Table 2. Demographic and clinical profiles of patients with a Clinical Dementia Rating of 0.5 or more at baseline.

		Baseline memory-only (N = 8)		Baseline memory-plus (N = 6)		Differences between groups
Age at baseline (years)		69.0±6.6		66.2±5.5		
Gender (male/female)		6/2		6/0		
Education (years)		12.3±2.3		14.3±2.7		
Test-retest interval (days)		1115.3±107.1		1096.7±54.7		
Disease duration at baseline (years)		6.8±3.3		9.7±6.8		
Age at onset (years)		62.4±6.6		56.6±8.0		
Levodopa equivalent dose at baseline (mg/day)		453.6±163.1		658.6±337.9		
UPDRS part III	Baseline	27.1±5.4		23.8±6.6		
	Progression rate (/years)	−0.7±3.3		4.6±5.0		Baseline memory-plus>Baseline memory-only[a]
UPDRS tremor¶	Baseline	0.7±0.5		0.4±0.6		
	Third year	0.3±0.2		0.4±0.7		Main effect of non-tremor score: Baseline memory-plus> Baseline memory-only[a]
UPDRS non-tremor¶	Baseline	1.2±0.2		1.0±0.1		
	Third year	1.1±0.2		1.7±0.7		
CDR sum of boxes	Baseline	0.5		2.1±1.3		NE
	Third year	1.4±1.2		5.3±4.1		NE
MMSE	Baseline (/30)	27.0±3.0		27.0±2.2		
	Progression rate (/years)	−0.3±0.7		−1.1±2.7		
ADAS word recall†	Baseline (/30)	17.9±4.1		14.3±5.4		
	Progression rate (/years)	−0.1±1.4		−0.3±1.2		
Overlapping figure‡	Baseline (/40)	29.6±4.1		29.4±6.2		
	Progression rate (/years)	0.1±1.1		−2.4±3.1		
Backward digit-span§	Baseline	3.6±1.0		3.8±0.5		NE
	Progression rate (/years)	−0.1±0.1		−0.3±0.3		NE
# of patients below −1 SD at baseline and at third year	ADAS word recall†	4/8	3/8	5/6	5/6	NE
	Overlapping figure‡	3/8	4/8	2/5	5/5	NE
	Backward digit-span§	3/7	4/7	1/4	2/4	NE

Two-sample *t*-tests were used for group-wise comparisons of baseline scores and progression rates except for the UPDRS tremor/non-tremor scores. A two-way analysis of variance was used for the UPDRS tremor/non-tremor scores. No group-wise comparisons were performed for the backward digit-span owing to the small number of subjects. Data are given as the mean±SD except for the fields with asterisks. a and b indicate $p<0.05$ and $p<0.01$, respectively.

*Data are given as (the number of patients below −1 SD)/(the number of patients who underwent the test).

¶The scores were calculated according to Lewis and colleagues. [5] Data were obtained from 6 baseline memory-only and 6 baseline memory-plus patients.

†The mean score of controls (n = 20, 65.5±4.8 years) is 21.3±3.5. [49].

‡The mean score of controls (n = 24, 66.1±5.3 years) is 32.9±4.4. [32].

§The mean score of controls (n = 20, 65.5±4.8 years) is 4.8±1.0. [49]; a statistical comparison was not performed owing to an insufficient number of subjects.

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale; NE, not examined.

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memory-only patients (**Figures 2E and 3E**). These findings can be interpreted in two ways: the posterior neocortical hypometabolism found in these patients may represent pathological changes in Braak stages 5–6, or they may represent a pathological progression pattern that does not conform to Braak's scheme. [7] The latter was suggested by the following clinical and neuroimaging findings. First, the severity of motor symptoms at baseline was equivalent in the memory-plus converters, non-converters and memory-only converters, suggesting that the three groups had similar degrees of midbrain pathology. In other words,

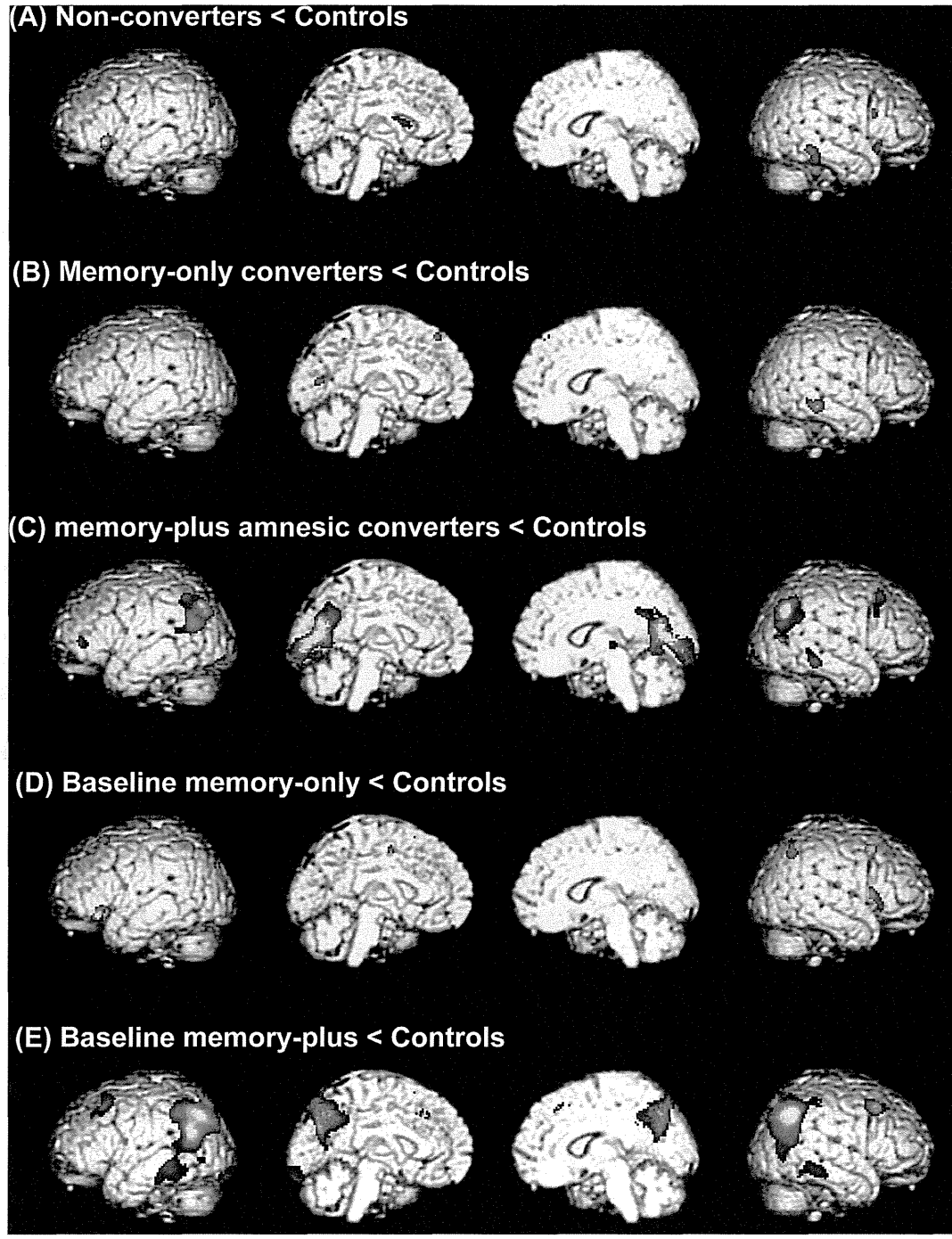

Figure 2. Areas of relative reduction in regional cerebral glucose metabolism in the patient groups compared with controls. Rendered images are shown in the order of the left lateral, left medial, right medial and right lateral.
doi:10.1371/journal.pone.0110547.g002

if the memory-plus converters represented a more advanced stage of the disease than did the other groups, they would not present with an equivalent severity of motor symptoms. Second, a comparison of metabolic patterns between the baseline memory-only and the baseline memory-plus patients showed a double dissociation in which posterior neocortical hypometabolism was more severe in the baseline memory-plus patients, whereas hypometabolism in the medial temporal lobe was more severe in the baseline memory-only patients (**Figures 3D and 3E**). These findings suggest that the brainstem and neocortex may be affected nearly simultaneously without marked limbic involvement in the memory-plus converters and the baseline memory-plus patients. A parallel finding was reported in a population-based cohort study in which incidental Lewy-related pathology was found in the

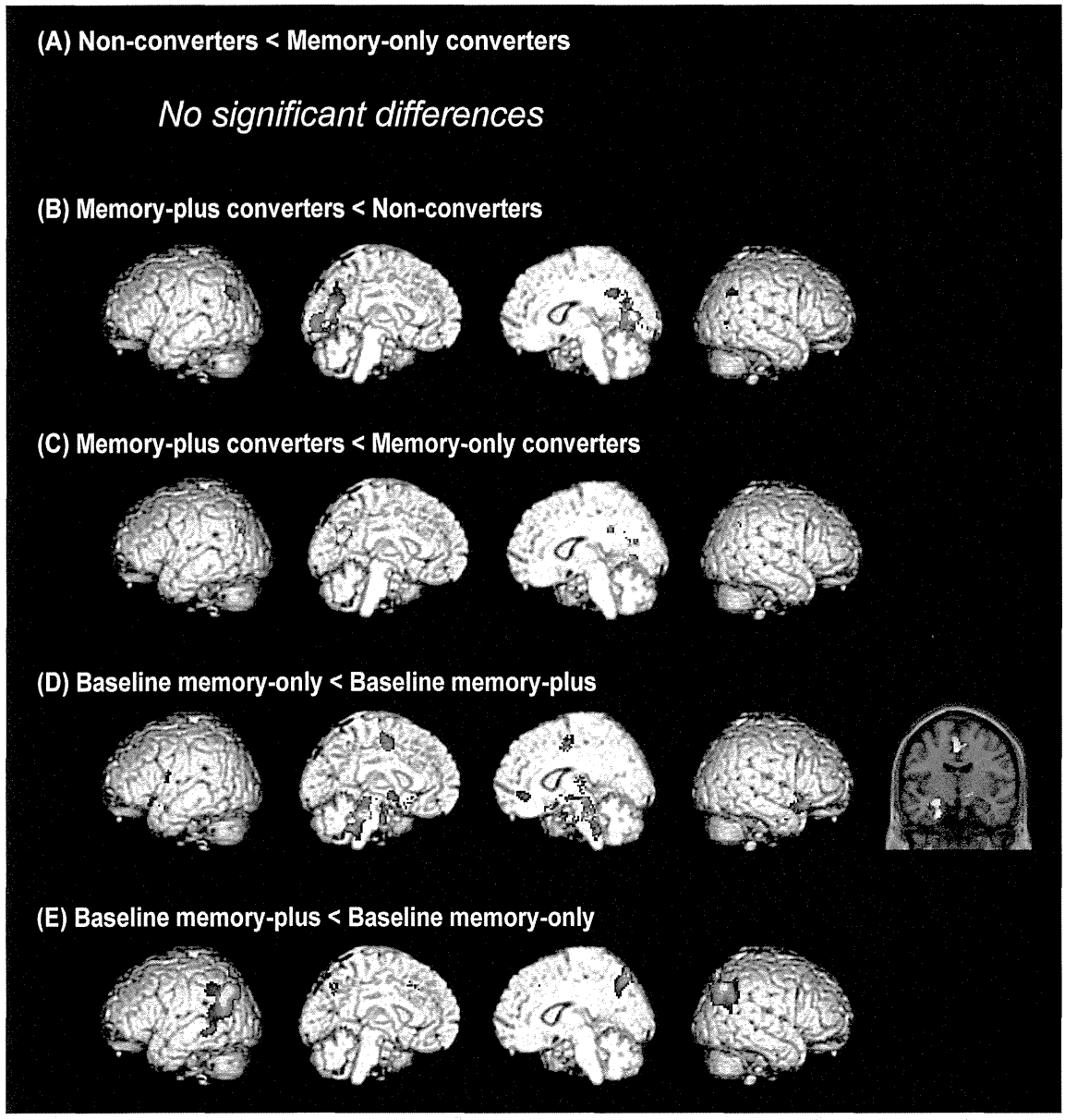

Figure 3. Group comparisons of regional cerebral glucose metabolism at baseline. (A) to (C) show the results of comparisons between patient groups with baseline Clinical Dementia Rating (CDR) 0, and (D) and (E) show the results of comparisons between groups with baseline CDR 0.5. Rendered images are shown in the order of the left lateral, left medial, right medial and right lateral. The left side of a coronal section corresponds to the left side of the brain.
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brainstem and neocortex but not in the limbic structures (medial temporal and cingulate cortices) in 3% of cases. [36].

From the viewpoint of prediction and early intervention, it is critical to establish the cognitive and neuroimaging features that are associated with rapid symptomatic deterioration and the future development of dementia. [2] In the current study, the memory-plus converters exhibited clinical features that are consistent with those of the clinical subtype associated with the rapid progression of motor symptoms and/or dementia, including rapid declines in the CDR sum of boxes and the UPDRS part III scores, and non-tremor dominant motor features (**Table 1**). [4,5,6] They had impaired performance on the overlapping-figure test (**Table 1**) and posterior cortical hypometabolism at baseline (**Figures 2C, 3B and 3C**), suggesting that early visuoperceptual impairment and posterior neocortical involvement may be risk factors for rapid symptomatic deterioration and the future development of dementia. The predictive value of visuoperceptual impairment for the future development of dementia in PD has been demonstrated in 3 of the 4 previous longitudinal neuropsychological studies with a follow-up of 2 years or more. [37,38,39,40] Similarly, a recent study demonstrated that patients with non-amnestic multi-domain MCI that had visuoperceptual deficits were associated with bradykinesia and gait disturbance (non-tremor-dominant motor features), suggesting a link to the rapidly progressive, dementia-

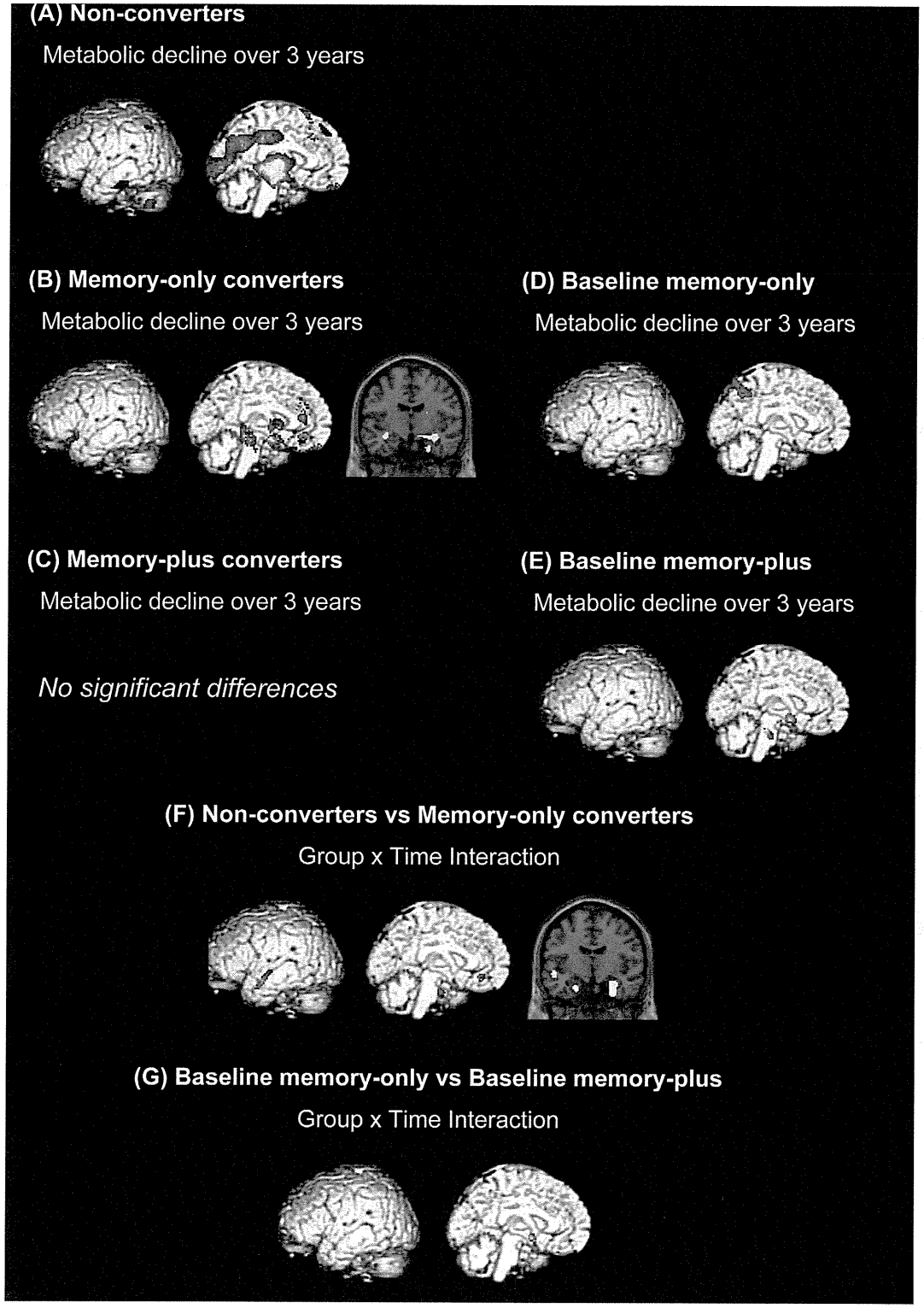

Figure 4. Longitudinal changes in regional cerebral glucose metabolism. (A) to (E) show 3-year metabolic declines in the individual patient groups. (F) and (G) show group x time interactions between the non-converters and the memory-only converters and between the baseline memory-only patients and the baseline memory-plus patients, respectively. Rendered images show the left hemisphere. The left sides of coronal sections correspond to the left side of the brain.
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related clinico-pathological subtype. [41] Although there is no neuropathological evidence for the relationship between lesions in the particular cortical regions and rapid symptomatic progression and dementia in PD, a previous longitudinal FDG-PET study demonstrated that parieto-occipital hypometabolism preceded the development of dementia. [42].

Memory impairment and its predictive value for future development of dementia in PD

Recent studies have demonstrated that memory impairment is the most common cognitive deficit in non-demented PD. [43,44] In agreement with these findings, positive scores on the memory subdomain were the most commonly observed CDR findings and baseline impairment in the ADAS-word recall test was found in 45% of the patients in the current study (**Tables 1 and 2**). However, the results of the previous longitudinal neuropsychological studies were split regarding the predictive value of memory impairment for dementia in PD. [37,38,39,40] One of the possible factors associated with this inconsistency is the variability of memory tests. The materials to be remembered (words, stories or figures) and the duration of retention (immediate or delayed) vary from test to test. Another possible factor which contribute to the low predictive value of memory impairment for dementia is the variability of the neural substrates of memory impairment in PD. Memory impairment in PD is associated with both dysexecutive retrieval deficits due to fronto-striatal dopaminergic insufficiency and mnemonic dysfunction due to hippocampal degeneration. [45] In the current study, baseline impairment on the backward digit-span observed in the memory-only converters suggests the possible contribution of executive/working memory deficits to memory complaints in PD (**Table 1**), whereas the relative medial temporal hypometabolism in the memory-only converters and the baseline memory-only patients suggested the role for hippocampal/medial temporal dysfunction (**Figures 3D, 4B and 4F**). Furthermore, a third mechanism of memory impairment is indicated by the findings of the current study; the memory-plus converters and the baseline memory-plus patients did not show significant hypometabolism in the medial temporal lobe despite their obvious memory problems, but they instead showed temporo-parietal and medial parietal hypometabolism (**Figures 2C, 2E, 3B, 3C and 3E**). The involvement of the parietal lobe in memory tasks has been documented in functional neuroimaging studies, but its functional role has been a matter of debate. [46].

Limitations

There are a number of limitations in the current study. First, although we claim that the memory-plus converters represent the rapidly progressive clinical subtype, no significant metabolic changes over 3 years were observed in this patient group. The following reasons can be suggested for this negative finding: (1) the small sample size may have result in a low statistical power; and (2) diffuse metabolic decline across the entire cerebral cortex may have obscured by the proportional scaling in the PET analysis. Consistent with the latter, a supplementary PET analysis in which a cerebellar reference was used instead of the proportional scaling demonstrated a CMRglc reduction over 3 years in the prefrontal cortex in the memory-plus converters (**Figure S1**).

Second, there were substantial inconsistencies between the CDR-based criteria and performance on the individual neuropsychological tests. Although patients with a CDR of 0 were defined as cognitively normal' according to our criteria, some were impaired in one or more neuropsychological tests. This inconsistency is most likely due to the insensitivity of the CDR to slight cognitive impairment, particularly in the executive and visuoperceptual domains. By contrast, neuropsychological tests failed to detect cognitive declines over time in the memory-only converters and memory-plus converters, despite the obvious cognitive deterioration documented by the CDR (**Table 1**). Measuring longitudinal cognitive changes using neuropsychological tests is contaminated by spurious improvement associated with practice effects. [20,21,22,23] Although the neuropsychological tests were administered twice with a relatively long interval of 3 years in the current study, previous studies demonstrated that practice effects persist over 5 years and are strongest between the first and second administrations. [20,47,48] Furthermore, the impact of dopaminergic therapy on cognition and mood should be taken into account in PD patients. A formal definitions of clinically meaningful cognitive decline' in PD should be established in future studies. [29] In addition, the criteria for at-risk state for dementia or PD-MCI should be not only sensitive but also specific. Insensitive criteria would lead to the oversight of at-risk patients of dementia, whereas an overly sensitive and insufficiently specific ones would make every PD patient an at-risk one because almost every PD patient is impaired in some of highly-demanded cognitive tasks.

Third, we separately analyzed the patient groups with a baseline CDR of 0 and those with a CDR of 0.5 and integrated the results obtained from these separate analyses to discuss long-term (more than 3 years) cognitive changes. Our findings and discussion should be examined by studies with longer follow-up periods.

Finally, the reduction in glucose metabolism may reflect not only neurodegeneration itself but also the remote effects of lesions in distant neural structures. In addition, because FDG-PET is unable to differentiate between Alzheimer's disease-related and Lewy-related pathologies, further studies utilizing amyloid-PET and other neuroimaging techniques are necessary to examine these issues.

Supporting Information

Figure S1 The results of a cerebellar-referenced PET analysis for the patient groups with baseline CDR 0 (non-converters, memory-only converters and memory-plus converters). A two-way repeated-measures ANOVA with variables of no interest of age, sex and UPDRS part III score was used. The statistical threshold was set at an uncorrected $p<0.001$ at the voxel level and at 20 voxels at the cluster level.
(TIF)

Author Contributions

Conceived and designed the experiments: YS YN TB EM. Performed the experiments: YN TB MU KY TI YH KH AT. Analyzed the data: YS YN. Contributed reagents/materials/analysis tools: HF MA TH EM. Contributed to the writing of the manuscript: YS YN.

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Review

Olfactory Dysfunction and Dementia in Parkinson's Disease

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Abstract. Dementia is one of the most debilitating symptoms of Parkinson's disease (PD), but the development of dementia is still difficult to predict at early stages of the disease. We recently found that hyposmia, one of the most typical non-motor features of PD, was a predictive feature of Parkinson's disease with dementia (PDD). In that work, multivariate logistic analysis identified severe hyposmia and visuoperceptual impairment as independent risk factors for subsequent dementia within 3 years. The patients with severe hyposmia had an 18.7-fold increase in their risk of dementia for each 1 SD (2.8) decrease in scores on the odor stick identification test for Japanese (OSIT-J). We also found an association between severe hyposmia and a specific pattern of cerebral metabolic decline, which was identical to findings observed in PDD. Furthermore, volumetric magnetic resonance imaging analyses demonstrated close relationships between olfactory dysfunction and atrophy of focal brain structures, including the amygdala and other limbic structures. Our findings suggest that brain regions related to olfactory function are closely associated with cognitive decline and that severe hyposmia is a prominent clinical feature that predicts the subsequent development of PDD. We have now started a randomized, double-blind study using donepezil for the PD group with severe hyposmia. We hope that this clinical trial will allow us to establish a therapeutic intervention that can improve the prognosis of advanced PD.

Keywords: Hyposmia, Parkinson's disease with dementia, OSIT-J, PET, MRI

INTRODUCTION

Although James Parkinson first described that intellects are uninjured in Parkinson's disease (PD) [1], it has more recently become apparent that specific cognitive dysfunctions are observed at a high rate even in early stages of PD [2]. Such dysfunction gradually worsens with disease progression and eventually leads to dementia in approximately 80% of cases [3–5]. In addition, it has been recently suggested that Parkinson's disease with dementia (PDD) is one of the biggest risk factors of mortality in PD [6], highlighting the importance of effectively managing PDD. Thus, now the complicating dementia becomes one of the most important prognostic indicators in PD. These changes are at least partly due to the fact that the long-term alleviation of motor dysfunction can be achieved by treatments including dopamine-replacement therapy. Moreover, the number of cases of elderly-onset PD, the high risk group to develop PDD, is increasing as the population ages.

We recently reported that hyposmia, one of the representative non-motor symptoms of PD, is closely associated with cognitive dysfunction [7] and that 40% of patients displaying severe hyposmia develop PDD within 3 years [8]. In this review, we elaborate on the nature of PDD, describe characteristics of hyposmia in

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PD as well as the association between hyposmia and cognitive dysfunction, and comment on future directions in this area.

PD AND DEMENTIA

In addition to motor symptoms such as tremor and muscle rigidity, other non-motor symptoms can be observed in PD. Dysautonomia is commonly associated with PD, and psychiatric symptoms such as increased depression and anxiety have recently attracted increased attention [9]. Another common symptom is cognitive dysfunction, which is often observed early in the course of PD [10]. In particular, executive dysfunction, attention deficits, and visuospatial impairments are observed in many cases. These symptoms develop gradually with the progression of PD, and impairment of memory and language also develops at later stages of the disease. The task force committee of the Movement Disorder Society (MDS) has defined such conditions as PDD when these symptoms are severe enough that they interfere with the patient's everyday life [11]. According to the task force, after excluding other diseases that are associated with cognitive dysfunction, probable PDD is defined as "the condition that presents after the onset of PD and displays cognitive disorder to the level of the patient's progressed and exacerbated everyday life becoming interfered with and is the one that is accompanied by at least 2 features out of the following 4 central cognitive dysfunctions, i.e., changing attention deficit, executive dysfunction, visuospatial cognitive impairment, and memory disorder [11]." The task force committee also recommended that PDD be diagnosed using two algorithms: a more basic level 1 algorithm for routine medical practice, and the level 2 algorithm, which is intended for research purposes at medical institutes [12].

Risk factors that are predictive of PDD include older age and more severe motor dysfunction. Some reports have identified additional risk factors, including a clinical subtype of postural instability gait difficulty (PIGD) [13], attention deficits at early stages [14], and REM sleep behavior disorder [15]. According to one cross-sectional study, approximately 20 to 40% of PD patients are classified as PDD [5]. Some differences in the rate of PDD in previous reports are most likely due to differences in the ages of PD patients included in different analyses. Some longitudinal studies have reported that the progression from PD to PDD occurs in an average of 10 years and that approximately 80% of PD cases eventually progress to PDD over the course of 20 years [3, 5]. The prevalence of PDD is approximately 1/10 that of Dementia with Lewy bodies (DLB) [5]. Assuming that there are 150,000 PD patients in Japan, it can be estimated that there are between 30,000 and 60,000 PDD patients in Japan, and that the number of DLB patients is 10 times that of patients with PDD, or between 300,000 and 600,000.

HYPOSMIA IN PD

As mentioned above, PD is associated with a high incidence of various non-motor symptoms, including hyposmia, dysautonomia (constipation, dysuria, impotence, orthostatic hypotension, and dyshidrosis), sleep disorders, higher brain dysfunction, and psychological symptoms. These non-motor symptoms are in addition to characteristic motor symptoms such as tremor, rigidity, akinesia, and postural instability that result from degeneration of dopamine neurons in the substantia nigra [9]. Because hyposmia is already observed before the onset of motor symptoms (i.e., during the pre-motor phase), many studies have investigated this symptom as an early diagnostic marker of PD. According to these reports, it is estimated that approximately 75% of PD patients have an elevated odor detection threshold, and approximately 90% of PD patients suffer from odor identification deficits [16, 17]. These statistics suggest that hyposmia is more frequently observed than tremor, which is one of the four major motor symptoms of PD. Additionally, it has previously been reported that the degree of hyposmia is not associated with the severity of motor impairments, that hyposmia is already present bilaterally at the disease diagnosis, and that the severity of hyposmia remains essentially constant throughout the course of PD. Based on these findings, it can be inferred that the hyposmia progression is largely complete before the onset of motor symptoms of PD. Interestingly, however, patients are often not aware of their own hyposmia, and hyposmia is likely to be overlooked in the clinic unless olfactory tests are performed. It has also been reported that complete anosmia is uncommon, that the degree of hyposmia tends to be milder in women than in men, and that hyposmia is not improved by dopamine-replacement therapies [17].

Ansari and Johnson first described hyposmia in PD in 1975 [18], and subsequent, more detailed studies were conducted mainly by Doty and colleagues at University of Pennsylvania [16, 17]. It had previously been believed that the presence or absence of hyposmia in

PD was not associated with other clinical symptoms, including cognitive dysfunction. With recent advances in pathological and brain imaging analyses, it has been found that neurodegenerative changes, including the appearance of Lewy bodies, are commonly observed in regions of the brain that are responsible for olfactory perception, such as the amygdala, hippocampus, and orbitofrontal cortex [19, 20]. These changes are apparent from the earliest stages of the disease [19, 20], and the degree of atrophy in these areas is correlated with the severity of hyposmia in early PD [21]. Furthermore, clinical studies have reported that PD patients with severe hyposmia are more likely to suffer from PD-specific cognitive dysfunction, such as memory disorders and visuospatial dysfunction [7, 22]. Based on these results, it has more recently been inferred that severe hyposmia is closely associated with cognitive dysfunction in PD [23].

SEVERE HYPOSMIA IS A PRODROMAL SYMPTOM OF PDD

As mentioned above, it is very difficult to accurately predict the onset of PDD at early stages [24]. Therefore, we conducted a 3-year longitudinal study in 82 PD outpatients without dementia to analyze factors predicting the development of PDD. Inclusion criteria were: 1) age at onset ≧40, 2) age at enrollment between 55–75, and 3) Hoehn-Yahr classification of severity from stage I to stage III. Exclusion criteria were: 1) any other history of psychological or neurological disease, 2) any abnormal head MRI finding, 3) MMSE ≦24, and 4) clinical dementia rating (CDR) ≧1. Olfactometry was performed using the odor stick identification test (OSIT-J) at the initial study visit. The OSIT-J is a Japanese modification of an odor identification test and consists of 12 microcapsules of different odorous substances that are mixed into stick-formed paraffin [25]. During testing, the examiner rubs each of the odor sticks on paper so that the microcapsules give off their smell, and the examinee is asked to judge what type of smell it is.

FDG-PET and brain MRIs were collected before and after the 3-year period, and 47 patients who completed both brain scans and a clinical evaluation were eventually selected for the main analysis. In the severe hyposmia group, consisting of individuals with OSIT-J score ≦4, hypometabolism in the frontal lobe and occipital lobe was observed at the time of entry, compared with the normal olfaction group or the mild hyposmia group with OSIT-J score ≧5 (Fig. 1) [8]. These differences were greater at the 3-year follow-up, such that the severe hyposmia group had not only

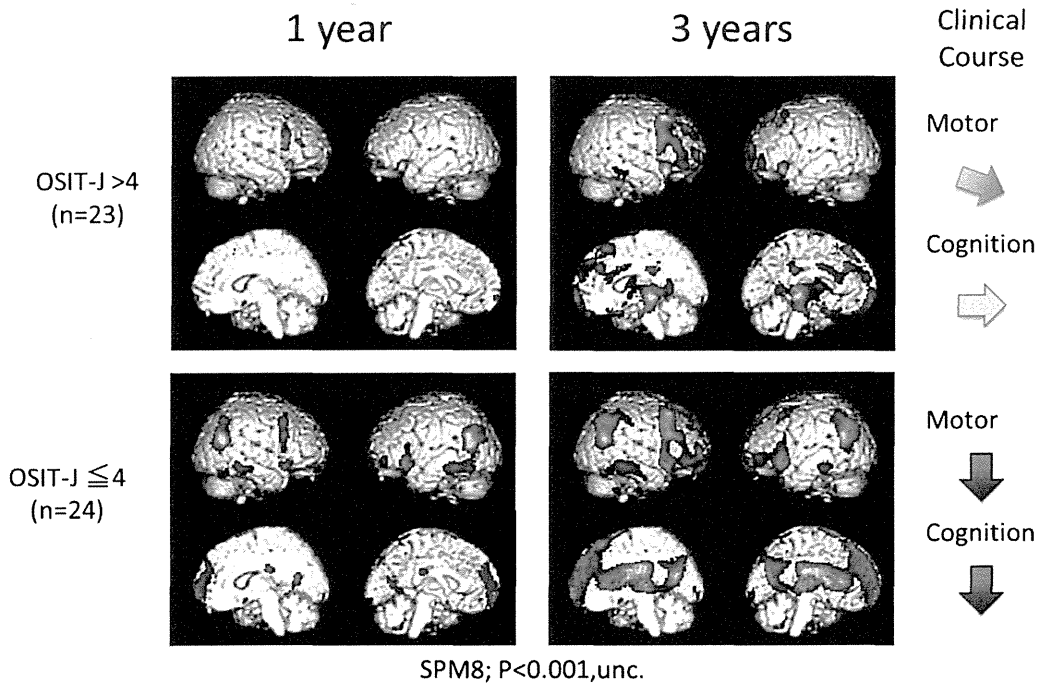


Fig. 1. Changes in brain metabolism measured by FDG-PET.

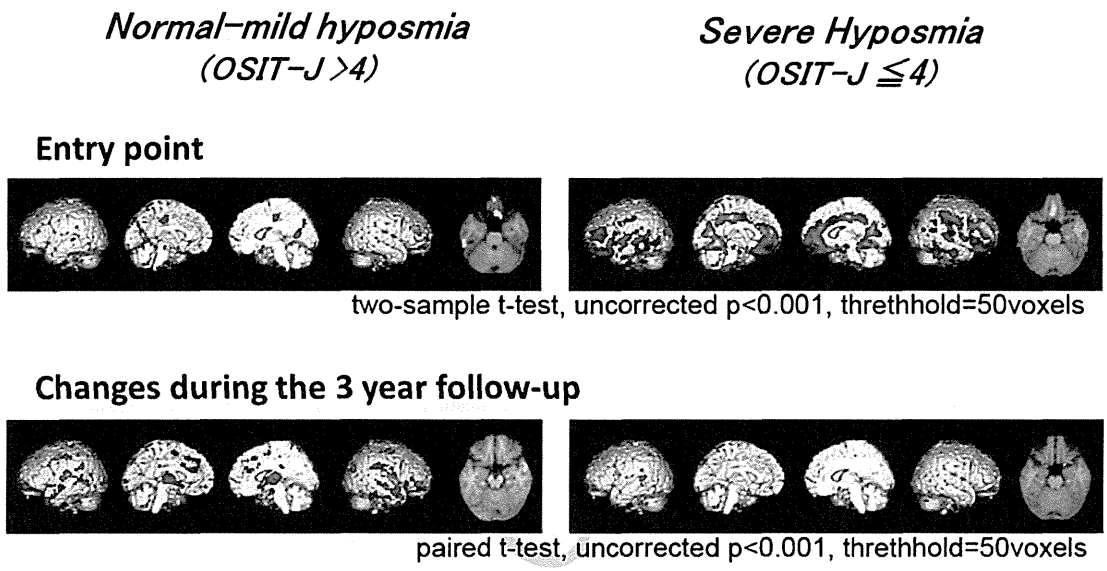


Fig. 2. Changes in brain atrophy measured by volumetric MRI.

widespread hypometabolism in the frontal and occipital lobes, but also remarkable hypometabolism on the medial surface of the brain, centered on the cingulate gyrus (Fig. 1). Volumetric MRI at the time of the initial scan revealed that the severe hyposmia group also exhibited brain atrophy centered on the cingulate gyrus and the orbital surface of the frontal lobe (Fig. 2). Interestingly, over the course of the 3-year study period, the severe hyposmia group did not show increasing brain atrophy, even though these individuals had a remarkable decline in brain metabolism (Figs. 1 and 2) [8].

Regarding clinical symptoms, the severe hyposmia group exhibited significantly exacerbated motor dysfunction as well as a remarkable decline in cognitive function; this group was thus classified as the poor prognosis group [8]. A total of 10 out of 47 cases had developed PDD by the 3-year follow-up visit. Table 1 summarizes the clinical characteristics of the cases that progressed to PDD, all of which showed an OSIT-J score $\leqq$4, but the mean scores of their cognitive or motor scales were not apparently different from the rest of the cohort. Conversely, not a single individual with an OSIT-J score $\geqq$5 progressed to PDD. Multivariate logistic regression analysis (stepwise method) was implemented to confirm that severe olfactory dysfunction was the most useful predictor of the onset of dementia. The odds ratio for the onset of dementia increased 18.7-fold for each 1 SD (2.8 points) decrease in OSIT-J scores [8].

In a recent study that investigated abnormalities of the acetylcholine system, the functional decline of acetylcholine in the amygdala and the hippocampus was correlated with hyposmia [26]. Furthermore, it has been reported in several imaging studies that hyposmia in PD is closely associated with limbic dysfunction [7, 21, 27, 28]. The association between limbic dysfunction and dementia has long been known, and olfactory tests should be particularly useful for detecting such dysfunction. In summary, it is possible that hyposmia in PD reflects limbic dysfunction, and it may be possible to predict the onset of PDD by quantitatively evaluating the level of hyposmia using olfactory tests.

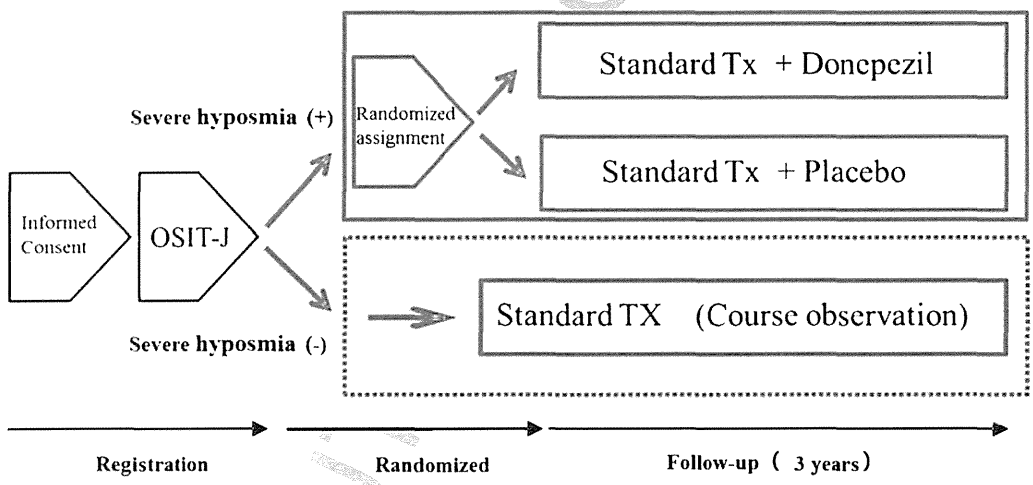
CONCLUSIONS: FUTURE PROSPECTS

Acetylcholine function suffers in patients with PDD to a greater degree than in Alzheimer's disease [29], and cholinesterase inhibitors shows some efficacy in treating cognitive dysfunction in PDD [30]. However, as the average life expectancy after the onset of PDD is approximately 3 years [31], it is likely too late to start therapeutic interventions after the onset of dementia, thus limiting the efficacy of cholinesterase inhibitors. In addition, there are cases in which dopamine replacement therapy must be restricted and motor function sacrificed due to accompanying psychiatric symptoms such as hallucinations and delusions, which can further worsen prognoses for PDD cases. As mentioned above, no biomarkers have been found that can predict PDD onset at early stages, and the appropriate timing for therapeutic intervention has not been established.

Table 1
Clinical features of cases developing dementia

No.	OSIT-J	Age	Onset	H-Y	UPDRS3	LED	MMSE	ADAS	Figure correct	Figure error
1	1	61	51	3	29	1025	29	17	25	3
2	4	63	56	3	16	451.125	26	16	21	13
3	4	63	59	3	27	301.5	25	19	30	4
4	3	59	55	2.5	18	500	25	19	30	6
5	2	72	70	2.5	16	150	30	10	36	2
6	2	72	70	2	14	200	25	15	28	7
7	0	69	56	3	25	650	26	9	33	5
8	0	73	71	2.5	9	500	30	16	34	1
9	2	70	70	2	18	225	26	23	34	3
10	1	68	61	3	17	451.25	27	15	29	3

Abbreviations: OSIT-J; The Odor Stick Identification test for Japanese, H-Y; Hoehn-Yahr scale, UPDRS3; Part 3 of unified Parkinson disease rating scale, LED; levodopa equivalent dose, MMSE; Mini-mental state examination, ADAS; Alzheimer's Disease Assessment Scale, Figure correct; number of correct answers in figure identification test, Figure error; number of incorrect answers in figure identification test.



- Double-blinded, Randomized, controlled-study
- 200 cases
- End-point: onset of PDD

Fig. 3. Double-blind, randomized, controlled study using 5 mg of donepezil for the PD group with severe hyposmia (The DASH-PD (Donepezil Application for Severe Hyposmic-Parkinson Disease) study).

However, under circumstances in which anticholinergic agents have been used for the improvement of motor symptoms of PD, the predominant opinion was that the use of cholinesterase inhibitor for PD should be avoided. Nevertheless, other than some tremor exacerbation, no remarkable declines in motor function have been attributed to therapeutic intervention with cholinesterase inhibitors, either in PDD or in the similar disease, DLB [32, 33]. Furthermore, activation of the acetylcholine system could potentially improve motor function in PD, based on a recent report of reduced risk of falling following the use of cholinesterase inhibitors [34] as well as another report of a correlation between reduced acetylcholine activity and a decline in walking speed in early PD patients without dementia [35].

The above results suggest that it may be possible to improve PD prognosis by intervening with cholinesterase inhibitors prior to the onset of PDD, with severe hyposmia serving as a biomarker. We have now started a therapeutic intervention study using cholinesterase inhibitor in the PD group that showed

severe hyposmia. This is a randomized, double-blind study using 5 mg of donepezil for the PD group with OSIT-J scores $\leqq$4 (Fig. 3). We hope that this clinical trial will help establish therapeutic interventions that can dramatically improve the prognosis of PD patients who suffer from declining cognitive function.

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CONFLICT OF INTEREST

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VIEWPOINT

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 nonsupporting 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 visuospatial functions also may 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, the authors propose future avenues of research that ultimately may lead to diagnostic criteria for cognitive impairment and dementia associated with multiple system atrophy. © 2014 International Parkinson and Movement Disorder Society

Key Words: cognition; multiple system atrophy; neuropsychology

Historically, multiple system atrophy (MSA) has been considered a rapidly progressive movement disorder for which the future occurrence of dementia leads to reappraisal of the primary diagnosis.[1] Multiple system atrophy can be divided into two motor phenotypes: a parkinsonian variant with prominent akinetic-

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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 functions	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.

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 defined as a nonsupporting diagnostic feature 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 neuroepidemiologic studies, with demented MSA cases being excluded ante mortem, in line with prevailing diagnostic criteria.

The 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 that of 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 before 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 of 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 nonsupportive criterion.[2] However, several investigators have attempted to circumvent this obstacle by either (1) omitting the dementia criterion of the consensus statement or (2) using 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] Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-revised 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 ultimately may lead to operational criteria for cognitive impairment and dementia associated with MSA.

Cognitive Impairment in MSA

Most 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 showed reduced Mini-Mental State Examination[23] scores in 26% of MSA patients.[3] Evidence from neuropsychological studies suggests executive dysfunction as a prominent

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 with 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 with controls. MSA patients had prolonged MTs compared with 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 patients compared with controls and different strategy for dealing with the task compared with PSP and PD patients. MSA patients were slower in the subsequent thinking time on planning task compared with 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 with controls. Compared with PD patients, MSA patients scored better on WCST. PSP patients were more impaired on executive functions tests compared with MSA patients. MSA patients were impaired on short delayed cued recall from CVLT and on short and late delayed free recall from GB test.
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 with controls. MSA-P patients made higher number of errors on TMT A and B and were slower to complete Stroop interference (especially 2nd section), with high number of errors and no amelioration of Stroop effect in 2nd section compared with PD. PD patients were impaired on WCST but performed normally on Stroop and verbal fluency tests.

TABLE 2. *Continued*

Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
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 with controls and performed worse on Phonemic Verbal Fluency Test than PD patients. MSA patients were slower on the tapping sequence test compared with PD patients. MSA patients had impaired imitation of single gesture compared with controls, and in sequence gestures compared with both PD patients and 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 with PD patients, and in Nelson's test in PSP compared with MSA and PD patents. Progression in demented PSP (from 2/21 at baseline to 6/21 at follow-up), whereas no demented patients were observed in MSA and PD groups. Decline in DI score in 2/14 MSA, 6/11 PSP and in none of PD patients.
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 (SRT); 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 with controls. MSA-C subjects scored worse on retrieval on verbal list learning task (SRT) and verbal fluency tests compared with controls and on recognition task from SRT compared with 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, and Stroop and tended to make more perseverative errors on Spatial sequence generation task compared with 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 with 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.

TABLE 2. *Continued*

Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
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; word lists; phonemic, semantic and alternating verbal fluency; Rey-Osterrieth complex figure; WCST	MSA-C subjects were impaired on verbal memory and verbal fluency compared with controls.
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 with controls. MSA-P performed worse on phonemic and semantic fluency and Rule shifting card test compared with controls and on Rule shifting card test compared with MSA C. MSA C showed impairment only in visuospatial functions compared with 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 1 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 semantic fluency; BNT; Digit forward and backward; Stroop interference; Design fluency; TMT B; Face recognition test; calculation	MMSE and CDR scores correlated with disease duration. MSA-C performed worse on CVLT-MS, pentagon copy, sematic fluency, comprehension, TMT B and Stroop interference compared with controls. MSA-C performed worse on CVLT-MS, Stroop interference, and TMT compared with MSA-P.
Kao 2009[27]	MSA/PD/DLB	12 MSA not classified		66.9 ± 11.3	5.4 ± 3.6	MMSE; Modified Trials B (ModTrials 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 with DLB patients. MSA patients performed worse on ModTrials B, Design Fluency, RCFT, M's and N's and semantic fluency compared with PD patients.

TABLE 2. *Continued*

Study	Groups investigated	MSA-P	MSA-C	Mean age (years)	Disease duration (years)	Neuropsychological tests	Results
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	372 MSA P+C		61.71 ± 8.34	4.55 ± 1.92	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.
	Pathologically correlated (49 MSA/63 PSP)			MSA-impaired 65.07 ± 8.53 MSA-unimpaired 60.57 ± 7.92	MSA-impaired 4.99 ± 2.3 MSA-unimpaired 4.24 ± 1.76		
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 with controls and MSA-ND and on RCFT and BNT compared with MSA-ND.
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 in cognitive performance between MSA-P and MSA-C on all employed tests.

sOPCA, sporadic olivopontocerebellar degeneration; dOPCA, dominantly inherited olivopontocerebellar degeneration; MSA-D, multiple system atrophy, demented; MSA-ND, multiple system atrophy, nondemented; MSA P+C, multiple system atrophy, 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.

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, approximately 20% of MSA patients have frontal lobe release signs,[4] and apraxia is present in 8% to 10% of MSA of both motor subtypes.[4,28] Conflicting evidence exists on whether MSA-related attention deficits occur.[3,24,26] Impairments of working memory are similar to those found in other parkinsonian disorders.[3,27] Memory disturbances, observed in up to 66% of MSA patients, commonly present with impaired verbal learning[24] and immediate[6] and delayed recall,[3,12,24] and less often with impaired recognition,[3] although this finding is not universal.[26] Multiple system atrophy patients may experience visuospatial and constructional difficulties compared with controls,[6,12,26] despite inconsistent reports.[3,29] Language functions such as 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 nondemented 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 indicate 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. Whether memory and visuospatial deficits are also caused by executive impairment remains unclear.[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 the Trail Making Test.[20] In addition, conflicting reports have been made 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, relatively few detailed neuropsychological evaluations have been made 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] Controversial reports have been made 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 Versus MSA-C

Comparative studies of cognitive impairment in MSA-P and MSA-C produced controversial results (Table 2).[20,24,26] Kawai and colleagues[26] reported that multiple domains were affected in MSA-P as opposed to MSA-C, in which only visuospatial deficits were observed. 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 compared to controls likely reflect different subcortical degeneration patterns.[19]

Cognitive Impairment in MSA Versus 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] Furthermore, 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 nondemented PD patients.

The cognitive profile of demented MSA patients appears to differ from that of PD dementia (PDD) patients. Patients with PDD experience cognitive decline at approximately 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% to 65% of PDD patients[42] experience hallucinations, they are infrequent in MSA patients.[43] Information processing speed is severely affected in PDD[41]; however, whether similar deficits occur in MSA remains to be determined.

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, multiple 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] Furthermore, 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 Versus 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,[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

Most MRI studies (Table 3) indicate 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