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COGNITIVE SCIENCE & NEUROSCIENCE | RESEARCH ARTICLE

Neuropsychiatric symptoms and their impact on quality of life in multiple system atrophy

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Abstract: *Background:* Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterized by severe dysautonomia and atypical Parkinsonism or cerebellar dysfunction. Disease-modifying treatment is not available and the main-stream of care is supportive. Neuropsychiatric symptoms are frequent in MSA and their successful management can improve patients' quality of life (QOL). This study aimed to define a comprehensive neuropsychiatric profile in MSA patients in relation to QOL. *Methods:* In 48 MSA patients and 40 controls neuropsychiatric symptoms were assessed using Neuropsychiatric Inventory. MSA patients completed Beck Depression Inventory and QOL questionnaire (SF12), including Mental and Physical subscales. *Results:* Eighty-seven percent of MSA patients had neuropsychiatric symptoms as compared with 10.4% of controls. Depression (56%), apathy (48%), anxiety (27%), and agitation (27%) predominated. The Physical SF-12 scores were lower in the patients as compared with the controls. Neuropsychiatric Inventory (NPI) scores did not correlate with QOL measures. Depression, as reflected by the BDI, correlated with the mental component score of the SF-12 in MSA patients. *Conclusions:* Neuropsychiatric symptoms are very frequent in patients with MSA and are dominated by depression and apathy. They appear independent from physical disability and loosely map onto the known brain pathology of MSA. Only depression,

ABOUT THE AUTHORS

This study was done under the lead of professor I. Litvan, a world-renowned expert in movement disorders and a director of the University of California, San Diego National Parkinson Foundation Center of Excellence. The Center does clinical, basic, and cutting edge technology research aiming at the improvement of the diagnosis, understanding etiopathogenesis of motor, autonomic, and cognitive manifestations of parkinsonian disorders, as well as developing new treatments and comprehensive care models. Atypical parkinsonian disorders is special interest and expertise of Litvan's. This study examined the neuropsychiatric aspects of Multiple System Atrophy, a relatively neglected aspect of the disorder with a potential to affect quality of life. R. Ceponiene has published extensively in the field of cognitive neurodevelopmental neurophysiology and aging. During preparation of this manuscript, she acted as a movement disorders fellow in the Center and now works as a movement disorders specialist at Kaiser Permanente, San Diego.

PUBLIC INTEREST STATEMENT

Multiple system atrophy (MSA) is an atypical parkinsonian condition manifested by severe autonomic dysfunction and movement difficulties. No treatments are available to slow down the disease, and patient care focuses on symptom treatment. Neuropsychiatric symptoms have been reported in MSA however their extent and nature has not been investigated. In this study, we showed that these symptoms affect almost 90% of MSA patients, the most frequent being depression, apathy, anxiety, and agitation. Depression showed a strong negative impact on mental quality of life, when assessed by a patient-reported questionnaire. Therefore, it will be important to evaluate the relationships between all neuropsychiatric symptoms and quality of life using self-reported measures. Awareness of the prevalence and nature of the neuropsychiatric symptoms in MSA will help to detect and treat them, as well as counsel the patients and their families, thereby improving the quality of life in individuals with this unforgiving disorder.

as reflected by the BDI, negatively affected mental QOL. The discrepancy between the BDI and NPI-depression scores likely stems from the different approaches to symptoms by these questionnaires.

Subjects: Bioscience; Health and Social Care; Medicine, Dentistry, Nursing & Allied Health

Keywords: apathy; depression; multiple system atrophy; Parkinsonism; neuropsychiatric symptoms

1. Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset neurodegenerative disorder manifesting primarily with autonomic dysfunction and an atypical Parkinsonism or ataxia (Gilman et al., 2008). The prevalence of MSA is 2–5 per 100,000 and average life expectancy is 7–9 years from diagnosis. At this time no disease-modifying treatments are available and the mainstream of care is supportive. Mood and behavioral symptoms are potentially modifiable and their successful management may improve the quality of life (QOL) of the MSA patients and help to understand the underlying pathophysiology. In previous studies, we were able to delineate distinct neuropsychiatric impairment profiles in related neurodegenerative disorders including corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (Litvan, Cummings, & Mega, 1998; Litvan, Mega, Cummings, & Fairbanks, 1996; Litvan, Paulsen, Mega, & Cummings, 1998), and these profiles paralleled the known structural and functional abnormalities of CBD and PSP.

Depression is the best studied neuropsychiatric symptom in MSA. Its prevalence is as high as 40–86% (Balas, Balash, Giladi, & Gurevich, 2010; Kao et al., 2009; Schrag et al., 2010; Siri et al., 2013; Tison, Yekhelef, & Chrysostome, 2006), and its impact on QOL in MSA patients was found to be comparable to that of motor and autonomic symptoms (Benrud-Larson, Sandroni, Schrag, & Low, 2005; Schrag et al., 2006, 2010). Only two studies so far studied a broader neuropsychiatric symptom profile in MSA (Kao et al., 2009; Siri et al., 2013). They used the Neuropsychiatric Inventory (NPI) to assess the frequency and severity of 10 behavioral and 2 neurovegetative symptoms (Cummings et al., 1994). In a multi-center European study Siri et al. (2013) found that in their MSA patients with Parkinsonism (MSA-P, $n = 39$) the highest NPI scores were for depression, irritability, and anxiety, while in the MSA patients with ataxia (MSA-C, $n = 22$) the highest scores were for apathy, agitation, and depression. Further, the NPI-depression scores were comparable between the MSA ($n = 61$) and Parkinson disease (PD) patients ($n = 20$) but the self-reported Geriatric Depression Scale (GDS) scores were higher in the MSA than in the PD patients of that study. In the second study that utilized NPI, Kao et al. (2009) compared cognitive and psychiatric profiles between patients with PD, MSA, and LBD. In their 10 patients with MSA the most prevalent symptoms were depression, apathy, and anxiety. The NPI-depression scores were significantly lower in the MSA than in the other patient groups, while the GDS did not differ among the three groups.

Therefore, while several neuropsychiatric symptoms appear to be frequent in MSA, including depression, irritability, anxiety, and apathy, more studies are needed to determine their relative prevalence and impact on QOL in MSA. Further, the comparison groups in the aforementioned studies were patients with PD and Lewy Body Dementia, without an inclusion of a healthy control group. Using healthy peers as controls would minimize the reference group variability and increase generalizability of the results. Finally, the self-reported (GDS) vs. caregiver-reported (NPI) measures yielded somewhat different results in these previous studies, warranting further inquiry into these measures. Therefore, the main aims of the present study were to determine a comprehensive neuropsychiatric profile in patients with MSA using the NPI (Cummings et al., 1994), in comparison with a healthy peer control group; to investigate the relationships between the neuropsychiatric symptoms captured by the NPI vs. BDI and QOL; and to compare the patient (self) and caregiver assessments of the depressive symptoms.

2. Methods

2.1. Subjects

This study included 48 consecutive MSA patients evaluated at the University of Louisville Movement Disorders Clinic between 2003 and 2008 who met the second consensus criteria for probable ($n = 21$) or possible ($n = 27$) MSA (Gilman et al., 2008). Forty-six patients had MSA-P and two patients had MSA-C. With patients' informed consent, their caregivers completed a NPI questionnaire (Cummings et al., 1994). The caregivers were spouses or other family members who interacted with the patients on a daily basis.

Forty healthy participants, similar to the MSA patients in age, gender, education, and ethnicity, served as controls. Control participant data were published previously (Litvan et al., 1996; Litvan, Cummings et al., 1998). Control participants were residents of a Southern California retirement community. They were administered the Mini-Mental State Examination (MMSE) and had to score 25 or above to be included in the study. In addition, their spouses were asked about any concerns regarding any signs of dementia or memory loss. If these concerns were denied, the spouses filled out the NPI questionnaire. All participants signed institutional informed consents. The study was approved by the IRBs of the University of Louisville and UCLA.

2.2. Measures

The *Mini-Mental State Examination (MMSE)* (Folstein, Folstein, & McHugh, 1975) was administered to each study participant. Patients completed the *Beck Depression Inventory-II (BDI-II)*, which is a 21-item scale assessing the behavioral, cognitive, somatic, and affective symptoms of depression within the past two weeks (Beck & Steer, 1993). BDI-II scores ≥ 14 indicate mild depression, ≥ 20 moderate depression, and those ≥ 29 indicate severe depression. The caregivers of the MSA patients (spouses or other family members) completed the *NPI* (Cummings et al., 1994), which assesses the frequency and severity of 10 behavioral (depression, apathy, anxiety, agitation, irritability, disinhibition, hallucinations, delusions, euphoria, and aberrant motor behavior) and two neurovegetative domains. The original, 10-item behavioral version was used in this study since it has been validated for content and reliability and avoided confounds with vegetative symptoms of MSA. Symptom frequency was rated using a 1–4 scale and the severity is rated using a 1–3 scale (higher scores for more severe). The composite score for each behavioral domain is the product of the frequency and severity subscores for that particular behavior and can attain a maximum value of 12. The total NPI score is the sum of the subscale scores. The *Unified Parkinson's Disease Rating Scale (UPDRS)* (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003) was administered to all MSA patients to assess the severity of motor and non-motor symptoms. The UPDRS is the main standardized clinical assessment tool in Parkinson's disease and atypical parkinsonian disorders. Of the four subscales of the UPDRS, we obtained the non-motor daily living subscale, UPDRS-1, which is obtained from the patient with help from a caregiver if needed. The motor subscale, UPDRS-3, is obtained during examination by a health care provider and assesses rigidity, bradykinesia, tremor, gait, and balance. Although there are now specific scales for MSA, those were not available when the study was conducted. To assess health-related QOL in the MSA patients, the Physical Component score and Mental Component score of the *Twelve-item Short-Form Health Survey (SF-12)* (Ware, Kosinski, Turner-Boweker, & Gandek, 2007), were used. The SF-12 is a US 1998 population-normed instrument allowing placement of an individual in a population-based reference framework. In this scale, the mean is 50 and the standard deviation is 10 (higher score means better QOL). The SF-12 was completed by the patients themselves.

2.3. Statistical analyses

The between-group comparisons of demographic characteristics and composite NPI scores were done using t-tests for continuous variables and Fisher's exact test for discrete variables. Correlation analyses assessing for associations between NPI scores, BDI scores, UPDRS, disease duration, and QOL measures from SF-12 Mental component and SF-12 Physical component scores in MSA cases were performed using the non-parametric Spearman Rank Correlation coefficient. Non-parametric

correlation coefficients were used to accommodate skewed distributions and the lack of linear association between some of the variables.

3. Results

Descriptive subject characteristics are presented in Table 1. There was between-group age difference ($p = .05$) and there were relatively more males in the MSA group. However, there was no between-group difference in the MMSE scores. Of the QOL measures, the distribution of SF-12 Mental component score of the MSA group was similar to that of the instrument population norms: 49.83 ± 9.29 vs. 50 ± 10 , respectively. The SF-12 Physical component score was significantly lower in the MSA group than that in the general population: 32 ± 8.7 vs. 50 ± 10 . The SF-12 Physical component score correlated negatively with the UPDRS motor examination score ($r = -.339, p < .02$; Table 2). The SF-12 Mental component score correlated negatively with disease duration ($r = -.293, p < .04$), UPDRS non-motor symptom subscale ($r = -.291, p < .02$), as well as BDI scores as noted in Table 2.

The BDI showed that 37.5% of patients with MSA had symptoms of depression, mild in 27% (13/48) of patients, moderate in 10.4% (5/48), and no patient had a BDI score in the severe range. However, nine patients reported having had recent suicidal ideations. The BDI scores correlated positively with the disease duration ($r = .337, p < .02$) and strongly and negatively with SF-12 Mental component scores ($r = -.542, p < .0001$).

According to NPI, 87% of MSA patients had at least one neuropsychiatric symptom, as compared with 10.4% of controls. In both groups, the most prevalent symptom was depression. In addition to depression (56%), MSA patients showed significantly more apathy (48%), anxiety (27%), agitation (27%), and hallucinations (15%) than controls (Table 3, Figure 1). There was a trend for apathy and depression to co-occur: of 27 patients with depression, 16 showed apathy (59%) while out of 21 patients without depression, 7 showed apathy (33%, Fisher's exact test $p = .09$).

The total NPI scores in the MSA group did not correlate with either the physical or mental component scores of SF-12 questionnaire (Table 2). There were no significant correlations between the NPI scores of depression, apathy, or anxiety and the BDI scores. The NPI depression scores correlated weakly but significantly with UPDRS non-motor symptom subscale that assesses cognitive, mood, sleep, and autonomic symptoms. The NPI apathy scores correlated significantly and positively with age while NPI anxiety scores tended to correlate negatively with age. Agitation correlated with irritability, and significantly and negatively with the UPDRS non-motor symptom subscale. Hallucinations correlated with delusions and the total NPI score. UPDRS motor examination score correlated negatively with SF-12 Physical component score and showed a trend for negative correlation with SF-12 Mental component score. The BDI scores correlated positively with the disease duration and strongly and negatively with SF-12 Mental component scores.

Table 1. Demographic characteristics and MMSE of MSA and control study groups (Mean \pm SD)

Characteristics	MSA (n = 48)	Controls (n = 40)
Age, years	69.75 \pm 10.58	73.55 \pm 5.97 *
Gender, M/F	35/13	20/20 *
Disease duration, years	5.56 \pm 3.55	na
MMSE	28.75 \pm 1.58	28.43 \pm 1.34
UPDRS-1 (out of 55)	2.04 \pm 1.54	n/a
UPDRS-2 (out of 55)	16.81 \pm 10.23	n/a
UPDRS-3 (out of 72)	24.21 \pm 10.11	n/a
UPDRS-total (out of 199)	41.73 \pm 15.89	n/a

* $p < .05$.

Table 2. Correlations that were significant or showed strong trends between the NPI, BDI, SF-12, UPDRS, disease duration in the MSA patient group. (r value/p value)

	Age	DUR	SF12-M	SF-P	U-1	U-3	DEP	HAL	IRR	DEL
BDI	-.201	.337	-.542	-.204	.128	.205	.111	.117	.036	.091
	.20	.02	.0001	.16	.39	.16	.45	.43	.80	.54
APA	.327	-.108	-.045	-.011	.004	.185	.225	.187	.250	.029
	.023	.47	.76	.93	.98	.21	.12	.20	.08	.85
DEP	-.103	-.186	-.065	-.065	.285	-.143	1	-.052	.083	.201
	.48	.21	.96	.66	.05	.33		.72	.57	.17
ANX	-.274	-.042	-.203	.065	-.262	-.049	.062	-.022	-.014	-.125
	.06	.78	.17	.66	.26	.74	.67	.88	.92	.40
AGI	-.099	-.073	.039	-.143	-.340	.003	.007	.174	.298	.148
	.50	.62	.79	.33	.02	.98	.93	.24	.04	.31
HAL	.151	.045	-.160	-.238	.124	.159	-.053	1	.247	.510
	.30	.76	.28	.10	.40	.28	.72		.09	.0002
SF12-P	.190	-.071	-.028	1	-.096	-.339	-.065	-.238	.003	-.187
	.20	.63	.85		.52	.02	.66	.10	.99	.20
SF12-M	.092	-.293	1	-.028	-.291	-.254	-.008	-.169	-.062	.022
	.54	.04		.85	.045	.08	.96	.28	.68	.88
U-2	.067	.255	-.193	-.145	.241	.590	-.238	.113	.038	-.034
	.65	.08	.19	.32	.10	.00001	.10	.45	.80	.82

Notes: AGE: age, AGI: agitation, ANX: anxiety, APA: apathy, BDI: Beck depression inventory, DEL: delusions, DEP: depression, DUR: disease duration, HAL: hallucinations, IRR: irritability, NPI-T: total NPI score, SF12-P: SF12 Physical score, SF12-M: SF12 Mental score, U-1: UPDRS part I (non-motor daily living score), U-3: UPDRS part III (motor score).

Table 3. Neuropsychiatric inventory (NPI) composite scores (maximum 12) in patients with MSA and their controls (Mean ± SD, % of patients)

Behavior	MSA (n = 48)	Controls (n = 40)
Depression/Dysphoria	1.56 ± 2.31, 56.3%**	.23 ± 1.06, 5.1%
Apathy/Indifference	1.65 ± 2.54, 47.9%***	0
Anxiety	.60 ± 1.28, 27.1%**	0
Agitation/Aggression	.60 ± 1.41, 27.1%**	0
Hallucination	.21 ± .54, 14.6%*	0
Disinhibition	.52 ± 1.97, 12.5%	.13 ± .656, 5%
Irritability/Lability	.21 ± .68, 10.4%	.05 ± .32, 2.5%
Delusions	.06 ± .32, 4.25%	0
NPI, total	5.42 ± 5.46, 87.55***	.41 ± 1.68, 10.35

*p < .05.

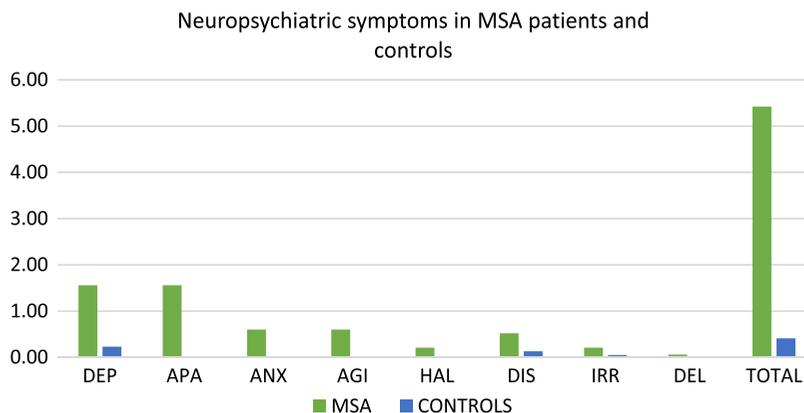
**p < .01.

***p < .001.

The frequency of depressive symptoms was higher (56.3%) when assessed by the NPI than by the self-reported BDI (37.5%). In the NPI, 39.5% (19/48) of patients showed mild, 12.5% (6/48) showed moderate, and 4% (2/48) showed severe symptoms, while in the BDI, no patient showed severe depression.

Figure 1. Total neuropsychiatric inventory scores (symptom severity x frequency) in MSA patients and controls.

Notes: AGI: agitation, ANX: anxiety, APA-apathy, DEL: delusions, DEP: depression, DIS: disinhibition, HAL: hallucinations, IRR: irritability, TOTAL: total NPI score.



4. Discussion

In summary, our study found that neuropsychiatric symptoms are very frequent in cognitively intact patients with MSA. Depression and apathy dominated profile, followed by anxiety and agitation. Depression, but only as reflected by BDI, correlated negatively with the mental QOL. In addition, mental QOL, as reflected by the SF-12 Mental component scores, correlated negatively with disease duration and with UPDRS non-motor symptom subscale. None of the NPI scores, including the NPI-depression score, correlated with any of the QOL measures. Physical QOL, as measured by the SF-12 Physical component scores, correlated negatively with UPDRS motor examination scores.

The high incidence of neuropsychiatric symptoms in MSA in our study was comparable to that in other parkinsonian disorders, and the symptom profile was most reminiscent of that in CBD which is also dominated by depression, apathy, irritability, and agitation (Litvan, Cummings, et al., 1998; Litvan, Paulsen, et al., 1998). The frequency of depression in MSA found in our study (56%) was within the 40–80% range reported in previous studies (Balas et al., 2010; Kao et al., 2009; Schrag et al., 2010; Siri et al., 2013; Tison et al., 2006). The strong negative correlation between the BDI and SF-12 Mental component scores suggests that depression worsens the QOL in these patients. Further, the fact that the BDI scores did not correlate with the SF-12 Physical component scores argues against the idea of physical disability being a significant contributor to the depression in MSA (or vice versa). Moreover, while both the depression (per the BDI) and mental QOL worsened with disease duration, physical QOL did not show such correlations. Even though the Physical QOL correlated with the objective measures of UPDRS motor examination scores, at least in this patient sample, neither correlated with the disease duration. This underscores the increasing impact of non-motor symptoms on the QOL as the disease progresses over time. Granted, patients with a progressive and potentially life-ending condition have strong objective reasons to feel depressed. However, less than half of our patients did not report depression; this suggests a range in the biologically based vulnerability to depression, which likely interacts with the pathological changes specific to MSA, resulting in the development of depression irrespective of motor or autonomic impairment. Specifically, depression in MSA can be mediated by the degeneration of noradrenergic and dopaminergic neurons of the brainstem (Lewis et al., 2012; Matsuura et al., 2013), as well as the prefrontal lobe and limbic systems (Balas et al., 2010; Herting et al., 2007; Siri et al., 2013; Stankovic et al., 2014).

In addition to depression (per the BDI), the mental QOL correlated with the UPDRS non-motor living subscale. The latter is mostly patient reported and assesses cognitive impairment, hallucinations, depression, anxiety, agitation, apathy, and impulsiveness (symptoms of dopamine dysregulation syndrome). However, these same symptoms, as measured by the NPI, did not correlate with the SF-12 Mental component scores. Further, there were no correlations between the BDI and the NPI scores of depression, anxiety, or apathy. It therefore appears that the BDI and NPI measure different aspects of depression; conceivably, the BDI is more reflective of the inner experiences (self-report) whereas the NPI is more reflective of the behavioral manifestations (caregiver

report). The non-demented patients, such as those with MSA, while being aware of their depression, may also be able and willing to conceal it from their caregivers. On the other hand, the caregivers themselves can be influenced by their observational skills, relationship with the patient, and their own distress. Low agreement rates between the self and caregiver reports have been reported earlier (McKinlay et al., 2008) and could explain the discrepancy between the different measures in this study as well as in the earlier studies that used NPI along with the self-reported measures (Siri et al., 2013). Interestingly however, the NPI depression scores correlated with the mostly self-reported UPDRS non-motor symptom subscale, suggesting that some symptoms from the self-reported UPDRS are reflected in the NPI as well, possibly those that are more readily observable. However, in non-demented populations such as MSA patients, self-reports might be preferable due to the better correlation with self-perceived QOL, as suggested by the findings of the present study. Clearly, further studies are needed to clarify these complex relationships between the self vs. caregiver reports. Larger numbers of healthy participants as well as patients with Parkinson spectrum disorders with and without cognitive impairment will need to be assessed using caregiver and self-reported questionnaires, including caregivers as a study population. This would also shed light onto the impact of a caregiver burden onto the QOL of MSA patients.

Apathy was the second most frequent neuropsychiatric feature of MSA in our study, affecting almost half of the patients. It was previously reported in PSP (91% of 22 patients (Litvan et al., 1996)) and CBD (40% of 12 patients (Litvan, Cummings, et al., 1998)). While apathy was previously reported in MSA (Fetoni, Soliveri, Monza, Testa, & Girotti, 1999; Kao et al., 2009; Siri et al., 2013), it had not been considered a salient aspect of the MSA profile. Nonetheless, in Siri et al. study (2013), the NPI apathy score was the fourth highest in their MSA-P patients, and it was the highest score in their 22 MSA-C patients. Further, Kao et al. (2009) found that 4 of their 10 patients with MSA exhibited apathy which was the second frequent symptom after depression. Finally, Fetoni et al. (1999) found that 11 out of 12 patients had blunted affect on a Brief Psychiatric Rating scale which may suggest apathy. The neuropathologic substrate of apathy/abulia is medial-opercular frontal lobe—basal ganglia circuit (Jorge, Starkstein, & Robinson, 2010). In addition, in a review of 240 stroke cases, basal ganglia lesions most frequently manifested with apathy, and the majority of abulia cases were associated with lesions in the caudate nucleus (Bhatia & Marsden, 1994). Deficiency in dopaminergic and cholinergic transmission has been implicated in apathy as well (Allain, Bentue-Ferrer, & Lacomblez, 2004). Therefore, apathy appears a frequent feature of MSA, and there is a substantial overlap between the neural bases of apathy and those of MSA. Given the involvement of frontal-subcortical networks in both, future studies should assess apathy in MSA in relation to executive functioning rather than in relation to MMSE that is insensitive to frontal lobe dysfunction.

In our study, apathy did not correlate with measures of QOL. It tended to correlate with irritability, as previously found in CBD (Litvan, Cummings, et al., 1998). While the NPI-apaty scores did not correlate with NPI-depression scores, there was a tendency for the patients who appeared depressed to also appear apathetic—more frequently than for those patients who did not appear depressed. This could be a true phenomenon but could also be caused by the overlapping overt manifestations of apathy and depression. Therefore, future studies should assess the impact of apathy on QOL using caregiver as well as self-reported measures, such as Apathy Evaluation Scale (Marin, Biedrzycki, & Firinciogullari, 1991) or a Dimensional apathy scale (Radakovic & Abrahams, 2014). Finally, in our study apathy worsened with age but not with the disease duration. This is puzzling since the disease duration increases with age. One possible explanation is smaller variance of the disease duration (standard deviation of 7 years) as compared with that of age (20 years). Alternatively, the diverging trajectories of apathy, anxiety, as well as depression with age may suggest differential susceptibilities of the respective underlying networks to aging and the disease process. However, clarification of the underpinnings of these different trajectories would require further, longitudinal studies, and utilization of functional imaging tools. Differentiating apathy from depression or physical symptoms of illness is very important due to their differential impact on prognosis and management. Specifically, apathy, and not depression, was associated with lower cognitive functioning, progressive decline, and lower QOL in patients with stroke and neurodegenerative disorders (Jorge et al., 2010; Levy et al., 1998;

Tang, Lau, Mok, Ungvari, & Wong, 2013). Further, apathy is a potential side effect of SSRI therapy (Zahodne et al., 2012) and therefore consideration should be given to treating apathy and depression in MSA with SNRIs (rather than SSRIs), cholinesterase inhibitors (Figiel & Sadowsky, 2008), MAO-B inhibitors, D2/D3 agonists (Thobois et al., 2013), or stimulants.

In our patient sample, over a quarter of patients exhibited symptoms of anxiety and over a quarter of patients exhibited symptoms of agitation. This is somewhat less than the earlier reported frequency of 33–37% (Kao et al., 2009; Schrag et al., 2010; Siri et al., 2013). In our study, these symptoms did not correlate with QOL. In contrast, Schrag et al. (2010) found a correlation between anxiety and health-related QOL in their large group of MSA patients ($n = 286$), however they used a self-reported questionnaire. Anxiety is always a rather disabling symptom and should be considered and treated in MSA patients. Hallucinations and delusions are unusual in MSA (Kao et al., 2009; Siri et al., 2013) and in our study, they were rare and explained by dopaminergic medications in all but one patient who had a concurrent urinary tract infection. Thus, presence of hallucinations in MSA points to medications, infections, or metabolic disorders.

The strengths of the present study are that it provides the full neuropsychiatric symptom profile in a relatively large group of well-characterized MSA patients, in comparison with their healthy peers. It emphasizes the high incidence of treatable neuropsychiatric symptoms in patients with MSA, including depression, apathy, anxiety, and agitation, offering the potential to improve their QOL. A variety of treatments are available including education, medications, support groups, and cognitive behavioral therapies, allowing for clinical intervention studies. One study limitation is a small number of MSA-C patients, since their neuropsychiatric profile may be different. Further, this study revealed the need for further research to characterize the relationships between the self vs caregiver reported neuropsychiatric symptoms in cognitively intact populations such as patients with MSA.

In summary, this study was the first to assess the frequency of neuropsychiatric symptoms in MSA in relation to healthy controls. It showed that these symptoms affect almost 90% of patients. Depression and apathy were encountered in about half of the patients each and anxiety and agitation were encountered in about a quarter of patients each. The neural bases of these symptoms appear to loosely map onto those of MSA, however further functional neuroimaging studies are needed to clarify the neural underpinnings. Neuropsychiatric symptoms did not correlate with objective measures of physical disability or subjective physical QOL, making the causal link between them unlikely. Depression showed a strong negative correlation with mental QOL, however only when assessed by a patient-reported instrument (BDI) and not when assessed by a caregiver reported instrument (NPI). Therefore, in the future it is important to evaluate the relationships between all neuropsychiatric symptoms and QOL using self-reported measures, which could be preferred in non-demented populations. Clinician's awareness of the prevalence and nature of the neuropsychiatric symptoms in MSA will help to detect and treat them as well as counsel the patients and their families, thereby improving the QOL in individuals with this unforgiving disorder.

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Competing interest

The authors declare no competing interest.

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