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Neuropsychiatric features of parkinsonian tauopathies and alpha-synucleinopathies.

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NEUROPSYCHIATRIC FEATURES OF PARKINSONIAN TAUOPATHIES
AND ALPHA-SYNUCLEINOPATHIES

By

Megan Rayne Thompson
B.S., University of Kentucky, 2007

A Thesis
Submitted to the Faculty of the
Graduate School of the University of Louisville
in Partial Fulfillment of the Requirements
for the Degree of

Master of Science

Department of Anatomical Sciences and Neurobiology
University of Louisville
Louisville, Kentucky

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A Thesis Approved on

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ABSTRACT

NEUROPSYCHIATRIC FEATURES OF PARKINSONIAN TAUOPATHIES AND ALPHA-SYNUCLEINOPATHIES

Megan R. Thompson

November 24, 2008

The goal of this thesis is to determine if neuropsychiatric features can differentiate parkinsonian patients with: tauopathies from those with alpha-synucleinopathies and explore caregiver distress. Three hundred and four patients (62 with tauopathies and 242 with alpha-synucleinopathies) diagnosed according to published diagnostic criteria were evaluated using the Neuropsychiatric Inventory (NPI), Mini-Mental State Examination (MMSE), and Unified Parkinson's Disease Rating Scale (UPDRS). To control for between-group differences a subsample of 235 patients were analyzed. Patients with tauopathies had significantly higher NPI total scores, more apathy, less hallucinations, lower MMSE scores and higher UPDRS scores than those with alpha-synucleinopathies. Hallucinations and delusions were not related to levodopa or dopamine agonist daily doses, but increased age was associated with these disturbances. There were moderate correlations between caregiver distress and severity of neuropsychiatric disturbances. Despite between-group neuropsychiatric differences at early stages, the symptom overlap does not allow to classify patients with these two proteinopathies.

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INTRODUCTION

The underlying abnormal accumulation of proteins in the brain among the different parkinsonian disorders leads to their molecular classification as tauopathies and alpha-synucleinopathies (1, 2). Tauopathies include progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (1). In both PSP and CBD tau accumulates as neurofibrillary tangles in neurons and threads in processes (3). In addition, tau deposits forming tufted astrocytes in PSP (3), and astrocytic plaques in CBD (3), are helpful features in their differentiation (7). Alpha-synucleinopathies include Parkinson's disease (PD), Parkinson's disease with dementia (PDD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) (2). In PD and DLB, α -synuclein constitutes the major component of the Lewy bodies (2, 4), and in MSA it deposits as glial cellular inclusions (2, 5).

While this molecular classification has important implications for the pathogenesis of these disorders and the development of novel therapeutic approaches, its role in clinical practice has not been fully investigated. Clinically, tauopathies share features such as frontal dysfunction, oculomotor disturbances, and early pseudobulbar palsy (6, 7). Similarly, there is clinical overlap in alpha-synucleinopathies such as autonomic dysfunction, urinary, olfactory and REM sleep behavior disturbances (8-11).

This study seeks to determine if the neuropsychiatric features could be used to clinically distinguish a patient's disorder as a tauopathy or an alpha-synucleinopathy. To better characterize the behavioral aspects of parkinsonian patients with tauopathies and those with alpha-synucleinopathies, we compared their performance on the Neuropsychiatric Inventory (NPI), a tool with established validity and reliability (Cronbach's $\alpha = 0.88$) (12). The NPI evaluates both the frequency and severity of delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and abnormal motor behavior (e.g., pacing), as well as nighttime behaviors, appetite/eating changes, and caregiver distress (12-14). While the NPI and other instruments have been used to investigate various parkinsonian diseases individually, PD (15-20), PDD (15, 21), DLB (21-26), CBD (27, 28), and PSP (18, 28-30), no previous study has attempted to determine if there are neuropsychiatric differences between patients with tauopathies and those with alpha-synucleinopathies, or to examine the caregiver distress.

Purpose and hypothesis

The purpose of this research is to differentiate patients with tauopathies from those with alpha-synucleinopathies using the NPI scale. To do so, we examined the individual NPI domains in the two proteinopathy groups. Based on the literature (Table 1) and our clinical experience, we hypothesize that: (1) delusions and hallucinations are more common in alpha-synucleinopathies than tauopathies, (2) the presence of these disturbances is not related to the use of Parkinson's medications, and that (3) the caregiver distress will increase as the severity of neuropsychiatric disturbances increases.

METHODS

This is an exploratory, cross-sectional, study that examined patients from 2003-2008 and included chart reviews. Three hundred and four patients, presenting as outpatients to the University of Louisville Movement Disorder Clinic were evaluated and diagnosed as having PD (n=143), PDD (n=12), DLB (n=36), MSA (n=51), PSP (n=49), and CBD (n=13), by three movement disorder specialists according to established criteria (PD (31), PDD (9), DLB (10), MSA (11), PSP (6), and CBD (7)). Exclusion criteria for all patients included history of alcohol or substance abuse, head trauma with loss of consciousness, and diagnosis of a psychiatric disorder preceding the onset of the current disease. All participating patients gave institutional IRB consent at the University of Louisville. The neuropsychiatric, cognitive, and motor assessments were usually conducted on the same day.

Cognition was assessed with the Mini-Mental State Examination (MMSE) scale, a widely used tool to detect cognitive decline. The MMSE includes a series of questions examining orientation, registration, attention and calculation, recall, and language skills. The maximum total score is 30, which is considered a normal score. Patients presenting with cognitive problems will have a lower total score (32).

Motor symptoms and signs were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS), which is divided into three sections: mentation, behavior, and

mood (UPDRS I), activities of daily living (UPDRS II), and motor abilities (UPDRS III). Patients' individual symptoms were evaluated by movement disorder specialists. The normal UPDRS score is zero and the total score will increase with enhanced motor disturbances (33).

The NPI was administered as previously described (12-14) to the caregivers of the patients in a separate room. Briefly, screening questions are used to assess the behaviors, and if a positive response is obtained for one of the ten neuropsychiatric domains, then this aspect is further explored with scripted questions. Each behavior is individually scored by multiplying the frequency (1-4, occasionally to very frequently) by the severity (1-3, mild to marked), yielding a scale of 1 to 12. Although, this multiplication cannot lead to a variable measured on a continuum because some values are impossible to obtain (i.e., 5, 7 etc), the resulting distribution can still be analyzed with non-parametric tests. The total NPI score is the sum of all added subscale composite scores. The normal score is zero and will increase with the presence of neuropsychiatric symptoms. In some cases (11.8% of the sample) the NPI was administered more than once. We chose the most recent NPI scores to be used in the analyses.

Two versions of the NPI were used to assess the neuropsychiatric disturbances of our patient sample. The new NPI version has two additional behavioral domains (nighttime behavior and appetite/eating change), although, neither of these domain scores are added to the total NPI score used in the analyses. Moreover, the new NPI scale includes a section for the assessment of the caregiver distress associated with the patients' neuropsychiatric characteristics. After the caregiver rated the severity and frequency of an NPI domain, the caregiver was further asked to rate the distress caused

by the presence of the individual domain (0-5, no distress to very severe or extreme distress). Once more, the caregiver distress score did not affect the NPI total score. Caregiver distress was recorded for 73 caregivers, including 15 caregivers of patients with tauopathies and 58 caregivers of patients with alpha-synucleinopathies.

Exploratory univariate (frequencies, central tendency, and dispersion measures) and bivariate parametric and non-parametric statistical analyses (Mann-Whitney *U* and independent *t* tests, Pearson Chi-Square, Pearson *r* and Spearman's *rho* correlations) were applied as appropriate (34). Due to the distributions being skewed or non-linear, non-parametric tests were primarily used to explore the relationships between variables. Statistical tests were conducted with a 95% confidence level and significance was accepted at $p < 0.05$.

RESULTS

Sample characteristics using NPI:

Analyses of the full sample (N=304 patients) showed significant between-group differences in patient symptom duration and age at NPI evaluation. There was a mild but significant association between symptom duration and MMSE total ($r = -0.23$, $p < .000$). The patients with longer symptom duration scored lower on the MMSE, indicating cognitive decline. There were also significant associations between age at NPI evaluation and NPI total ($r = 0.12$, $p = .032$), MMSE total ($r = -0.24$, $p < .000$), and UPDRS total ($r = 1.42$, $p = .013$). These results suggest that the age at NPI evaluation is significantly associated with increased neuropsychiatric, cognitive, and motor disturbances. To adjust for the differences between the proteinopathy groups, the patients presenting symptoms for eight years or more were excluded from further data analyses. Additionally, three patients with alpha-synucleinopathies were excluded from further analyses because the NPI total score was an outlier, and would have skewed the results if they were maintained in the sample. With the new exclusion criteria, the resulting sample included 232 patients: 59 patients with tauopathies (PSP ($n = 47$), and CBD ($n = 12$)) and 173 patients with alpha-synucleinopathies (PD ($n = 101$), PDD ($n = 5$), DLB ($n = 31$), MSA ($n = 36$)). For demographics see Table 2. There were no significant between-group differences in patient's age at NPI evaluation ($U = 4288$, $p = .067$), symptom duration ($U = 5019$, $p = .848$), and education level ($U = 4627$, $p = .272$).

NPI characteristics of the patients with tauopathies:

The average total NPI score for the patients with tauopathies was 10.3 (range 0-34, SD = 8.6) and apathy was the most frequent NPI domain present (67.8%) (Table 3). Apathetic disturbances were mild in severity 37.5%, moderate 47.5%, and severe 15% and the frequencies were occasional 7.5%, often 20%, frequent 22.5%, and very frequent 50%. In addition, depression (55.9%), nighttime behavior (51.3%), and appetite/eating changes (43.6%) were commonly reported for the patients with tauopathies. Less frequently, aberrant motor behaviors (8.5%), delusions (6.8%), hallucinations (3.4%), and euphoria (1.7%) were recorded. The highest average composite score was for apathy (4.0), followed by nighttime behavior (2.4), depression (2.1), and appetite/eating changes (2.0) (Table 3).

NPI characteristics of the patients with alpha-synucleinopathies:

The average NPI total score for the patients with alpha-synucleinopathies was 6.1 (range from 0-39, SD = 7.5) and depression (54.3%) was the most common neuropsychiatric symptom reported. Of the patients with alpha-synucleinopathies who exhibited depression, 70.2% were mild in severity, 26.6% moderate, and 3.2% severe. The frequency with which these disturbances occurred was occasional 41.5%, often 19.1%, frequent 27.7%, and very frequent 11.7%. Other NPI domains commonly observed in this group were abnormal nighttime behaviors (41.5%) and apathy (40.5%). Disinhibition (8.7%), delusions (7.5%), and aberrant motor behaviors (5.8%) were less frequently reported. Euphoria was not exhibited by any patient with alpha-synucleinopathies. The highest NPI composite score in the patients with alpha-synucleinopathies was for nighttime disturbance (2.2) followed by depression (1.6), and apathy (1.6) (Table 3).

Differentiating patients with tauopathies and alpha-synucleinopathies based on neuropsychiatric, cognitive, and motor disturbances:

The patients with tauopathies scored significantly higher on the NPI (10.3 ± 8.6) than patients with alpha-synucleinopathies (6.1 ± 7.5). There was a significant difference in the total NPI score between the two proteinopathy groups ($U = 3486, p < .000$).

There were significant between-group differences in the NPI apathy and hallucination scores. The patients with tauopathies were more likely to express apathy (67.8%) than those with alpha-synucleinopathies (40.5%; $\chi^2 = 13.2, p < .000$). On the other hand, hallucinations were more frequent in the patients with alpha-synucleinopathies (17.9%) than those with tauopathies (3.4%; $\chi^2 = 7.6, p = .006$). Of the total sample of patients who reported hallucinations, 93.9% had an alpha-synucleinopathy. There were no significant between-group differences in any of the other NPI domains.

The MMSE score was significantly lower ($U = 3577, p = .001$) for the patients with tauopathies (25.3 ± 5.9) than for the patients with alpha-synucleinopathies (27.0 ± 6.3). The patients with tauopathies scored significantly higher on the total UPDRS (54.2 ± 18.5) compared to the patients with alpha-synucleinopathies (37.5 ± 20.5), thus there was a significant difference between the UPDRS score and the two proteinopathy groups ($U = 2540, p < .000$). On the UPDRS III, the patients with tauopathies (29.3 ± 12.5) scored significantly higher ($U = 3244, p < .000$) than the patients with alpha-synucleinopathies (21.8 ± 12.9).

Correlations between neuropsychiatric, cognitive, and motor disturbances between the patients with tauopathies and alpha-synucleinopathies:

In the patients with tauopathies there are no significant associations between NPI total and MMSE total ($r = -0.02$, $p = .895$), NPI total and UPDRS total ($r = -0.01$, $p = .925$), and MMSE total and UPDRS total ($\rho = -0.13$, $p = .317$). Results suggest no correlations between neuropsychiatric, cognitive, and motor disturbances in the patients with tauopathies.

In the patients with alpha-synucleinopathies there was a moderate negative correlation between NPI total score and MMSE total score ($r = -0.35$, $p < .000$) also shown by the non-parametric test ($\rho = -0.39$, $p < .000$). Results suggest there is a relationship between neuropsychiatric and cognitive disturbances in the patients with alpha-synucleinopathies. There was also a weak positive correlation between the total NPI score and total UPDRS score ($r = 0.18$, $p = .020$) in the patients with alpha-synucleinopathies. These results are the same when using the Spearman's rho correlation coefficient ($\rho = 0.26$, $p = .001$). A weak, positive correlation between total NPI score and UPDRS III ($\rho = 0.20$, $p = .010$) indicates that the neuropsychiatric disturbances increase with the higher occurrence of motor disturbances.

In the group of patients with alpha-synucleinopathies, there was a weak negative correlation between total MMSE score and total UPDRS score ($r = -0.29$, $p < .000$; $\rho = .30$, $p < .000$). There was also a weak negative correlation between total MMSE score and UPDRS III score ($r = -0.21$, $p = .009$; $\rho = -0.23$, $p = .003$). These results suggest that as the cognition is more impaired, patients with alpha-synucleinopathies also exhibited more motor disturbances.

Comparison of patients presenting with and without hallucinations and delusions:

Levodopa daily dose was calculated according to published criteria (35). The average levodopa daily dose for the sample was 581 mg \pm 684 mg (range 0 mg- 3417 mg). There were no significant differences in the daily levodopa dose between patients reporting hallucinations (715 mg \pm 869 mg) and those without hallucinations (559 mg \pm 648 mg; U = 2961, p = .360). Similarly, there were no significant differences in the daily levodopa dose between patients with delusions (657 mg \pm 889 mg) and those without delusions (575 mg \pm 667 mg; U = 1820, p = .976). The average daily dose of dopamine agonists including Pramipexole, Rotigotine, Ropinirole, and Pergolide, was 42 mg \pm 110 mg (range 0 mg- 1106 mg). There was no significant difference between the daily dopamine agonist dose in the patients who reported hallucinations (81 mg \pm 200 mg) compared to patients without hallucination disturbances (35 mg \pm 86 mg; U = 2959, p = .256). There was no significant difference between the daily dopamine agonist dose in the patients who reported delusion disturbances (83 mg \pm 145 mg) and those that did not (38 mg \pm 107 mg; U = 1451, p = .077). These findings suggest dopamine agents are not associated with the appearance of delusions or hallucinations in our total sample.

There was a significant difference in the age at NPI evaluation between the patients who reported hallucinations (72 \pm 8.6) and those who did not (68 \pm 9.5; U = 2382, p = 0.014). Additionally, the patients with hallucinations (69 \pm 9.2) were significantly older at disease onset than the patients without hallucinations (66 \pm 9.6; U = 2408, p = 0.014). In the total sample, the number of patients presenting with hallucination disturbances increased symptomatically as they aged.

The age at NPI evaluation was greater (74 ± 7.4) for the patients with delusions than for the patients without delusions (69 ± 9.6). This difference was significant at 95% confidence level ($U = 1284$, $p = 0.041$). Moreover, there was a marginally significant difference ($U = 1337$, $p = 0.065$) in the age at disease onset between the patients with delusions (70 ± 7.7) and those without delusions (66 ± 9.7).

Caregiver distress differences between the patients with tauopathies and alpha-synucleinopathies:

There were no significant differences between the distress total scores reported by the caregivers of the patients with tauopathies (7.9 ± 5.6) and alpha-synucleinopathies (5.7 ± 5.3 ; $t = 1.37$, $p = .176$). These results are supported using a non-parametric test ($U = 318$, $p = .107$).

In the patients with tauopathies, the mean caregiver distress score was 7.9 ± 5.6 (range 0-5). The highest distress scores were in agitation (4.0), disinhibition (3.0), and apathy (2.7), although the agitation score is only representative of one caregiver and disinhibition of two caregivers (Table 4). Twenty percent of caregivers rated apathy disturbances as severely or very severely distressing.

In the patients with alpha-synucleinopathies, the mean caregiver distress score was 5.7 ± 5.3 (range 0-5). The highest distress was with delusions (3.2), followed by apathy (2.4), and then agitation (2.3) (Table 4). Forty percent of caregivers reported the emotional distress caused by delusion as severely or very severely distressing.

Caregiver distress and NPI domain severity:

There was a moderate association between the depression caregiver distress score and depression severity ($r = 0.55$, $p < .000$), as well as with apathy severity ($r = 0.39$, $p = .003$).

There was a moderate relationship between the anxiety caregiver distress score and

nighttime severity ($r = 0.56, p = .006$). Additionally, there was a moderate correlation between the apathy caregiver distress score and depression severity ($r = 0.33, p = .044$), and with apathy severity ($r = 0.56, p < .000$). These associations are sustained by non-parametric tests as well. There was a moderate positive relationship between anxiety caregiver distress and depression severity ($\rho = 0.41, p = .047$).

DISCUSSION

According to our knowledge, the present study is the first to determine the neuropsychiatric differences between patients with tauopathies and alpha-synucleinopathies using the NPI as a measuring tool. Additionally, this study is the first to evaluate caregiver distress using the NPI for patients with tauopathies or alpha-synucleinopathies. Our study deduced several major findings. First, we found that at early stages patients with tauopathies exhibited significantly more apathy than those with alpha-synucleinopathies, and that patients with alpha-synucleinopathies reported significantly more hallucinations. Second, despite significant between-group differences in apathy and hallucinations, overlap and overall frequency of these specific neuropsychiatric symptoms do not allow to classify individual patients as having a specific proteinopathy. Third, at early disease stages the patients with tauopathies had more neuropsychiatric disturbances (higher total NPI), were more cognitively impaired (lower MMSE scores), and had more motor disturbances (higher UPDRS scores) than those with alpha-synucleinopathies. Fourth, while there were no associations between neuropsychiatric, cognitive, and motor symptoms in the group of patients with tauopathies, all three disturbances were correlated in the group of patients with alpha-synucleinopathies. Fifth, we found that the hallucinations and delusions cannot be explained by the patient's total levodopa daily dose or dopamine agonist daily dose, suggesting that these disturbances may be related to the accumulated

proteinopathy. Moreover, the patients with hallucinations and the patients with delusions were significantly older at NPI evaluation and older at disease onset, compared to patients who did not present these symptoms. Lastly, there were no significant differences in caregiver distress between the patients with tauopathies and those with alpha-synucleinopathies. When analyzing depression, anxiety, apathy, and nighttime behaviors only, caregiver distress correlated with the severity of these disturbances.

Comparing the patients with tauopathies and alpha-synucleinopathies based on neuropsychiatric, cognitive, and motor disturbances:

As expected, patients with tauopathies exhibited significantly more apathy, and those with alpha-synucleinopathies exhibited more hallucinations. Our results are supported by the literature. One study directly compared PSP and PD patients' neuropsychiatric features and showed that PSP patients exhibited more apathetic disturbances and PD patients more hallucinations (17). Several studies show that apathy frequently occurs in patients with specific tauopathies (27-30) and hallucinations in those with specific alpha-synucleinopathies (15, 17, 21, 23), but none of the studies compared these two proteinopathies.

Even at early disease stages, patients with tauopathies had more neuropsychiatric disturbances than those with alpha-synucleinopathies. This finding is supported by a study that showed PSP patients had significantly higher total NPI scores compared to PD patients (18). The published literature using the NPI to examine patients with tauopathies report average total NPI scores comparable to our data (18, 27-30), thus our sample set is representative of tauopathy patients reported in past studies. On the other hand, current literature recording neuropsychiatric disturbances in patients with alpha-synucleinopathies, report higher average NPI totals compared to our findings (15-19, 21-

25, 36). One explanation for the differences with the literature is that our alpha-synucleinopathy sample has a large proportion of PD patients, who show the least neuropsychiatric disturbances than the other alpha-synucleinopathy diseases (15-18). Moreover, in the previous studies, patients at later stages who exhibit more neuropsychiatric disturbances were included (15-18). Additionally, no studies have reported neuropsychiatric disturbances using the NPI in patients with MSA, an alpha-synucleinopathy disease included in our sample. Thus, effects on the average NPI total are unknown.

The patients with tauopathies had lower overall cognition levels than those with alpha-synucleinopathies. Our findings are supported by the literature (37-39). A study using the MMSE to examine cognitive differences in PSP, MSA, and PD patients showed that the mean score of the PSP patients was lower than that of MSA patients and that there were no significant cognitive differences between the PD and MSA patients (37). In a second study, cognition was assessed in atypical parkinsonian patients using four different tools including the MMSE. PSP and CBD patients exhibited significantly impaired cognitive abilities when compared to the controls and MSA patients (38).

Our patients with tauopathies also had significantly more motor disturbances (UPDRS and UPDRS III scores) than patients with alpha-synucleinopathies. These results are also supported by the literature. A study comparing PD and PSP patients, showed that the total UPDRS score was higher for PSP patients compared to the PD patients (40). Furthermore, a second study examining the UPDRS III score in MSA, PSP, and PD patients showed that the average UPDRS III score was higher in PSP patients compared to MSA patients. On the other hand, it concluded that the UPDRS III score was

significantly higher in PD patients compared to PSP and MSA patients (37). However, in that study, the PD patients had a significantly longer disease duration compared to the PSP and MSA patients, and motor disturbances increase with disease progression, explaining the differences found (41, 42).

Neuropsychiatric, cognition, and motor correlations:

Our study confirmed that in the patients with tauopathies there are no correlations between neuropsychiatric, cognitive, and motor disturbances, suggesting that in the tauopathies the affected pathways degenerate independently. Prior studies using the NPI and MMSE in tauopathy patients found the same results (15, 18, 28-30), showing no association between motor and cognitive functions. Similar to our findings, a study of CBD patients showed that the neuropsychiatric features were not associated with the motor scores, but found that the CBD patients with higher UPDRS scores also had higher MMSE scores, suggesting a relationship between cognitive and motor skills (28). On the other hand, a study in PSP patients found that the total UPDRS score was inversely related to the total MMSE score (29). A possible explanation of the difference in our results and those of the literature may be related to differences in disease stages (26, 27).

Furthermore, patients with alpha-synucleinopathies had a significant association between neuropsychiatric, cognitive and motor disturbances. Our results show that as the cognition worsens (or as the total MMSE score decreases), patients have increased neuropsychiatric disturbances. These findings are supported by a study that examined the relationship between cognitive and neuropsychiatric disturbances in PDD patients using the same assessment tools, and found that patients who scored below the median total MMSE had higher NPI scores (15). Two other studies found a relationship between the

total NPI score and the MMSE total in patients with alpha-synucleinopathies (17, 26). In addition, patients exhibiting more neuropsychiatric disturbances were more likely to have a motor decline.

No previous studies have used the NPI and UPDRS to compare neuropsychiatric and motor disturbances in the patients with alpha-synucleinopathies, although there are two studies that support our findings using different instruments. The first supporting study shows a direct relationship between neuropsychiatric symptoms and motor disturbances in PD patients using the UPDRS I score to measure neuropsychiatric symptoms, and the UPDRS III score to measure motor symptoms (43). A second study that measured the neuropsychiatric disturbances in PD patients with the Hamilton rating Scale of Depression and Hamilton Anxiety Scale showed that these scores were correlated with the UPDRS III score (44).

In addition, the MMSE score correlated with the total UPDRS score and UPDRS III score in the patients with alpha-synucleinopathies, showing that patients with more motor disturbances exhibit more cognitive disturbances. Our findings are supported by a study in DLB patients, which showed that patients who had MMSE scores less than 18 had a higher total UPDRS score (26). Similarly, a study in PD patients showed an inverse correlation between the MMSE score and the UPDRS III score (45).

Exploring increases in hallucination and delusion disturbances:

The presence and severity of the neuropsychiatric symptoms can affect a patient's quality of life (46), thus improvements of these symptoms are necessary. Psychotic symptoms, including delusions, hallucinations, and delirium, are typically observed in DLB and PDD, but would not occur in PD without medication treatment (47, 48) (49-54). Prior

studies showed that parkinsonian patients exhibiting psychosis had higher levodopa daily doses (51, 54-57) and higher dopamine agonist daily dose (55-58) than those without psychosis. However, our study found no significant differences in the levodopa daily dose or dopamine agonist daily dose used in the patients with and without hallucinations. Additionally, there was no significant difference in the levodopa daily dose or dopamine agonist daily dose used in the patients with and without delusions. There are a few studies that failed to find a relationship between the levodopa daily dose and the occurrence of delusions and hallucinations (18, 43, 59-62).

A review paper that reevaluated the frequency of psychotic symptoms and the doses of levodopa in studies conducted before 1998, suggests that the literature overestimated the relation between levodopa dose and psychotic adverse results (63). Causes of overestimation are related to different inclusion factors, classification of psychotic effects, and different levodopa dosages (48, 49).

Our findings on the other hand are suggestive that delusions and hallucinations are not the results of dopaminergic medications, and may be associated with disease progression. Patients with hallucinations were significantly older when the NPI was administered and older at disease onset compared to patients without hallucinations. Additionally, older age at evaluation and disease onset was also recorded in the patients with delusions compared to the patients without delusions. Our results are supported by prior literature that shows that the frequency of delusion and hallucination disturbances increased in older patients (43, 48, 64, 65). A study reported that age at evaluation and age at onset of PD were significantly associated with hallucinations. Hallucinations were

more frequent in PD patients with more than five year of disease duration and older age at evaluation (48).

Caregiver distress:

We found no significant differences in caregiver distress in caregivers of patients with tauopathies and those of patients with alpha-synucleinopathies. Additionally, this study found an association between caregiver distress and severity of neuropsychiatric disturbances when analyzing depression, apathy, anxiety, and nighttime domains only.

Current literature supports our findings that severity of neuropsychiatric disturbances correlate significantly with caregiver distress using different measuring tools other than the NPI (66-68). One supporting study reported association of both the Hamilton depression score and anxiety scores of the patient with caregiver burden, thus showing a correlation between neuropsychiatric disturbances and caregiver distress (68).

Associations with severity of symptoms should be cautiously interpreted because disturbances can fluctuate due to medication timing and degree of physical activity. Thus, caregiver distress can vary as well (69).

In administering the NPI, we noticed that five caregivers (3 with tauopathies and 2 with alpha-synucleinopathies) answered yes to the lead question regarding euphoria but did not answer positively to any of the subsequent questions. After reviewing the symptoms, we noted that 4 of the 5 patients were classified with pseudobulbar affect, which is an emotional disorder illustrated by uncontrollable laughing and crying outburst, reactions that do not reflect the patient's true feelings (70, 71). We did not use a standardized measuring tool for pseudobulbar affect, but this behavior was observed by the clinician. Other terms used to describe pseudobulbar affect are pathological laughing

and crying (71-74), emotional lability (72), emotional incontinence (72, 75), and emotionalism (72). Unexperienced clinicians should differentiate euphoria and depression from pseudobulbar affect, as treatments are specific and can improve patients and caregivers quality of life (70, 72, 73, 76-79).

Limitations:

One limitation in this study is that the NPI was administered by more than one trained personnel, potentially affecting the consistency of the methods. However, the NPI is an extremely structured measuring tool with high ratings of validity and reliability (12-14).

Additionally, this study used two versions of the NPI to evaluate the neuropsychiatric symptoms of our sample. There are slight differences between the new and old versions, although, the variations do not affect the total NPI score and allow for advanced investigations. The new version assesses two additional behavioral domains including nighttime behavior and appetite/eating changes. Moreover, the newer NPI tool evaluates the caregiver distress caused by the occurrence of individual neuropsychiatric disturbances.

Our entire patient sample was clinically diagnosed by three movement disorder specialist using established diagnostic criteria. Using clinical diagnosis is accurate although higher accuracy can only be achieved with pathological confirmation. Past studies report a high rate of misdiagnosis in parkinsonian patients (80-87).

We analyzed in detail a subsample rather than the full sample to account for between-group differences in disease duration and age at NPI evaluation. Although it would seem better to include the whole patient sample, and ideal that both proteinopathy groups were matched for overall cognition and motor disturbances, we believe that

including the full sample would have biased our results as disease duration and age at evaluation influence the conclusions.

This was a cross-sectional study observing a large number of patients; however, a longitudinal approach would yield a better understanding of the progression of the various neuropsychiatric features in the proteinopathies, as well as their relation with the treatment.

Summary and future studies:

This is the first study to assess neuropsychiatric disturbances to differentiate tauopathies and alpha-synucleinopathies. Our study included a relatively large sample with a variety of diseases, all presenting to one site for diagnosis and evaluation. This allows for a homogenous sample to analyze. Additionally, this study used valid and reliable instruments to assess the neuropsychiatric, cognitive, and motor disturbances and also assessed caregiver distress.

Patients with tauopathies significantly exhibited more apathetic disturbances and patients with alpha-synucleinopathies significantly reported more hallucinations. Our results suggest that the presence of hallucinations and delusions are not related to dopaminergic medication alone, and are due to disease progression and especially due to differences in age. From our results, we can conclude that patients with tauopathies and alpha-synucleinopathies cannot be differentiated based on neuropsychiatric features alone, because of the overlapping disturbances.

In the patients with alpha-synucleinopathies, the neuropsychiatric disturbances increased when the cognition and motor disturbances worsened. On the other hand, these associations were not observed in the patients with tauopathies. These findings suggest

that in patients with alpha-synucleinopathies motor, cognitive, and psychiatric pathways may degenerate in parallel. However, this is not the case for the tauopathies. Lastly, this study found no significant differences in caregiver distress between the two proteinopathy groups, but found that caregiver distress was related to the severity of neuropsychiatric disturbances. The use of the NPI in clinical practice could allow for treatment of neuropsychiatric symptoms and signs, thus improving the patient's quality of life and caregiver distress.

Table 1

NPI sources published from 1996-2008 evaluating PD, PDD, DLB, PSP and CBD

NPI Domain	Parkinson's disease ^{1, 2, 3, 4} (n=43-139)	Parkinson's disease with Dementia ⁵ (n=537)	Dementia with Lewy Body ⁶ (n=100)	Progressive Supranuclear Palsy ^{2, 7-9} (n=22-61)	Corticobasal degeneration ^{7, 10} (n=15-20)
Delusions	4.4-17%	24.6%	27%	0-3%	5-7%*
Hallucination	8.9-26.6%	44%	18%	0-2%	0%*
Agitation	12-22.4%	32.6%	48%	3-21%	20%
Depression	34-68.9%	58%	38%	18-25%	70-73%
Anxiety	16-68.8%	49%	46%	12-18%	13-15%
Euphoria	0.7-12.8%	3.7%	5%	0%	0%
Apathy	16.5-48.3%	54%	60%	82-91%	40%
Disinhibition	6.5-11%	11.70%	20%	35-56%	12-15%
Irritability	8-46.8%	29.70%	51%	9-20%	20%
Aberrant Motor Behavior	4.7-13.4%	22%	30%	6-9%	7-15%
Nighttime Behavior	44.2%	N/A	32%	N/A	N/A
Appetite/Eating Change	30.2%	N/A	24%	N/A	N/A

¹Aarsland D, et al. 1999, ²Aarsland D, et al. 2001, ³Kulisevsky, et al. 2008, ⁴McKinlay A, et al. 2008, ⁵Aarsland D, et al. 2007, ⁶Caputo M, et al. 2008, ⁷Litvan I, et al. 1998, ⁸Litvan I, et al. 1996, ⁹Litvan I, et al. 1998, ¹⁰Cummings JL, et al. 2000

* Delusions and hallucinations frequently occur in the patients with alpha-

synucleinopathies compared to the patients with tauopathies

† No previous study has used the NPI to examine neuropsychiatric disturbances in MSA

patients, an alpha-synucleinopathy disease

NPI = Neuropsychiatric Inventory

N/A = Not Applicable

Table 2Demographics

Demographics	Tauopathy		Alpha-synucleinopathy	
	Mean \pm SD	Range	Mean \pm SD	Range
Age at NPI evaluation (years)	67.7 \pm 7.3	53-85	69.4 \pm 10.1	42-93
Gender	27 M/ 32 F		116 M/ 57 F	
Education (years)	14.8 \pm 3.4	8-23	14.1 \pm 2.7	6-21
Duration of symptoms (years)	2.9 \pm 1.8	0-7	3 \pm 2.2	0-7
MMSE score	25.3 \pm 5.9	0-30	27.0 \pm 6.3†	0-30
Total UPDRS score	54.2 \pm 18.5	16-111	37.5 \pm 20.5†	3-116
UPDRS III score	29.3 \pm 12.5	4-84	21.8 \pm 12.9†	0-69

† p < 0.001

NPI = Neuropsychiatric Inventory

MMSE = Mini-Mental State Examination

Table 3NPI composite scores

NPI Domain	Tauopathy (N = 59)		Alpha-synucleinopathy (N = 176)	
	Mean ± SD	Frequency	Mean ± SD	Frequency
Delusions	0.1 ± 0.3	6.8%	0.2 ± 0.8	7.5%
Hallucinations	0.1 ± 0.3	3.4%	0.4 ± 0.9†	17.9%
Agitation	0.5 ± 1.1	18.6%	0.5 ± 1.4	16.2%
Depression	2.1 ± 3.0	55.9%	1.6 ± 2.3	54.3%
Anxiety	1.0 ± 2.2	27.1%	1.0 ± 2.0	32.4%
Euphoria	0.1 ± 0.1	1.7%	0.0 ± 0.0	0.0%
Apathy	4.0 ± 3.8	67.8%	1.6 ± 2.7*	40.5%
Disinhibition	0.9 ± 2.8	15.3%	0.3 ± 1.5	8.7%
Irritability	1.1 ± 2.4	25.4%	0.4 ± 1.2	16.8%
Aberrant Motor Behavior	0.5 ± 2.1	8.5%	0.2 ± 1.2	5.8%
Nighttime Behavior	2.4 ± 3.2	51.3%	2.2 ± 3.5	41.5%
Appetite/ Eating Change	2.0 ± 3.1	43.6%	1.2 ± 3.1	33.6%
Total NPI	10.3 ± 8.6		6.1 ± 7.5	

* p < 0.05

† p < 0.001

NPI = Neuropsychiatric Inventory

Table 4NPI Caregiver distress scores

NPI Domain	Tauopathy (N = 15)		Alpha-synucleinopathy (N = 58)	
	Mean ± SD	Range	Mean ± SD	Range
Delusions	N/A	N/A	3.2 ± 1.5	1-5
Hallucinations	N/A	N/A	1.8 ± 1.7	0-4
Agitation	4.0 ± 0.0	4	2.3 ± 1.5	0-4
Depression	2.5 ± 1.1	1-5	2.1 ± 1.2	0-5
Anxiety	1.6 ± 1.1	0-3	1.7 ± 1.4	0-5
Euphoria	N/A	N/A	N/A	N/A
Apathy	2.7 ± 1.2	1-5	2.4 ± 1.1	0-5
Disinhibition	3.0 ± 0.0	3-3	1.0 ± 1.0	0-2
Irritability	2.0 ± 1.4	0-4	1.9 ± 1.0	1-4
Aberrant Motor Behavior	N/A	N/A	N/A	N/A
Nighttime Behavior	1.8 ± 1.3	0-3	1.8 ± 1.2	0-5
Appetite/ Eating Change	0.6 ± 0.5	0-1	1.1 ± 1.2	0-4
Total Caregiver Distress	7.9 ± 5.6	0-5	5.7 ± 5.3	0-5

*Caregiver distress was recorded only when the patient exhibited a specific symptom.

Caregivers rated their distress caused by the presence of the individual domain (0-5, no distress to very severe distress)

NPI = Neuropsychiatric Inventory

N/A = not applicable

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Sacred Heart Academy, Louisville, KY	Aug 1999- May 2003 High School Degree
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HONORS, AWARDS, & SCHOLARSHIPS:

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May 2007 University of Kentucky Cum Laude in Biology –cumulative GPA 3.4 or above

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WORK AND/OR VOLUNTEER EXPERIENCE:

- Jan 2008- present Research Student, U of L Movement Disorder Clinic
Louisville, KY
Master thesis focuses on differentiating neuropsychiatric symptoms in Parkinsonian patients. Duties include spending time in clinic administering the Neuropsychiatric Inventory (NPI) and Mini-Mental State Examination (MMSE), as well as observing physical examinations. Additionally enter data collected in database, review literature, and write thesis.
- Aug 2006- May 2007 Research Student, Veterans Hospital
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Researching how different opioids are affected by various amounts of radiation. Duties include determining viability vs. morbidity of cell lines, counting cell ratios using a hemacytometer, irradiating different cell lines, plating cell cultures, graphing data.
- June 2005- present Patient Care Associate (PCA), Norton Kosair Children's Hospital
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Working in the operating room assisting with transporting patients, collecting and filing sterilized instruments, sterilizing surgical suites, obtaining items off the surgical floor including x-rays, blood, and surgical instruments. Duties also include assisting with sterile preps and patient care in operating room.

EXTRACURRICULAR ACTIVITIES AND COMMUNITY SERVICE:

- Habitat for Humanity- volunteered in building a home for a needy family in downtown Louisville.
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- Kappa Kappa Gamma Fraternity- Volunteer projects included Race for the Cure and raised money for physically challenged children. Other leadership positions included leading Kappa Konnection bible study, Continuous Open Recruitment representative which involved helping organize events for candidates interested in the Greek system, and slating nominations for future officers.
- University of Kentucky Pre-Professional Club Alpha Epsilon Delta: Secretary
- Intramural soccer and softball teams