, MSA patients scored b to controls. Compared to PD, MSA patients scored b to controls. Compared to PD, MSA patients scored b to controls. Compared to PD, MSA patients scored b to controls. Compared to PD, MSA patients scored b to controls. Compared to PD, MSA patients scored b
Meco 1996[31]	MSA/ PD/ normal controls	11	-	66.1±6.9	4.6±1.5	TMT A and B; Stroop; verbal fluency; AVLT; WCST; CPM;	MSA -P patients were impaired on AVLT, WCST and TMT compared to controls. MSA-P patients made higher number of errors on TMT A and B and were slower to complete Stroop interference (specially 2nd section) with high number of errors and no amelioration of Stroop effect in 2nd section compared to PD. PD patients were impaired on WCST but performed normally on Stroop and verbal fluency tests.
Monza 1998[28]	MSA/ PSP/ PD/ normal controls	19	-	59.2±7.9	4.2±1.2	MMSE, CPM Raven; Short Tale Test; Verbal Fluency Test; Visual Search Test; Visuospatial Orientation Line Test of Benton; Nelson modification of the WCST; De Renzi ideomotor apraxia test	MSA patients were impaired in all cognitive tests compared to controls and performed worse on Phonemic Verbal Fluency Test than PD. MSA patients were slower on the tapping sequence test compared to PD. MSA patients had impaired imitation of single gesture compared to controls, and in sequence gestures compared to both PDand controls. 2/19 MSA patients apraxic (85% of errors due to clumsiness and 15% due to sequence errors).
Soliveri 2000[38]	Baseline: 23 MSA/ PD/ PSP Follow up after mean 21 months: 14 MSA/ PD/ PSP	23	-	58.7±7.6	4.0±2.1	CPM Raven; Short Tale Test; phonemic verbal fluency; Visual Search test; Visuospatial Orientation Line Test of Benton; Nelson modification of WCST; Global cognitive decay index (DI)	Baseline: impaired phonemic verbal fluency in MSA compared to PD. PSP performed worse than MSA and PD in short tale, verbal fluency, visual search and Benton's test. Follow up: greater deterioration in visual search test in MSA compared to PD patients, and in Nelson's test

Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
							in PSP compared to MSA and PD patents. Progressi in PSP compared to MSA and PD patents. Progressi in PSP compared to MSA and PD patents. Progressi in PSP compared to MSA and PD patents. Progressi in PSP compared to MSA and PD patents. Progressi in PSP compared to MSA and PD patents. Progressi in PSP compared to MSA and PD patents. Progressi in PSP compared to MSA and PD patents. Progressi in PSP compared to MSA and PD patents. Progressi
Berent 2002[35]	MSA/ sOPCA/ dOPCA/ normal controls	-	28	MSA-C 64.5±7.8, sOPCA 54.0±11.3, dOPCA 49.1±14.9	NA	Arithmetic, Picture completion, Vocabulary, Block design, Picture arrangement, Digit symbol from WAIS-R; Wechsler Memory Scale MQ; Logical memory, Visual learning, Paired associates and Digits from WMS; Selective Reminding Test; Stroop interference; Verbal fluency; TMT A and B; Simple and choice reaction time	All groups performed worse on immediate verbal and visual memory and learning and on paired associates learning task compared to controls. MSA-C subjects scored worse on retrieval on verbal list learning task (SRT) and verbal fluency tests compared to controls and on recognition task from SRT compared to dOPCA.
Dujardin 2002[25]	MSA/PD matched for motor severity/ PD matched for disease duration/ normal controls	11 MSA not classified		65.09±9.04	3.17±2.24	Phonemic and semantic word fluency test; Spatial sequences generation task; Nelson modification of WCST; Stroop	MSA performed worse on phonemic and semantic word fluency task, WCST, Stroop and tended to make more perseverative errors on Spatial sequence generation task compared to both PD groups. PD subjects were impaired on WCST and Stroop, but not on verbal fluency.
Lange 2003[30]	MSA/ PSP/ PD/ normal controls	14	-	60.9±5.2	4.5±2.3	S-Word-Test; Animal-Test; H/T-Word-Test; Sport/Fruit-Test; Verbal Recency Task with recognition task; Forward and Backward Digit Span; Visual Working Memory Test; Tower of London	Disturbances in verbal fluency, working memory and problem solving in MSA patients compared to controls. MSA patients performed better on verbal fluency tasks than PSP patients.
Bak 2006[29]	MSA/ PSP/ CBD/ normal controls	20 MSA not classified		65.9±8.2	5.1±2.8	VOSP	No visuospatial impairment in MSA patients.
Burk 2006[36]	MSA/ normal controls	-	20	60.1±5	4.6±2.6	MMSE; Similarities and Picture completion test from WAIS; Digit Span forward and backward from WMS-R; Forward and Backward Digit Span; word lists; phonemic, semantic and alternating verbal fluency; Rey-Osterrieth complex figure; WCST	MSA-C subjects impaired on verbal memory and verbal fluency compared to controls.

Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
Paviour 2006[13]	MSA/ PSP/ PD/ normal controls **Longitudinal MRI study**	9	-	62.4±8.1	5.4±1.7	MMSE; FAB; Mattis DRS-2; Vocabulary, Similarities and Digit Span from WAIS-R; RAVLT; Short Recognition Memory for Faces; TMT A and B; WCST; semantic, phonemic and alternating semantic verbal fluency tests (Benton); PASAT	Rates of pontine atrophy correlated with decline on DRS total score, digit span and semantic verbal fluency. Rates of cerebellar atrophy correlated with decline on DRS total score, DRS conceptualization subtest and semantic verbal fluency. Rates of midbrain atrophy correlated with decline on DRS initiation and perseveration subtest, the recognition memory test for faces, digit span and intrusions on the verbal fluency test.
Kawai 2008[26]	MSA/ normal controls **^{99m}Tc-Ethylcysteine SPECT study**	14	21	61.0±8.1 (MSA C 60.3 ±8.3, MSA P 62.0±7.9)	2.9±1.7 (MSA C 2.6±1.6, MSA P 3.2±2.0)	Digit Span; Visual Paired Associates Subtests 1 and 2 from WAIS-R; Logical Memory Subtests 1 and 2 from WAIS-R; semantic and phonemic verbal fluency; WCST; Rule Shift Cards test from BADS; Block Design from WAIS-R	MSA as a group were impaired on Block design, phonemic and semantic fluency and Rule Shift Cards test compared to controls. MSA-P performed worse on phonemic and semantic fluency and Rule shifting card test compared to controls and on Rule shifting card test compared to MSA C. MSA C showed impairment only in visuospatial functions compared to controls but to a milder degree than MSA P. Cognitive impairment in MSA P tended to be to be more severe than in MSA C.
Lyoo 2008[12]	MSA P+C divided into 3 groups according to duration of disease (1, 2 and 3 years)/ normal controls **FDG-PET and MRI study**	17 Group I: 4 Group II: 6 Group III: 7	20 Group I: 9 Group II: 6 Group III: 5	61.0 Group I: 58.0 Group II: 60.5 Group III: 61.0	1.25 Group I: 0.7 Group II: 1.3 Group III: 2.7	SVLT; RCFT; Stroop, phonemic and semantic COWAT; contrasting program; go/no-go; fist-edge-palm; alternating hand movement; alternative square and triangle drawing; Luria loop; BNT; Forward and backward digit span	17.1% of MSA patients showed normal cognitive function, 40% endorsed single domain deficits and 42.9% multiple domains deficits (in 82.9% of MSA patients were impaired in at least one domain. 65.7% of MSA patients had memory, 48.6% executive, 25.7% visuospatial and 5.7% language domain impairment). Multiple domain deficits (42.9%) were most frequent in Group III.
Chang 2009[20]	MSA/ normal controls **MRI- VBM study**	13	10	MSA-P 59.8±8.1, MSA-C 57.1±9.9	MSA-P 2.6, MSA-C 2.4	MMSE; CDR; CVLT-MS; Ray-Osterrieth recall and recognition; VOSP; cube copy test; pentagon copy test; comprehension and	MMSE and CDR scores correlated with disease duration. MSA-C performed worse on CVLT-MS,

Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
						semantic fluency; BNT; Digit forward and backward span; Stroop	and Stroop interference; Design fluency
						semantic fluency; BNT; Digit forward and backward span; Stroop	and Stroop interference; Design fluency
						semantic fluency; BNT; Digit forward and backward span; Stroop	and Stroop interference; Design fluency
						semantic fluency; BNT; Digit forward and backward span; Stroop	and Stroop interference; Design fluency
						semantic fluency; BNT; Digit forward and backward span; Stroop	and Stroop interference; Design fluency
							MS, Stroop interference and TMT compared to MSA-P.
Kao 2009[27]	MSA/ PD/ DLB	12 MSA not classified		66.9±11.3	5.4±3.6	MMSE; Modified Trials B; Design Fluency from Delis-Kaplan Executive Functions Scale; Backward Digit Span; M's and N's task; Stroop; CVLT; RCFT; VOSP; BNT; phonemic (D-words) and semantic (Animals) verbal fluency	MSA patients performed better on ModTrials B, Stroop and CVLT compared to DLB patients. MSA patients performed worse on ModTrials B, Design Fluency, RCFT, M's and N's and semantic fluency compared to PD patients.
Balas 2010[19]	MSA/ PD/ normal controls	15	10	MSA P 61.8±9.6, MSA C 59.8±11.8	MSA P 5.3±4.1, MSA C 3.2±1.3	RAVLT; Digit Span from WAIS-III; Stroop; Similarities and Picture completion from WAIS-III; phonemic and semantic verbal fluency	MSA-P patients showed impaired retrieval without problem in ability to learn. MSA-C patients had difficulties in learning and long-term memory, but not in retrieval.
Brown 2010[3]	MSA-cognitively impaired/ MSA-cognitively unimpaired/ PSP- cognitively impaired/ PSP-cognitively unimpaired **Pathologically correlated** (49 MSA/ 63 PSP)	372 MSA P+C		61.71±8.34 MSA- impaired 65.07±8.53 MSA- unimpaired 60.57±7.92	4.55±1.92 MSA- impaired 4.99±2.3 MSA- unimpaired 4.24±1.76	MMSE, FAB, Mattis DRS	20% were impaired on DRS and 31.8% of MSA patients on FAB. 25.7% of MSA patients had MMSE 20-24. PSP group performed worse in global cognition (DRS) and on each subscale score on DRS compared to MSA group. MSA had close to population average mean scores on each DRS subscale, except for perseveration and initiation (36.8% impaired) and memory (10% impaired) subscales. 28.6% of MSA patients had single domain and 13%multiple domain deficits. 18.2% patients with pathologically proven MSA were initially assessed as cognitively impaired.
Kim 2013[6]	MSA-Demented/ MSA-Non-demented/normal controls **MRI and PIB PET study**	4 MSA-D 5 MSA-ND	2 MSA-D 4 MSA-ND	MSA-D 61.7±5.8, MSA-ND 62.8±8.3	MSA-D5.2±2.3, MSA-ND 3.6±1.7	MMSE; Seoul Verbal Learning Test; BNT; RCFT; forward and backward digit span; frontal letter fluency test	MSA-D performed worse on SVLT immediate recall compared to controls and MSA-ND and on RCFT and BNT compared to MSA-ND.

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Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
Siri 2013[24]	MSA/ PD	39	22	MSA-P 63.4±7.5 MSA-C 63.1±6.8	MSA-P 4.9±2.5 MSA-C 6.5±3.8	MMSE; FAB; CPM Raven; RAVLT; Digit span; Attentive matrices	No difference of cognitive performance between MSA-P and MSA-C on all employed tests.

sOPCA- sporadic olivopontocerebellar degeneration
dOPCA-dominantly inherited olivopontocerebellar degeneration
MSA-D … multiple systematrophy, demented
MSA-ND … multiple systematrophy, non-demented
MSA P+C … multiple systematrophy, mixed (multiple system atrophy, parkinsonian variant and multiple system atrophy, cerebellar variant)
ACE … Addenbrooke's Cognitive Examination
AVLT … Auditory Verbal Learning Test
BADS … Behavioral Assessment of the Dysexecutive Syndrome
BNT … Boston Naming Test
CANTAB … Cambridge Neuropsychological Test Automated Battery
CDR … Clinical Dementia Rating Scale
CMP Raven … Raven's Coloured Progressive Matrices
COWAT … Controlled Oral Word Association Test
CVLT-MS … California Verbal Learning Test- Mental Status
FAB … Frontal Assessment Battery
GB … Grober and Buschke's Test
Mattis DRS-2 … Mattis Dementia Rating Scale
MMSE … Mini Mental State Examination
NART … National Adult Reading Test
PASAT … Paced Auditory Serial Addition Test
RAVLT … Rey Auditory Verbal Learning Test
RCFT … Rey Complex Figure Test
TMT A … Trial Making Test A
TMT B … Trial Making Test B
VOSP … Visual Object and Space Perception
WAIS-III … Wechsler Adult Intelligence Scale, the third version
WAIS-R … Wechsler Adult Intelligence Scale, revised
WCST … Wisconsin Card Sorting Test
WMS … Wechsler Memory Scale

Table 3
Affected cortical regions in MSA assessed by different imaging procedures

	Frontal	Temporal	Parietal	Study
MRI VBM	• Left superior frontal region[#] • Left inferior frontal region[#] • Medial frontal region • Middle frontal region • Orbitofrontal cortex	• Right hippocampus • Right inferior temporal region • Insula • Hippocampus • Temporomesial-ventral enthorinal cortex	• Left posterior parietal cortex	9, 20[#], 46, 48, 49-51
FDG PET	• Dorsolateral prefrontal cortex[#] • Lateral frontal cortex (early)[#] • Medial frontal cortex (early)[#] • Orbitofrontal cortex	• Superior temporal region (advanced)[#] • Middle temporal region (advanced)[#] • Inferior temporal region (advanced)[#] • Fusiform gyrus (advanced)[#]	• Inferior parietal region • Left angular gyrus (advanced)[#] • Left precuneus (advanced)[#] • Right posterior cingulate cortex (advanced)[#]	12[#], 26[#], 55
^{99m}Tc-ECD SPECT	• Left lateral frontal region • Left prefrontal cortex • Right middle frontal region	• Insula (more pronounced on the left)		78, 79

[#]evidence from comparative studies of cognitive impairment and its imaging correlates

MRI … Magnetic resonance imaging
VBM … Voxel-based morphometry

FDG-PET … ^{18}F-fludeoxyglucose positron emission tomography
^{99m}Tc-ECD SPECT … ^{99m}Technetium-ethyl cysteinate dimer single photon emission computerized tomography