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Behavioral abnormalities in progressive supranuclear palsy

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Abstract

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder in which, classically, patients present with postural instability and falls, parkinsonism, and slowing of vertical saccades. PSP patients typically have deficits in cognitive functioning, difficulties with most daily activities, and present with notable behavioral disturbances—particularly apathy, impulsivity, and irritability. Using data from 154 patients meeting criteria for clinically probable PSP, domain and total scores of the Neuropsychiatric Inventory were examined and compared to demographics, disease severity, cognition, and motor features. Behavioral abnormalities were common in this cohort of PSP patients, with more than half experiencing apathy, depression, and sleeping problems, and approximately one third displaying agitation, irritability, disinhibition, and eating problems. Few clinical correlates of neuropsychiatric symptoms were observed in this cohort. Given the prevalence of neuropsychiatric symptoms in PSP, these patients are expected to be frequently seen by psychiatrists and other mental health professionals for symptom management and increased quality of life. Clinical trials are clearly needed to address the neuropsychiatric morbidity in these patients.

Keywords

Parkinsonism; Parkinsonian; Neuropsychiatric inventory; Neuropsychiatric functioning; Apathy; depression

1. Introduction

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder in which, classically, patients present with postural instability and falls, parkinsonism, and slowing of vertical saccades (Litvan et al., 2003). PSP patients display impairments in executive functioning, memory, and other cognitive abilities (Gerstenecker et al., 2003). Functionally, when diagnosed, they usually have difficulties with most daily activities (Duff et al., 2003).

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Finally, PSP patients present with notable behavioral disturbances, particularly apathy, impulsivity, and irritability.

In several small studies examining the neuropsychiatric symptoms in PSP, results have mirrored those exhibited by apathetic patients with dementias of the frontal lobe (Cordato et al., 2002). For example, negative symptoms (i.e., apathy, aspontaneity, and indifference) can dominate the neuropsychiatric profile of these PSP patients, with apathy being the most common negative symptom (Litvan et al., 1996b; Litvan et al., 1998; Aarsland et al., 2001; Borroni et al., 2009). Depression is another common symptom in PSP, although rates vary among studies (Menza et al., 1995; Millar et al., 2006; Schrag et al., 2010). Disinhibition can present in up to a third of patients (Litvan et al., 1996b; Aarsland et al., 2001), and sleep disorders (e.g., decreased REM sleep) also frequently occur (Gama et al., 2010). Less common neuropsychiatric symptoms include anxiety and irritability (Litvan et al., 1996b; Aarsland et al., 2001; Borroni et al., 2009). These psychiatric symptoms of PSP have also been linked to cognitive deficits. For example, apathy has been found to significantly correlate with executive dysfunction (Litvan et al., 1996b; Aarsland et al., 2001; Borroni et al., 2009). Similarly, anxiety and attention tend to be negatively associated in this cohort (Litvan et al., 1996b).

In addition, approximately 20% of PSP patients have been noted as exhibiting impaired interpersonal functioning including difficulties engaging in activities with family and friends, poor relationships within the family, and problems of communication (Schrag et al., 2003). Moreover, similar to patients with Parkinson's disease (Assogna et al., 2008; Assogna et al., 2010), the recognition of emotional expression is impaired in PSP. However, this ability is more impaired in PSP than in Parkinson's disease and worsens as cognitive impairments become more severe (Ghosh et al., 2009; Pontieri et al., 2012).

Better characterization of the behavioral abnormalities in PSP can potentially improve the clinical care of these patients in several ways. First, the neuropsychiatric profiles of PSP patients may help differentiate PSP from other degenerative brain diseases (Cordato et al., 2002). In one study, PSP patients were differentiated from patients with a more classical "cortical" dementia (i.e., Alzheimer's disease) in up to 85% of cases using only neuropsychiatric profiles (Litvan et al., 1996b). Second, apathy and depression are often confused in PSP, which can lead to unnecessary and unproductive treatment with antidepressants (Litvan et al., 1996b). Third, given that patients with more severe neuropsychiatric symptoms are reported as more burdensome by their caregivers, contribute to greater levels of depression in their caregivers, and are at a greater risk for institutionalization (Goetz and Stebbins, 1993; Uttl et al., 1998), knowledge and treatment of behavioral abnormalities can increase the quality of life of both the patient and caregiver.

The goals of this study were to: 1) describe the neuropsychiatric profile in PSP, and 2) examine the clinical correlates (e.g., demographics, disease severity, cognition, and motor features) of neuropsychiatric symptoms in PSP. Based on a review of the literature and our own experience, it was hypothesized that neuropsychiatric symptoms would be relatively common in patients with PSP, including high rates of apathy. Furthermore, it was anticipated that rates of apathy would be higher than rates of depression, and that apathy would be associated with greater executive dysfunction.

2. Methods

2.1. Participants

Following approval of institutional review boards at each site, 154 PSP patients were recruited at 13 sites (Baylor University, University of Colorado, Cornell University, Case

Western Reserve, Emory University, University of Louisville, University of Alabama Birmingham, University of California at Los Angeles, University of Kansas, Toronto Hospital, Mayo Clinic Jacksonville, Marquette University, and University of Washington). All met the National Institute of Neurological Disorders and Stroke and Society for PSP, Inc. (NINDS-SPSP) (Litvan et al., 1996a) criteria for clinically probable PSP. Probable PSP is defined in these criteria as gradually progressive, onset ≥40 years of age, vertical supranuclear palsy and postural instability with tendency to falls within the first year of symptom onset, and an absence of other explanatory conditions. To minimize the risk of enrolling patients with dementia, participants needed to score ≥24 on the Mini Mental Status Examination to be included in this study. Patients were excluded if they had other central nervous system disorders (e.g., stroke, tumor, Alzheimer's disease, etc.).

After informed consent, patients were evaluated by a clinical team consisting of a movement disorder specialist and trained research assistant to confirm diagnosis of probable PSP. This evaluation included a neurological history and examination, completion of a validated PSP instrument (PSP-Rating Scale) (Golbe and Ohman-Strickland, 2007), and the Unified Parkinson Disease Rating Scale (Fahn and Elton, 1987). Videotaping of motor functioning was also collected to monitor consistency among sites. Finally, a baseline neuropsychological evaluation was completed by healthcare personnel previously trained by a neuropsychologist. Accuracy of the evaluations was periodically checked at each site by a neuropsychologist, and all scoring and normative score conversions for data used in this study were double-checked by the first author of this study.

2.2. Measures

The Neuropsychiatric Inventory (NPI; Cummings et al., 1994) has been widely validated for use in studying the behavioral abnormalities of neurological diseases, has been shown to be a reliable and valid instrument (Cummings et al., 1994), and has been utilized to examine behavioral disturbances in PSP in prior studies (Litvan et al., 1996b; Litvan et al., 1998; Aarsland et al., 2001). The NPI assesses both the frequency and severity of behavioral abnormalities across 10 domains: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior. Domains designed to evaluate neurovegetative changes (i.e., sleep and nighttime behavior disorder, and appetite and eating disorder) are included in the NPI, but are not used when calculating Total score. Caregivers are asked to rate affected behaviors on a 4- point scale for frequency (1 occasionally, 2 often, 3 frequently, and 4 very frequently) and a 3-point scale for severity (1 mild, 2 moderate, 3 severe). Each domain is calculated by multiplying frequency and severity scores. NPI Total score is the sum of the 10 domains related to behavioral abnormalities. Higher scores indicate worse neuropsychiatric symptoms.

The Dementia Rating Scale-2 (DRS-2; Jurica et al., 2001) is a measure of general cognitive functioning that is widely used in geriatric clinical and research assessments. It yields age- and race-corrected scores on 6 subscales (Attention, Initiation/Perseveration, Construction, Conceptualization, Memory), and an age-, education-, and race-corrected Total score (Lucas et al., 1998; Rilling et al., 2005). Higher scores indicate better cognition.

The Frontal Assessment Battery (FAB; Dubois et al., 2000) assesses frontal lobe/executive function across 6 items (similarities, lexical fluency, motor series, conflicting instructions, Go-No-Go, prehension behavior). Each item is scored on a 3-point scale with 18 possible points comprising the FAB Total score. Higher scores indicate better cognition. Age- and education-corrected normative data were used (Appollonio et al., 2005).

The Progressive Supranuclear Palsy Rating Scale (PSPRS; Golbe and Ohman-Strickland, 2007) assesses impairments associated with PSP across six categories: health history,

mentation, bulbar function, eye and lid movement, limb movement, and trunk movement. Each item is rated on a 0–4 scale (0=no presence of symptom; 4=severe presence of symptom). A total score is the sum of all items and ranges from 0 to 100. Higher scores are indicative of greater impairment.

The Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton, 1987) was originally developed for use in evaluating impairment in Parkinson's disease, but has been extensively utilized to examine Parkinsonian features in PSP. The UPDRS is comprised of 42 items rated on a 0–4 scale (0=no presence of symptom; 4=severe presence of symptom). Three categories are rated: mentation, behavior, and mood (UPDRS I); activities of daily living (UPDRS II); and motor functioning (UPDRS III). A total score is the sum of all items and ranges from 0 to 124. Higher scores are indicative of greater impairment.

2.3. Statistical Analyses

To characterize the neuropsychiatric profile in PSP, descriptive statistics including means, standard deviations, and cumulative frequencies were calculated for NPI Total score and all 12 NPI domains. To examine the clinical correlates of neuropsychiatric symptoms in PSP, Pearson's product moment correlations were calculated between NPI Total and domain scores and several clinical variables: 1) demographic factors (i.e., age or education); 2) disease variables (i.e., age of onset and disease duration); 3) and neurocognitive performance (i.e., DRS-2 Total score and subscale scores and FAB Total score); and 4) severity of motor symptoms (i.e., UPDRS and PSP-RS Total score and category scores). A series of one-way ANOVAs were conducted to determine: 1) if NPI total or domain scores varied because of gender and 2) if NPI Delusions and/or NPI Hallucinations or any other domain score varied because of the presence or absence of Parkinsonian medication. Due to the number of comparisons, a more conservative alpha of 0.01 was used to guard against type 1 error. All tests of significance were two-tailed.

3. Results

Demographic, cognitive, and clinical data for the 154 participants are presented in Table 1.

3.1. Neuropsychiatric Profile in PSP

NPI composite scores and frequencies are listed in Table 2. The mean NPI score was 10.82 (SD=9.2) in this sample of PSP patients and this score reflects moderate disturbances. Apathy was the most frequently occurring behavioral symptom and was rated as present in 62% of patients (moderate-to-severe in 43%). Depression was also rated as present in a majority of patients (58%); however, it was noted as being less severe (e.g., moderate-to-severe in only 19%). Agitation (36%), Irritability (33%), Disinhibition (32%), and Anxiety (24%) were also rated as present in a large number of patients. Aberrant motor behavior, Delusions, Hallucinations, and Euphoria were each present in <14% of the sample. Fourteen of these patients were also noted as crying easily and at inappropriate times and rated as depressed as well. Consequently, patients identified as euphoric and the aforementioned 14 patients identified as depressed may be better conceptualized as displaying labile emotion. Neurovegetative symptoms were common in the current sample: sleep and nighttime behavior disorders were reported in 52% of patients (24% moderate-to-severe) and appetite and eating disorders were reported in 40% of patients (29% moderate-to-severe).

Associations among all 12 NPI domains were examined. Disinhibition was significantly correlated with Agitation (r=0.366, p<0.001), Irritability (r=0.281, p<0.001), and Aberrant Motor Behavior (r=0.268, p=0.001). Agitation was significantly associated with Irritability (r=0.343, p<0.001) and Aberrant Motor Behavior (r=0.211, p=0.008). Depression was significantly related to Anxiety (r=0.325, p<0.001). Anxiety was significantly correlated

with Irritability (r=0.255, p=0.001) and Aberrant Motor Behavior (r=0.272, p=0.001). The two NPI domains evaluating neurovegetative symptoms (sleep disorders and eating disorders) were associated with each other (r=0.245, p=0.002). No other associations between NPI domains were significantly associated at the 0.01 level. Of particular interest is the lack of significant correlations between Apathy and any other NPI domain. The correlation between Apathy and Depression was: r=0.119, p=0.142.

3.2. Clinical Correlates of Neuropsychiatric Symptoms in PSP

Neither demographics (i.e., age or education) nor disease severity variables (i.e., age of onset or disease duration) were significantly correlated with any NPI domain or NPI Total score. There was no effect of gender on either NPI Total or domain scores.

NPI Total score was significantly associated with DRS Attention (r=−0.255, p=0.002) but no other neurocognitive measures. NPI Disinhibition was also significantly correlated with DRS Attention (r=−0.241, p=0.003). NPI Aberrant Motor Behavior was significantly related to DRS Memory (r=−0.242, p=0.003) and FAB Total score (r=−0.225, p=0.005). NPI Delusions was significantly associated with DRS Memory (r=−0.243, p=0.003). No other associations between neuropsychiatric and cognitive variables were significant at the .01 level. It is of particular note that associations between measures of executive functioning (FAB and DRS Initiation/Perseveration) and apathy did not approach significance.

UPDRS I (Mentation, Behavior, and Mood) score was significantly correlated with NPI Total (r=0.330, p<0.001), NPI Apathy (r=0.334, p<0.001), and NPI Depression (r=0.219, p=0.006). However, these correlations were expected given that UPDRS Mentation, Behavior, and Mood includes questions designed to evaluate for symptoms related to depression and apathy. UPDRS II (activities of daily living) and UPDRS III (motor functioning) were not significantly associated with NPI Total or domain scores. NPI Disinhibition was significantly correlated with PSP-RS Total score (r=0.212, p=0.008), History (r=0.208, p=0.01), and Ocular (r=0.217, p=0.007). The associations between NPI Disinhibition and PSP-RS Total and History are not surprising given that NPI History is significantly associated with NPI Total (r=0.641, p<0.001) and contains a question about a common behavior noted in patients with disinhibition (i.e., aggressiveness). No other associations between NPI variables and severity of motor symptoms were significant at the 0.01 level.

There was no effect of Parkinsonian medication on either NPI Delusions or NPI Hallucinations or any other NPI domain score. NPI Hallucinations was not significantly associated with duration of use (r=0.045, p=.575). NPI Delusions was also not significantly associated duration of use (r=−0.094, p=0.245).

4. Discussion

The current study sought to characterize the neuropsychiatric profile in a large cohort of patients with PSP, as well as examine clinical correlates of these neuropsychiatric symptoms. As expected, most patients were noted as displaying significant levels of apathy. However, apathy was not associated with general cognitive or executive functioning. Rates of depression were unexpectedly high, and have implications for treatment and future research. Scores and rates of impairment on other NPI domains were expected for this population.

Consistent with previous studies and a priori expectations, apathy was the most common behavioral symptom observed in the current sample. However, both the prevalence of apathy (62%) and NPI Apathy score (3.47) were well below those observed in previous

studies (82–91% and 6.0–6.9, respectively) despite similar Mini Mental State Examination scores across studies (Litvan et al., 1996b; Litvan et al., 1998; Aarsland et al., 2001). Although the exact reason for this finding is unknown, the current sample was larger, slightly more educated, and noted as having a shorter duration of disease than samples examined in previous studies. One of or a combination of these factors may have contributed to this incoherence. Interestingly, the estimate of apathy prevalence in the current sample closely matches an estimate obtained using the Frontal Behavioral Inventory (Kertesz et al., 2000) to evaluate for behavioral abnormalities in a PSP sample (Borroni et al., 2009) despite the NPI and Frontal Behavioral Inventory having been noted as utilizing different methods of assessing for apathy (Alberici et al., 2007). However, the average disease duration in the current study more closely matches the average disease duration noted in the study by Borroni and colleagues than studies utilizing the NPI in a sample of PSP patients.

Patients with apathy exhibit a lack of subjective distress, a lack of negative thoughts about their condition, and unresponsiveness to negative as well as positive events (Brown and Pluck, 2000). Patients with apathy are less likely to engage in work or family activities or show interest or pleasure in life. These behaviors can be distressing for family members and caregivers of patients with PSP and highlight the need for further education about apathy and its implications. First, caregivers can misinterpret symptoms of apathy as being characteristic of depression, and this may lead to an unnecessary initiation of antidepressant medication. Second, families of patients with PSP may believe that the patient is not as interested in family activities and interactions because of something they are doing wrong or something they are not doing right. Regardless, education about apathy and its commonality in PSP may provide some comfort to patients and their caregivers.

Depression prevalence was unexpectedly high in our sample compared to prior estimates in PSP (Litvan et al., 1996b; Litvan et al., 1998; Aarsland et al., 2001). In our sample, nearly 6 in 10 patients had depressive symptoms reported by their caregivers, with most having symptoms in the mild to moderate severity range. There are likely several factors that explain the differences in the prevalence of depression in this study and those reported in other studies of PSP. First, “depression” may elicit responses to any mood disturbance (e.g., depression, general sadness, euphoria, etc.). Second, the NPI might be more or less sensitive to depressive symptoms than measures used in other studies. Third, the reliance on caregiver report, although typical, might not accurately capture the often internal symptoms associated with depression (e.g., anhedonia, worthlessness, hopelessness).

Given the lack of agreement in the literature about depression in PSP in combination with the lack of association between depression and apathy noted in this study, these findings have particular significance. In PSP, disruptions to the cortical circuits associated with depression are far less affected than those associated with apathy (Agid et al., 1987; Javoy-Agid et al., 1994; Litvan et al., 1996b). This suggests that the depressive symptoms experienced by patients with PSP may not solely be a function of brain changes associated with the disease but also related to the functional consequences of the disease (i.e., loss of mobility, loss of independence, etc.); however, in a study examining functional abilities in this cohort, depression was not found to be significantly associated with difficulty performing daily activities (Duff et al., 2013). But as noted by Duff and colleagues, current scales used to assess for functional impairments in PSP offer no insights on functioning in higher level activities such as driving, managing finances or medication, etc., and a more accurate assessment of daily functioning in PSP patients may provide insights about what factors are primarily contributing to depression in the population. That being said, treatments including psychotherapy and antidepressant medication may be effective for PSP patients reporting significant symptoms of depression, and caregivers of patients with PSP

can be utilized to aid in these treatments. In turn, the quality of life of both patient and caregiver may be modifiable.

Since depression and apathy can appear similar and co-occur in neurodegenerative disorders, some have posited that these might represent a single construct, whereas others think that they are two clearly different neuropsychiatric phenomena (Levy et al., 1998). In our large sample, apathy and depression were the two most commonly reported symptoms, but were not statistically correlated, sharing only 1% of variance. Furthermore, despite an overwhelming majority of patients in the current study displaying moderate to severe apathy or depression, only 13 (8.4%) patients were rated as exhibiting moderate to severe symptoms of both apathy and depression. This latter finding seems to suggest that depression was seen as distinct from apathy. Furthermore, anxiety is commonly associated with depression but not apathy and this association was observed in the current study. This finding not only gives further support that apathy and depression are distinct in the current sample of PSP patients but also that the NPI is sensitive in differentiating between these two syndromes.

Although apathy and depression dominated the neuropsychiatric profiles of these patients, other behavioral abnormalities are of note. Approximately a third of all patients had elevated levels of disinhibition, agitation, or irritability. Over half to a third of the current sample exhibited disruptions to sleep and eating patterns, respectively. Finally, 11% had hallucinations and 5% delusions. These behaviors pose a particular challenge in regards to patient management for caregivers of patients with PSP. Overall, there is significant neuropsychiatric morbidity in these patients who are primarily seen by movement disorder specialists and neurologists. However, results of this study indicate that PSP patients should also be seen by psychiatrists or other mental health professionals for neuropsychiatric symptom management and increased quality of life. Furthermore, caregivers should also be seen as a focus of intervention, as they may need education and instruction about methods of coping with the disabling neuropsychiatric symptoms of their affected family members. These caregivers may also require more opportunities for respite, as psychiatric symptoms can be particularly difficult to manage on a regular basis.

Overall, our findings are consistent with prior studies using the NPI in PSP samples (Litvan et al., 1996b; Litvan et al., 1998; Aarsland et al., 2001), where their Total scores ranged between 9.2–12.4. Our mean Total score of 10.8 places the general behavioral functioning of the current sample within this range and indicates that PSP patients typically present with significant behavioral deficits. However, it should also be noted that there was considerable variability in these behavioral symptoms (standard deviation of the Total score being 9.2). This indicates that in patients with mild to moderate PSP, some may have very minimal neuropsychiatric symptoms, whereas others may have more significant difficulties with apathy, depression, and agitation.

Patterns of neurocognitive deficits in this sample have been previously described and were dominated by executive dysfunction (Gerstenecker et al., 2013). In contrast to previous studies, measures of executive dysfunction were not related to most behavioral abnormalities (apathy in particular) (Litvan et al., 1996b; Aarsland et al., 2001; Borroni et al., 2009). NPI scores were also not related to measures of PSP severity. Conversely, measures of attention and memory showed some mild associations with various NPI scores and disinhibition was associated with ocular motor functioning. These observations may indicate that some overlap exists between behavioral abnormalities and neurocognitive functioning due to the parallel disruption of neural connections mediating these processes. However, given the relatively few statistically significant correlations in this large sample, it may be that behavioral abnormalities and neurocognitive functioning are largely

independent in PSP. Moreover, although executive functioning, apathy, and disinhibition are thought to be mediated by frontal and/or frontal-subcortical connections, progressive dysfunction of these circuits may not proceed in parallel in PSP patients. These circuits may be differentially affected in individual patients with PSP such that some have executive functioning without apathy, and others have apathy without executive functioning. Given these observations, interventions aimed at addressing one set of symptoms (e.g., motor) may not be expected to affect another set of symptoms in this disease (e.g., neuropsychiatric).

There are a number of limitations and future directions to be considered. First, like most other multisite studies of rare disorders, the current sample may not be representative of the population. Participants needed to agree to participate in several hours of testing, score >24 on the Mini Mental Status Examination be able to provide informed consent, and not have other central nervous system disorders. This likely yields a select, and perhaps milder, group of PSP patients, and, therefore, results might not generalize to all patients with PSP. Second, it has recently been demonstrated by pathological confirmation that PSP can be divided into several phenotypes that are difficult to differentiate during life (Williams et al., 2005; Williams et al., 2007; Hassan et al., 2012). Consequently, to provide a more complete description of behavioral abnormalities in PSP, future studies should classify patients according to their subtype as the methodology for distinguishing between subtypes improve. Third, although this study provides compelling evidence that rates of depression may be higher in PSP than previously thought, the NPI, nevertheless, utilizes caregiver ratings. Thus, certain symptoms (e.g., emotional lability vs. depression and euphoria and apathy vs. depression) may be misrepresented to some degree. For example, a family member may rate a historically extroverted patient that became increasingly introverted after symptom onset as depressed. However, the increase in introversion may be unrelated to an emotional response and, therefore, more indicative of apathy than of depression. Moreover, it is our experience that the patients themselves can often provide insights about this distinction. Another example may include a caregiver who observes a patient crying in situations where crying was not observed before. Although the patient may have been rated as depressed by the caregiver, the same patient may also have been rated as euphoric because she was observed to laugh in situations where laughing had not previously been observed. In fact, these two scenarios fit well with our experience working with PSP patients and their families. But, making these distinctions oftentimes requires a clinician skilled in the differentiation of apathy and depression and with experience working with patients with PSP. However, as with most multisite studies of patients with rare neurodegenerative disorders, it is often not possible for such clinicians to be utilized. Consequently, future studies should not only utilize clinicians skilled both in making distinctions between apathy and depression but also utilize measures that more extensively assess for the differentiation between apathy and depression. By doing so, a better understanding of the rates of apathy and depression in the population may be gained. Fourth, the NPI does not contain a domain designated for emotional lability. However, by using a measure that assess for this symptom, further insights may be gained about patients that are rated as both depressed and euphoric on the NPI and, consequently, into the overall neuropsychiatric functioning of the population. Finally, it is unclear what role current treatments might have had on reported neuropsychiatric symptoms, and any psychiatric medication being taken by participants in the current sample could have affected the reports given by their caregivers. However, with the high levels of symptoms found in this sample, if medications were being taken, they appear to be less than optimally managing any such symptoms. Nonetheless, future studies might attempt to more closely consider benefits of treatment in these patients. Despite these limitations, the current results continue to add to our knowledge about the various symptoms in this complex and disabling disease. The current findings also indicate that clinical trials are clearly needed to address the neuropsychiatric morbidity in these patients.

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References

Aarsland D, Litvan I, Larsen JP. Neuropsychiatric symptoms of patients with progressive supranuclear palsy. Journal of Neuropsychiatry and Clinical Neuroscience. 2001; 13:42–49.

Agid Y, Javoy-Agid F, Ruberg M, Pillon B, Dubois B, Duyckaerts C, Hauw JJ, Baron JC, Scatton B. Progressive supranuclear palsy: anatomoclinical and biochemical considerations. Advances in Neurology. 1987; 45:191–206. [PubMed: 2881445]

Alberici A, Geroldi C, Cotelli M, Adorni A, Calabria M, Rossi G, Borroni B, Padovani A, Zanetti O, Kertesz A. The Frontal Behavioural Inventory (Italian version) differentiates frontotemporal lobar degeneration variants from Alzheimer's disease. Neurological Sciences. 2007; 28:80–86. [PubMed: 17464470]

Appollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, Forapani E, Russo A, Nichelli P. The Frontal Assessment Battery (FAB): normative values in an Italian population sample. Neurological Sciences. 2005; 26:108–116. [PubMed: 15995827]

Assogna F, Pontieri FE, Caltagirone C, Spalletta G. The recognition of facial emotion expressions in Parkinson's disease. European Neuropsychopharmacology. 2008; 18:835–848. [PubMed: 18707851]

Assogna F, Pontieri FE, Cravello L, Peppe A, Pieratozzi M, Stefani A, Stanzione P, Pellicano C, Caltagirone C, Spalletta G. Intensity-dependent facial emotion recognition and cognitive functions in Parkinson's disease. Journal of the International Neuropsychological Society. 2010; 16:867–876. [PubMed: 20663240]

Borroni B, Alberici A, Agosti C, Cosseddu M, Padovani A. Pattern of behavioral disturbances in corticobasal degeneration and progressive supranuclear palsy. International Psychogeriatrics. 2009; 21:463–468. [PubMed: 19323870]

Brown RG, Pluck G. Negative symptoms: the 'pathology' of motivation and goal- directed behavior. Trends in Neuroscience. 2000; 23:412–417.

Cordato NJ, Pantelis C, Halliday GM, Velakoulis D, Wood SJ, Stuart GW, Currie J, Soo M, Olivieri G, Broe GA, Morris JG. Frontal atrophy correlates with behavioural changes in progressive supranuclear palsy. Brain. 2002; 125:789–800. [PubMed: 11912112]

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44:2308–2314. [PubMed: 7991117]

Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000; 55:1621–1626. [PubMed: 11113214]

Duff K, Gerstenecker A, Litvan I. Functional impairment in progressive supranuclear palsy. Neurology. 2013; 80:380–384. [PubMed: 23303854]

Fahn, S.; Elton, RL. Unified Parkinson's Disease Rating Scale. In: Fahn, S.; Marsden, CD.; Calne, DB., editors. Recent developments in Parkinson's disease. Florham Park, NJ: Macmillan Health Care Information; 1987. p. 153-164.

Gama RL, Távora DG, Bomfim RC, Silva CE, de Bruin VM, de Bruin PF. Sleep disturbances and MRI morphometry in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy—a comparative study. Parkinsonisms and Related Disorders. 2010; 16:275–279.

Gerstenecker A, Mast B, Duff K, Ferman TJ, Litvan I. Executive Dysfunction is the Primary Cognitive Impairment in Progressive Supranuclear Palsy. Archives of Clinical Neuropsychology. 2013; 28:104–113. [PubMed: 23127882]

Ghosh BC, Rowe JB, Calder AJ, Hodges JR, Bak TH. Emotion recognition in progressive supranuclear palsy. Journal of Neurology, Neurosurgery, and Psychiatry. 2009; 80:1143–1145.

Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. Neurology. 1993; 43:2227–2229. [PubMed: 8232934]

Golbe LI, Ohman-Strickland PA. Aclinical rating scale for progressive supranuclearpalsy. Brain. 2007; 130:1552–1565. [PubMed: 17405767]

Hassan A, Parisi JE, Josephs KA. Autopsy-proven progressive supranuclear palsy presenting as behavioral variant frontotemporal dementia. Neurocase. 2012; 18:478–488. [PubMed: 22181323]

Javoy-Agid F. Cholinergic and peptidergic systems in PSP. Journal of Neural Transmision: Supplementum. 1994; 42:205–218.

Jurica, PJ.; Leitten, CL.; Mattis, S. Dementia Rating Scale-2: Professional manual. Lutz, FL: Psychological Assessment Resources; 2001.

Kertesz A, Nadkarni N, Davidsob W, Thomas AW. The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia. Journal of the International Neuropsychological Society. 2000; 6:460–468. [PubMed: 10902415]

Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig MD, Paulsen JS, Litvan I. Apathy Is Not Depression. Journal of Neuropsychiatry and Clinical Neuroscience. 1998; 10:314–319.

Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, Zee DS. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology. 1996a; 47:1–9. [PubMed: 8710059]

Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, McKeith I, Quinn N. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Movement Disorders. 2003; 18:467–486. [PubMed: 12722160]

Litvan I, Cummings JL, Mega M. Neuropsychiatric features of corticobasal degeneration. Journal of Neurology Neurosurgery and Psychiatry. 1998; 65:717–721.

Litvan I, Mega MS, Cummings JL, Fairbanks L. Neuropsychiatric aspects of progressive supranuclear palsy. Neurology. 1996b; 47:1184–1189. [PubMed: 8909427]

Lucas JA, Ivnik RJ, Smith GE, Bohac DL, Tangalos EG, Kokmen E, Graff-Radford NR, Petersen RC. Normative data for the Mattis Dementia Rating Scale. Journal of Clinical and Experimental Neuropsychology. 1998; 20:536–547. [PubMed: 9892057]

Menza MA, Cocchiola J, Golbe LI. Psychiatric symptoms in progressive supranuclear palsy. Psychosomatics. 1995; 36:550–554. [PubMed: 7501785]

Millar D, Griffiths P, Zermansky AJ, Burn DJ. Characterizing behavioral and cognitive dysexecutive changes in progressive supranuclear palsy. Movement Disorders. 2006; 21:199–207. [PubMed: 16200534]

Pontieri FE, Assogna F, Stefani A, Pieratozzi M, Meco G, Benincasa D, Colosimo C, Caltagirone C, Spalletta G. Sad and happy facial emotion recognition impairment in progressive supranuclear palsy in comparison with Parkinson's disease. Parkinsonism and Related Disorders. 2012; 18:871–875. [PubMed: 22595619]

Rilling LM, Lucas JA, Ivnik RJ, Smith GE, Willis FB, Ferman TJ, Petersen RC, Graff-Radford NR. Mayo's Older African American Normative Studies: Norms for the Mattis Dementia Rating Scale. Clinical Neuropsychology. 2005; 19:229–242.

Schrag A, Selai C, Davis J, Lees AJ, Jahanshahi M, Quinn N. Health-Related Quality of Life in Patients With Progressive Supranuclear Palsy. Movements Disorders. 2003; 18:1464–1469.

Schrag A, Sheikh S, Quinn NP, Lees AJ, Selai C, Mathias C, Litvan I, Lang AE, Bower JH, Burn DJ, Low P, Jahanshahi M. A comparison of depression, anxiety, and health status in patients with

progressive supranuclear palsy and multiple system atrophy. Movement Disorders. 2010; 25:1077–1081. [PubMed: 20535826]

Uttl B, Santacruz P, Litvan I, Grafman J. Caregiving in progressive supranuclear palsy. Neurology. 1998; 51:1303–1309. [PubMed: 9818850]

Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, Holton JL, Revesz T, Lees AJ. Characteristics of two clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain. 2005; 128:1247–1258. [PubMed: 15788542]

Williams DR, Holton JL, Strand K, Revesz T, Lees AJ. Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. Movement Disorders. 2007; 22:2235–2241. [PubMed: 17712855]

Table 1

Demographics, Parkinsonian Severity, and Neuropsychological Functioning

Demographic	Mean±SD (Range)
Age (years)	68.0±6.6 (53–87)
Sex	89 M, 65 F
Education (years)	15.3±3.5 (8–20)
Symptom duration (years)	3.8±1.6 (6–10)
UPDRS Total	57.8±18.8 (16–102)
PSP-RS Total	37.1±11.6 (13–70)
DRS-2 Total	123.7±11.7 (88–144)
FAB Total	12.5±2.7 (5–18)
MMSE	26.7±2.26 (24–30)

Note. UPDRS = Unified Parkinson Disease Rating Scale; PSP-RS = Progressive Supranuclear Palsy Rating Scale; DRS = Dementia Rating Scale; FAB = Frontal Assessment Battery; MMSE = Mini-Mental Status Examination

Table 2

Neuropsychiatric Inventory Composite Scores and Frequencies

Behavior (NPI Domain)	**Mean Frequency × Severity ± SD**	**Mild *N* (%)**	**Moderate *N* (%)**	**Severe *N* (%)**	**Total *N* (%)**
Apathy/Indifference	3.5±3.7	42 (27.3)	40 (26.0)	13 (8.4)	95 (61.7)
Depression/Dysphoria	1.7±2.2	64 (41.6)	25 (16.2)	1 (0.6)	90 (58.4)
Sleep and Nighttime Behavior Disorders	3.0±3.8	31 (20.1)	35 (22.7)	14 (9.1)	80 (51.9)
Appetite and Eating Disorders	2.6±3.9	16 (10.4)	31 (20.1)	14 (9.1)	61 (39.6)
Agitation/Aggression	1.1±1.9	39 (25.3)	15 (9.7)	1 (0.6)	55 (35.6)
Irritability/Lability	1.0±1.9	33 (21.4)	16 (10.4)	2 (1.3)	51 (33.1)
Disinhibition	1.1±2.3	28 (18.2)	19 (12.3)	2 (1.3)	49 (31.8)
Anxiety	0.6±1.4	23 (14.9)	13 (8.4)	1 (0.6)	37 (23.9)
Elation/Euphoria*	0.4±1.6	13 (8.4)	7 (4.5)	1 (0.6)	21 (13.5)
Aberrant Motor Behavior	0.7±2.1	9 (5.8)	7 (4.5)	3 (1.9)	19 (12.2)
Hallucinations	0.3±1.0	12 (7.8)	5 (3.2)	0 (0.0)	17 (11.0)
Delusions	0.1±0.4	7 (4.5)	1 (0.6)	0 (0.0)	8 (5.1)
NPI Total	10.8±9.2				

Note. NPI=Neuropsychiatric Inventory