COGNITIVE CORRELATES OF NEUROPSYCHIATRIC SYNDROMES MEASURED OVER TIME IN PATIENTS WITH ALZHEIMER'S DISEASE

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A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

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In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

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By

Jennifer N. Travis Seidl

July, 2014

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Abstract

Previous research has demonstrated an association between the emotional and behavioral symptoms of dementia, known as neuropsychiatric symptoms, and cognitive and functional decline among patients with Alzheimer's disease (AD). The present study aimed to identify baseline associations, as well as relationships over time, between neuropsychiatric symptoms and cognitive and functional performance. Participants were 288 AD patients enrolled in the Alzheimer's Disease and Memory Disorders Center (ADMDC) at Baylor College of Medicine. An exploratory factor analysis of a measure of neuropsychiatric symptoms, the Neuropsychiatric Inventory-Questionnaire (NPI-Q), indicated a two-factor structure consisting of Negative/Oppositional and Anxiety/Restlessness factors. At an initial evaluation, regression analyses revealed significant associations between greater total severity of neuropsychiatric symptoms and poorer performance on measures of overall dementia severity, immediate verbal recall, and basic and instrumental activities of daily living (ADLs). Greater severity of Anxiety/Restlessness symptoms was associated with poorer performance on measures of overall dementia severity, executive functioning, visuospatial functioning, and basic and instrumental ADLs. The Negative/Oppositional factor was not related to cognition or functioning. Greater initial neuropsychiatric symptom severity was also associated with worsening overall dementia severity over time. Worsening severity of neuropsychiatric symptoms over time, and particularly worsening of Anxiety/Restlessness symptoms, were related to worsening overall dementia severity over time, as well as a deceleration of overall dementia severity progression. In summary, neuropsychiatric symptoms (particularly Anxiety/Restlessness symptoms) were related to cognition, everyday functioning, and decline over time. Proper assessment and treatment of these symptoms is essential for improving cognition and functioning in AD patients.

Acknowledgments

I'd like to thank the members of my committee, Dr. Paul Massman, Dr. Siva Tian, Dr. Rheeda Walker, and Dr. Mario Dulay, for their help and support in completing this dissertation. I'd especially like to thank Dr. Massman for his support throughout my graduate career at University of Houston. Finally, I'd like to express my appreciation and gratitude to my family, especially my parents, my grandparents, and my husband, for their constant love and support.

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In loving memory of my great-grandmother, Hélène Vaudou Tellone, whose spirit and courage throughout her own struggle with dementia were an inspiration to me.

Introduction

Alzheimer's disease (AD) involves a progression of cognitive decline. However, in addition to these cognitive symptoms, changes may occur in a patient's mood, behavior, or psychological functioning. These symptoms, known as neuropsychiatric symptoms, include delusions, hallucinations, agitation or aggression, depression, anxiety, euphoria, apathy, disinhibition, and irritability (Kaufer et al., 2000). Neuropsychiatric symptoms can be distressing to both the patient and caregiver, and evidence suggests that the presence of these symptoms can lead to earlier placement in a nursing home (Tun et al., 2007). Previous research has investigated the association between neuropsychiatric symptoms, cognitive and functional decline, and the presence of the apolipoprotein E (APOE) ε4. Neuropsychiatric symptoms may negatively impact cognition and functioning through many possible mechanisms. The perceptions the patient has of their cognitive decline may worsen any emotional or behavioral problems they are experiencing, and conversely, negative emotions and behaviors may lead to impairments in cognition and functioning. Neuropsychiatric symptoms may also be associated with more severe and widespread neuropathological abnormalities that are associated with a more rapid progression of AD and poorer functioning.

The Neuropsychiatric Inventory (NPI) was developed to assess behavioral and psychiatric symptoms in dementia (Cummings et al., 1994). The measure was designed to assess delusions, hallucinations, agitation or aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior. The NPI is administered to the caregiver of the person with dementia, and a screening item of each domain is asked in an interview format. If the caregiver responds that the patient has experienced that symptom in

the past month, then questions are asked about the frequency, severity, and distress that the problem causes. Frequency of the symptom is rated on a four point scale, severity is rated on a three point scale, and distress is rated on a five point scale. Higher scores indicate higher frequency, severity, and level of distress. A second version of the NPI was developed to include appetite changes and nighttime behavior (Cummings et al., 1997).

The Neuropsychiatric Inventory-Questionnaire (NPI-Q) was developed to address the issue of time constraints in administering the NPI in a clinical setting (Kaufer et al., 2000). The interview format of the NPI made it difficult to administer in a setting when time constraints were present, so the NPI-Q, a questionnaire filled out by the caregiver, was developed (see Appendix 1). The questionnaire can be completed in about five minutes and consists of the same domains as the 12-item version of the NPI. For each symptom, a written version of the screening item from the NPI is completed by the caregiver. If the caregiver circles "yes", they rate the severity of the symptom over the past four weeks on a three point scale and the distress the symptom has caused them on a five point scale. For the NPI-Q, the scores range from 0 to 36 for severity and 0 to 60 for caregiver distress. Frequency is not assessed in the NPI-Q, as it was found that frequency and severity are highly correlated. The NPI-Q was found to have adequate test-retest reliability and convergent validity for the symptom domain scores and caregiver distress scores on the NPI.

Neuropsychiatric Factors Identified in Previous Research

Previous research has sought to identify neuropsychiatric syndromes from the symptoms covered in the Neuropsychiatric Inventory (NPI). As many patients have more than one symptom, and some symptoms appear to co-occur more often than others, identifying syndromes allows researchers to group symptoms in a clinically meaningful way

that enhances the investigation of the relationship between those syndromes and other factors. Methods for identifying neuropsychiatric syndromes, as well as the number of factors identified, have varied in the literature. See Table 1 for a review.

Relatively few studies have used the NPI-Q to identify neuropsychiatric syndromes; however, of those studies that have, most have tended to identify a three-factor model. A study comparing neuropsychiatric profiles of different dementias found a three factor model that was consistent across all dementias: mood (anxiety, depression, and apathy), psychotic (irritability, agitation, delusions, and hallucinations), and frontal (euphoria and disinhibition) (Johnson, et al. 2011). AD patients, compared to patients with other causes of dementia, were found to have moderate levels of all three syndromes. A more recent study using principal component analysis to investigate the NPI-Q in 1145 patients with MCI, 853 MCI convertors, and 3160 AD patients, identified a slightly different model consisting of the following three factors: frontal, agitation/aggression, and mood (Trzepacz, et al. 2013).

Of those studies using the 10-item NPI, most have supported a three-factor model of neuropsychiatric syndromes. In a study of 491 AD patients, Garre-Olmo and colleagues (2010) used exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) to identify a psychotic factor (delusions and hallucinations), an affective factor (depression, anxiety, irritability, and agitation), and a behavior factor (euphoria, disinhibition, apathy, and aberrant motor behavior). When measured every 6 months for a period of two years, this grouping of three factors was found to be moderately stable. The subscales that comprised each factor were also found to be stable over this time period. Frisoni et al. (1999) found a three factor model consisting of mood, psychotic, and frontal factors, as did a later study by Starr and Lonie (2007).

However, a study of 1015 AD patients using principal component analysis found five factors of the 10-item NPI: apathetic, affective (anxiety and depression), psychomotor (agitation, irritability, aberrant motor behavior), psychosis (delusions and hallucinations), and manic (disinhibition and euphoria) (Spalletta, et al. 2010). This study also found an increasing occurrence of these syndromes with increasing dementia severity, with the exception of the affective syndrome.

The previously mentioned studies used factor analysis or principal component analysis to group symptoms on the 10-item NPI into syndromes. However, Lyketsos et al. (2001) proposed grouping patients on the basis of symptom similarity rather than grouping symptoms themselves. The advantage of this is that the patient grouping may reveal subgroups of AD which have differing etiologies and presentation. In their study of 198 AD patients, they discovered three distinct patient groups through the use of latent class analysis: those with no neuropsychiatric symptoms or one symptom only, those with predominantly affective symptoms, and those with predominantly psychotic symptoms. Similarly, Tun et al. (2007) found three groups of patients: minimally symptomatic, highly symptomatic, and affective/apathetic.

Those studies that have used the 12-item NPI were more likely to identify four factors. Hollingworth et al. (2006) identified behavioral dyscontrol (euphoria, disinhibition, aberrant motor behavior, and sleep and appetite disturbances), psychosis (delusions and hallucinations), mood (depression, apathy, and anxiety), and agitation (aggression and irritability) in a sample of 1,120 AD patients. A study of 224 AD patients in Hong Kong found a different four factors using CFA: behavioral problems (agitation/aggression, disinhibition, irritability, and aberrant motor behavior), psychosis (delusions and

hallucinations), mood disturbance (depression, anxiety, sleep, appetite, and apathy), and euphoria (Cheng, et al. 2012). In this study, the authors found that the behavioral syndrome was strongly correlated with other factors and suggested that as a syndrome, it may be a measure of the patient's distress regarding other psychopathology. Mirakhur et al. (2004) identified the following factors: affect, physical behavior, psychosis, and hypomania. A study of 2,808 patients with dementia identified the factors of hyperactivity, psychosis, affect, and apathy (Aalten et al., 2008). However, a study by Chen et al. (2012) in a group of 96 AD patients identified five factors of the 12-item NPI: agitation/aggression-delusion, euphoria-disinhibition, depression-apathy, hallucination-nighttime behavior, and appetite.

Relationship of Neuropsychiatric Symptoms and Cognition and Functional Abilities in Studies Using the NPI

Disease Progression

Neuropsychiatric symptoms may be associated with higher risk of conversion from mild cognitive impairment (MCI) to AD. A study by Palmer et al. (2010) found that in a sample of 131 amnestic MCI patients, those with apathy at baseline evaluation had a seven-fold risk of developing AD by follow-up. This effect held after adjusting for depression, age, education, gender, and cognitive and functional status. Those patients who had depressive affect but not apathy had no increased risk of developing AD.

Rate of decline once a patient has developed AD may also be influenced by neuropsychiatric symptoms. In 362 patients who were without dementia at baseline and developed MCI or AD at follow-up, those who developed psychosis were more likely to have rapid cognitive decline in the early stages of AD (Emanuel, et al. 2011). Frisoni et al. (1999) also found that those patients with psychosis had a faster rate of cognitive decline. These

patients were also more likely to be older and male. Patients with frontal symptoms had a slower rate of progression, longer disease duration, and higher education. Interestingly, those patients with mood symptoms did not differ from patients with no neuropsychiatric symptomatology. In a study by Palmer and colleagues (2011) of 177 patients, it was found that patients who experienced the most rapid functional and cognitive declines differed in their neuropsychiatric profiles. Those with the most rapid functional decline were more likely to have an affective syndrome and those with manic syndrome were most at risk for cognitive decline.

Functional Decline

In addition to cognitive progression, patients who have neuropsychiatric symptoms may experience more rapid functional declines. Vilalta-Franch et al. (2013) found that those AD patients with apathy syndrome had increased functional disability, but no differences in cognitive impairment from those without apathy. Those with apathy also experienced higher rates of mortality, leading the authors to conclude that apathy syndrome is a particularly severe AD profile. Survival was also lower in a group of patients who were highly symptomatic, as identified in a study of 122 patients (Tun et al., 2007). The highly symptomatic patients were also more likely to be placed in a nursing home. Hallucinations have been identified as a risk factor for impaired functionality as measured by ADLs, even when controlling for depression and apathy (Rapoport et al., 2001). This study included patients of several dementia types. In a study of 812 subjects consisting of normal controls, MCI and AD patients, Wadsworth et al. (2012) found that participants with higher scores on NPI-Q items assessing hallucinations, anxiety, and apathy had greater global functional

impairment at baseline. In addition, greater global impairment across the three year period of time was associated with hallucinations and apathy.

Global Cognitive Functioning

Findings have been mixed on the association between neuropsychiatric symptoms and global cognitive functioning. Yener (2009) found that the highest number of neuropsychiatric symptoms occurred in patients classified as severely demented based on performance on the MMSE. Ryu et al. (2005) found in a sample of 224 AD patients that deterioration in neuropsychiatric symptoms was predicted by decline on MMSE performance. Likewise, in a group of 54 patients followed for one year, a significant correlation was found between cognition and behavior at baseline and during disease progression (Serra, et al. 2010). According to a study by Shimabukuro et al. (2005), total NPI scores increase with dementia severity. In a study of 482 patients with mild and moderate AD, it was discovered that those with mild AD had an increase in apathy and aberrant motor behavior, while those in the moderate stage of AD had disinhibition, aberrant motor behavior, and sleep disturbances (Benoit, et al. 2005). Among these patients, a subset was institutionalized by the end of the one-year study period. This group had a lower MMSE score and higher NPI scores on the symptoms of agitation and disinhibition at the baseline evaluation. Apathy and depression have been found to be more common in AD and MCI patients than in controls, and the prevalence of all items on the NPI, with the exception of the sleep and appetite items, was found to increase with increasing disease severity (Fernandez-Martinez, et al. 2010).

A study of 228 patients by Hirono et al. (1998) found that patients with psychosis had more severe cognitive impairment, as well as longer duration of illness. Patients with psychosis were also more likely to be female or older. In a study of 435 patients, the

symptoms earliest to appear in the course of the disease were apathy and depression (Craig, et al. 2005). Hallucinations, elation/euphoria, and aberrant motor behavior were latest to appear. Neuropsychiatric score was found to correlate with MMSE score as well as performance on a test of functional performance. Among a group of 328 patients with dementia, increasing hallucinations were associated with decreased risk of depression as well as increasing dementia severity (Steinberg, et al. 2006).

In a large study of 1850 AD patients, Proitsi et al. (2011) developed a model to predict various neuropsychiatric symptoms. The authors found that lower MMSE scores predict psychosis, agitation, and behavioral dyscontrol. Predictors of psychosis included greater cognitive impairment and female gender. Predictors of mood included greater cognitive impairment and younger age. Predictors of agitation were psychosis and mood, younger age, and male gender. Hollingworth et al. (2006) found that lower age of onset was associated with scores on the behavioral dyscontrol, agitation, and mood factors. Sex was also associated with mood and behavioral dyscontrol, such that women experienced more of these symptoms than men. However, Spalletta et al. (2004) conducted a factor analysis including both cognitive and behavioral variables and found that they loaded on separate factors, suggesting that cognitive and behavioral symptoms of AD are caused by separate etiologies.

Executive Functioning

Senanarong et al. (2004) suggested that agitation is linked to frontal lobe dysfunction and other frontally mediated behaviors such as irritability, delusions, and disinhibition. The authors also found that agitation is related to dementia severity as measured by the MMSE. Agitation and disinhibition were also found to be related to executive dysfunction, even after

correcting for MMSE score in a sample of 31 patients (Chen, et al. 1998). Additionally, total neuropsychiatric score was found to be related to executive dysfunction.

In addition to agitation, psychosis has been linked to functioning of the frontal lobes. SPECT imaging in a group of 20 patients showed that patients with psychosis had a disproportionate degree of dysfunction in the frontal lobes, as well as related structures in the subcortical and parietal areas (Mega, et al. 2000). In a comparison of 24 dementia patients with psychosis to 24 dementia patients without psychosis, Hopkins and Libon (2005) found that those patients with psychosis had poorer performance on a test of executive functioning (WMS Mental Control). The groups did not otherwise differ in age, education, depression, or severity of dementia. However, the groups consisted of both AD and Ischemic Vascular Dementia patients.

Other Cognitive Domains

In a large study of 556 AD patients, the authors determined that the relationship between neuropsychiatric symptoms and cognition could be largely explained by premorbid IQ (Starr & Lonie, 2007). Mood symptoms were significantly negatively correlated with AMNART and verbal fluency performance, and psychotic symptoms were correlated negatively with performance on the MMSE and HVLT- a measure of verbal memory. Impairments in memory, language, and executive functioning were found to predict score on the NPI after controlling for demographics and clinical information in a sample of 125 AD patients (Garcia-Alberca, et al. 2011). The authors also found that MMSE scores did not significantly predict NPI scores, and suggested that a more complete neuropsychological battery was necessary to capture the relationship between cognition and neuropsychiatric symptoms. Mood symptoms were found to be associated with impaired executive

functioning, speed of processing, visual memory, working memory, and a worsening CDR score in a sample of 50 AD and 26 MCI patients (Koppel, et al. 2012). In this same sample, psychosis was also found to be associated with worse working memory performance.

Relationship of Neuropsychiatric Symptoms and Cognition in Studies Not Using the NPI

In 397 patients with MCI followed for an average of 2.7 years, Richard et al. (2012) found 41% of the patients converted to AD. Using the Geriatric Depression Scale (15-item version), apathy, but not depressive affect, was found to significantly increase the risk of conversion from MCI to AD. Using the Behavioral Pathology in Alzheimer's Disease rating scale, Gallagher et al. (2010) found in a group of 161 MCI patients that anticipatory anxiety and activity disturbance were associated with conversion to AD, but not after disease severity and cognitive status were accounted for. Doody et al. (1995) found in a sample of 101 AD patients that patients with any neuropsychiatric features had a more rapid rate of disease progression, and had more severe cognitive and comprehension difficulties.

Using factor analysis to examine the Geriatric Depression Scale, Havins et al. (2012) found that apathy, but not dysphoria, was associated with greater cognitive and functional impairments in AD patients, including greater impairments in verbal memory and motor speed. In a study by Binetti et al. (1993), those patients with delusions were found to have higher MMSE scores and fewer functional impairments. However, a study of 1229 AD patients found that patients with delusions were more likely to be female and older age (Rockwell, et al. 1993). Patients with delusions also had more severe global cognitive impairments, more difficulty with self-care, and higher prevalence of other neuropsychiatric symptoms such as hallucinations, agitation, and depression. Swanberg et al. (2004) found

that patients who had executive dysfunction at baseline testing were more likely to have psychotic symptoms at follow-up testing.

Relationship of Neuropsychiatric Symptoms and APOE ε4 Status

Findings have been mixed on the relationship between APOE ε4 status and neuropsychiatric symptoms. While some researchers have found a relationship between the two, others have not. The most common symptoms identified as related to the APOE ε4 allele are agitation/aggression, delusions, and hallucinations.

In a study of 96 AD patients, it was found that APOE ε4 allele carriers had a higher risk of developing a neuropsychiatric syndrome identified by the authors as agitation/aggression-delusion (Chen, et al. 2012). Severity of dementia as measured by the CDR was controlled for. However, these authors note that as their sample was recruited from geriatric psychiatric outpatient centers, they may have had more severe neuropsychiatric symptoms than what may be seen in the general population. The authors suggest that ε4 allele carriers may be at higher risk for agitation/aggression-delusion symptoms because of hypoperfusion to the frontal lobes (Chen et al., 2012). Higher frequency of APOE ε4 alleles among patients who had displayed aggressive symptoms within the previous month was also found in a study of 400 patients with moderate to severe AD (Craig et al., 2004). Likewise, Xing et al. (2012) found that the presence of the APOE ε4 allele modified the effect of sex hormones, such that female patients with high levels of estradiol and the ε4 allele had higher levels of agitation and aggression. In female patients, there was also an interaction of testosterone and the presence of the ε4 allele, which were positively associated with the presence of hallucinations.

There is also evidence of APOE genotype influencing the presence of psychotic symptoms such as delusions and hallucinations. In a sample of 266 patients, the APOE ε4 allele was found to be significantly associated with the presence of psychotic symptoms, even after adjusting for age, education, sex, and MMSE scores (Zdanys, et al. 2007). The authors found that this effect was primarily accounted for by patients in the severe stage of dementia. Delusions accounted for most of the psychotic symptoms experienced. The authors speculate that this association may be due to the more profound cholinergic loss in the frontal and medial temporal lobes that is experienced by carriers of the ε4 allele, although evidence directly linking psychotic symptoms to the presence of the ε4 allele is conflicting (Zdanys et al., 2007). An association with delusions was also found by Spalletta et al. (2006) in a study of 171 patients. The only neuropsychiatric symptom that was found to be related to APOE genotype was delusions, which were more common among those patients with the ε4 allele. In a group of 53 AD patients (24 of whom were followed for a year), the APOE ε4 allele as associated with a wider range of neuropsychiatric symptoms, and more specifically, more hallucinations and aberrant motor behavior at baseline (Del Prete, et al., 2009). At follow-up, carriers of the ε4 allele displayed worsening of some neuropsychiatric symptoms but improvement of others, while patients without the ε4 allele were likely to experience only symptom worsening. In a study of 790 patients by Christie et al. (2012), it was revealed that those patients with no ε4 alleles were more likely to have hallucinations than those with any ε4 alleles. The authors found no association between APOE genotype and delusions, agitation, or aberrant motor behavior. However, those patients with delusions and hallucinations had lower initial MMSE scores, longer duration of illness, and higher CDR scores than those patients who only had delusions.

Michels et al. (2012) found that patients who were homozygous for the APOE ε4 allele had the highest rates of anxiety. Depression was also more common among carriers of the ε4 allele than those without the allele. Hallucinations were more common among those who were homozygous for the ε4 allele than those who were heterozygous or did not carry the allele at all. Van der Flier et al. (2007) also noted that there may be a dose effect of the ε4 allele, finding that those patients who were homozygous for the ε4 allele were more likely to have delusions and agitation/aggression. In addition, these symptoms were likely to be more severe in those patients. No difference was found between heterozygous carriers and non-carriers of the ε4 allele.

In a study of 605 AD patients examining the relationship between the 10 item NPI and APOE ε4 status, it was found that there were no correlations between any of the items and APOE ε4 after controlling for severity of cognitive impairment (Levy, et al. 1999). Similarly, D'Onofrio et al. (2011) found no significant association between neuropsychiatric syndromes (as identified by the European Alzheimer's Disease Consortium Neuropsychiatric Symptoms classification system) and APOE ε4 status. Those with and without neuropsychiatric symptoms were equally likely to carry the APOE ε4 allele. A study of 120 patients by Lyketsos et al. (1997) also found no significant relationship between APOE ε4 status and psychiatric symptoms. Hirono and colleagues (1999) reached the same conclusion in a Japanese sample.

Purpose of the Current Study

Neuropsychiatric symptoms are particularly distressing to AD patients and their families, and these symptoms may be related to cognitive and functional decline over time. Certain patients may be more at risk for the development of neuropsychiatric symptoms, such

as those patients who are carriers of the APOE ε4 allele. However, to date, little research has been conducted on the longitudinal changes of these symptoms and possible correlates of these changes. The purpose of the current study is to examine, within a large and well-defined sample of AD patients, the cognitive and functional correlates of total NPI-Q score, as well as domain scores. Domain scores will be identified by conducting an exploratory factor analysis. The relationship of these domains to APOE ε4 allele status will also be examined. Additionally, the current study will examine the longitudinal course and correlates of these syndromes, to determine the stability of neuropsychiatric syndromes over time and establish whether cognitive and functional declines are related to changes in neuropsychiatric symptoms. Few studies to date have used a longitudinal design to investigate the relationships between neuropsychiatric symptoms and changes in cognition and function over time. The current study will expand on previous research to investigate not only the relationship between neuropsychiatric symptoms with cognitive and functional decline over time, but also the relationship between change in neuropsychiatric symptoms with cognitive and functional decline. A better understanding of the relationship between neuropsychiatric symptoms and cognitive and functional changes over time could be beneficial for clinicians and caregivers in providing appropriate care.

Hypotheses

The first four hypotheses entail investigation of the factor structure of the NPI-Q and baseline associations involving the NPI-Q, and the last two hypotheses examine progression of cognitive and NPI-Q changes over time.

1. It is predicted that the NPI-Q will consist of a three-factor structure consisting of psychosis, mood, and frontal factors.

2. It is predicted that patients with higher scores overall on the NPI-Q will have more cognitive impairment on a battery of neuropsychological tests than patients with lower scores on the NPI-Q. It is also expected that patients with more frontal or psychosis symptoms will experience greater impairments on tests of executive functioning than those with primarily mood symptoms.
3. It is expected that patients with higher baseline NPI-Q total scores will have greater functional impairments in activities of daily living (ADLs) than those with lower scores. It is predicted that those patients with primarily symptoms of psychosis will have more functional impairments than those with primarily frontal or mood syndromes.
4. Carriers of APOE ε4 allele are expected to have higher total scores on the NPI-Q.
5. It is expected that patients with higher baseline NPI-Q total scores will have a faster rate of cognitive decline than those patients with lower scores on the NPI-Q. It is also expected that patients with higher baseline NPI-Q total scores will have a faster rate of functional decline over time. Neuropsychiatric syndrome is predicted to have an influence on rate of progression, such that patients with high baseline levels of symptoms of psychosis will have a faster rate of progression than those with frontal or mood symptoms.
6. It is expected that worsening in neuropsychiatric symptoms over time will be associated with declines in performance on cognitive and functional measures.

Methods

Participants

Participants were 288 AD patients enrolled in the Baylor College of Medicine's Alzheimer's Disease and Memory Disorders Center (ADMDC) in Houston, Texas. All participants met the National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann, Drachman, & Folstein, 1984) criteria for a diagnosis of probable AD. Diagnoses were made in a consensus conference composed of neurologists, neuropsychologists, and nurses. While the Baylor ADMDC database has been in existence since 1989, the NPI-Q was not regularly administered as a standard part of the neuropsychological battery until 2008. Therefore, some of the participants in the current study had one or more neuropsychological testing sessions prior to their initial NPI-Q visit. Of the 288 participants included in the sample, approximately 75% received the NPI-Q at their first visit to the Baylor ADMDC. Of the 288 participants, 28 had just one visit with NPI-Q data, 81 had two NPI-Q visits, and 179 had three or more NPI-Q visits. Another inclusion criterion was an initial CDR score of 0.5 or 1, indicating a very mild or mild dementia at the initial neuropsychological evaluation, so that decline over time from the initial visit could be well characterized. Therefore, most of the sample was very mildly or mildly demented at the time of their initial NPI-Q visit, although a portion (28 participants, or 11% of the sample) had a CDR of 2 or greater. Moderately to severely demented participants at initial neuropsychological visit were excluded from analyses due to concerns about potential floor effects on the neuropsychological measures administered over time. One hundred eleven (39%) of the sample had no APOE ε4 alleles, while 131 (46%) had 1 ε4 allele, 35 (12%) had 2 ε4 alleles, and 3% did not have genotype data available. As shown in Table 3, mean follow-up times from the initial visit with NPI-Q data to the last neuropsychological visit and the last NPI-Q

visit were 3.10 and 2.56 years, respectively. Consent forms permitting storage and use of data were signed by all participants or legally designated representatives. See Table 3 for demographic and clinical characteristics of the sample.

Measures

Participants completed a neuropsychological battery consisting of the following measures at the initial evaluation, as well as all follow-up evaluations.

Neuropsychiatric Inventory- Questionnaire (NPI-Q; Kaufer et al., 2000): The NPI-Q is a caregiver-completed questionnaire consisting of 12 items (delusions, hallucinations, agitation or aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, motor disturbance, nighttime behaviors, and changes in appetite). For the current analyses, nighttime behaviors and changes in appetite will be excluded. The caregiver is asked to identify if the symptom was present over the past four weeks. If the symptom was present, the caregiver is then asked to rate the severity of the symptom on a scale of 1 to 3, and their level of distress over the symptom on a scale of 0 to 5. Severity scores will be used in the analyses. Factors scores were be calculated as a sum of severity scores for each of the factors identified in the exploratory factor analysis.

<u>Dementia Severity</u>

Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog; Rosen et al., 1984): The ADAS contains 11 subtests/ratings which assess orientation, attention, memory, language, ideational praxis, and visuoconstructional ability.

Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975): The MMSE is a brief measure that screens for cognitive impairment. A total of 30 points can be

earned over the areas of orientation, attention and calculations, immediate and delayed recall, repetition, naming, following commands, reading, visual construction, and writing.

Clinical Dementia Rating (CDR) scale (Morris, 1993): The CDR is a scale of severity of dementia. Scores indicate the level of dementia: 0 indicates no symptoms of dementia, 0.5 indicates very mild symptoms of dementia or MCI, 1 indicates mild dementia, 2 indicates moderate dementia, and 3 indicates severe dementia. Scores are assigned to participants based on their everyday functioning in the areas of memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Language Functioning

Animal Fluency (Rosen, 1980)*:* Animals is a test of semantic (category) fluency requiring the participant to name as many animals as he or she can think of in one minute.

Multilingual Aphasia Examination's (MAE) Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1976): The COWAT is a test of phonemic fluency in which the participant names as many words as he or she can think of that begin with the letters F, A, and S. There is a one minute time limit for each letter.

Boston Naming Test (Kaplan et al., 1983): The Boston Naming Test is a test of naming to confrontation in which drawings must be named by the participant.

Wechsler Adult Intelligence Scale-R and III (WAIS-R and WAIS-III): Similarities subtest (Wechsler, 1981; Wechsler, 1997)*:* Scaled scores will be used for WAIS subtests. The Similarities subtest assesses a participant's abstract verbal reasoning by requiring the participant to describe how two words are similar.

Attention and Executive Functioning

Verbal Series Attention Test (VSAT; Mahurin & Cooke, 1996*)*: The VSAT allows participants one minute to complete various tasks of attention and mental control as quickly and accurately as possible, including counting forwards and backwards, serial subtraction of 3's, days of the weeks and months of the year forward and backwards, and saying numbers and letters in ascending, alternating order (i.e., 1-A-2-B, etc.). The time taken to complete each task is recorded.

Memory Functioning

Wechsler Memory Scale-Revised (WMS-R): Logical Memory I and Visual Reproduction I subtests (Wechsler, 1987): Logical Memory is a measure of verbal memory. Logical Memory I measures the ability to recall a story immediately after it is read. Visual Reproduction is a measure of visual construction and memory. During Visual Reproduction I, participants are presented with cards with line drawings for ten seconds each. After the card is removed, the line drawing(s) must be reproduced.

Visuospatial Functioning

Rey-Osterrieth Complex Figure Test (ROCFT; Osterrieth, 1944*)*: The Rey-Osterrieth Complex Figure Test is a test of visual construction. The test requires that the participant to copy a two dimensional line drawing.

Wechsler Adult Intelligence Scale-R and III (WAIS-R and WAIS-III): Block Design subtest (Wechsler, 1981; Wechsler, 1997)*:* Scaled scores will be used for WAIS subtests. The Block Design subtest is a test of visual construction requiring participants to arrange blocks to form various patterns to match target designs of increasing complexity.

Everyday Functional Abilities

Physical Self-Maintenance Scale (PSMS- basic ADLs; Lawton & Brody, 1969*):* PSMS-basic ADLs assess functional abilities in six basic activities of daily living, including: continence, ambulation, feeding, bathing, grooming, and dressing. Scores range from five to 30, and a higher score indicates greater dependence on others.

Instrumental Activities of Daily Living (IADLs; Lawton & Brody, 1969*):* The IADL scale assesses independence in eight daily living tasks, including: using the telephone, shopping, housekeeping, cleaning, laundry, driving, and management of medications and finances. Scores range from zero to 31. Higher scores indicate a greater level of dependence. Since some items may not be applicable for a given participant, a highest potential score is calculated for each patient, and their obtained score is divided by the highest potential score to yield a ratio. Higher ratios indicate a greater level of impairment.

Analyses

1. To determine the factor structure of the NPI-Q, exploratory factor analysis was conducted using principal axis factoring and varimax rotation. Severity scores were used for each symptom. Factors with eigenvalues greater than 1 were retained.

2. To test whether higher initial NPI-Q scores are associated with poorer baseline cognitive performance, regression analyses were performed with test scores as the dependent variable, and age, gender and education as covariates (significant covariates were retained in the final model). NPI-Q total score was the predictor variable. To test whether different neuropsychiatric syndromes are associated with different cognitive profiles, regression analyses were performed with test scores as the dependent variable; age, gender and education as covariates; and NPI-Q factor scores as predictor variables.

3. To determine whether total and factor initial NPI-Q scores are related to functional impairment, regression analyses were performed with functional scores as the dependent variable, and age, gender and education as covariates. NPI-Q total and domain scores were the predictor variables.

4. To determine if APOE ε4 status is associated with NPI-Q score, analysis of covariance (ANCOVA) was performed with age, sex, and education as possible covariates (depending on relationship to NPI-Q scores), number of APOE ε4 alleles (0, 1 or 2) as the between-subjects factor, and the NPI-Q total and domain scores as dependent variables.

5. To test whether total and domain baseline NPI-Q scores are related to rate of cognitive and functional progression, mixed effects regression analyses were performed. Covariates included baseline dementia severity (MMSE), age, gender, and education.

6. To determine whether changes in neuropsychiatric symptoms over time are related to changes in cognition and functioning, linear mixed models were again used, with age, education, gender, and baseline dementia severity (MMSE) as covariates, NPI total and domain scores over time as the predictors, and changes in cognitive or functional scores over time as the dependent variables.

Results

For descriptive purposes, mean neuropsychological test performances at the initial NPI-Q visit are presented in Table 4. Initial NPI-Q total and factor scores, as well as item scores, are presented in Table 5. The items with the highest average scores were anxiety, apathy, and agitation, and the items with the lowest average scores were delusions, euphoria, and hallucinations. In Table 6, the Pearson correlations between the neuropsychological measures and the NPI-Q total and factor scores at the initial visit are presented.

Exploratory Factor Analysis (Hypothesis 1)

Results of exploratory factor analysis using principal axis factoring with Varimax rotation indicated a two-factor structure based on examination of the scree plot and retention of factors with eigenvalues greater than one. Two neuropsychiatric symptoms (motor behavior and euphoria) were excluded from the factor analysis. Motor behavior was excluded as it had similar, low loadings on both factors, and euphoria was excluded as it was the only symptom loading onto a third factor. After excluding these symptoms, a two-factor structure was identified. Factor 1, Negative/Oppositional behavior, consisted of the following symptoms: agitation, irritability, apathy, depression, disinhibition, and delusions, and explained 36.5% of the variance. The second factor, Anxiety/Restlessness, consisted of the symptoms of nighttime behaviors, anxiety, hallucinations and appetite, and explained 12.3% of the variance. See Table 7 for the rotated factor matrix. As shown in Table 5, the mean score for the Negative/Oppositional factor was 3.74, and the mean score for the Anxiety/Restlessness factor was 2.23.

Initial NPI-Q associations with cognitive performance (Hypothesis 2)

Regression analyses utilizing the NPI-Q total and factor scores were conducted. The alpha level was set to .025 for all regression analyses as two sets of analyses were conducted for each dependent variable- one using the NPI-Q total score and the second using the NPI-Q factor scores. For each dependent variable, an initial regression with the covariates age, sex, and education was conducted. Covariates that were significant at $p < .15$ were retained in the final model including NPI-Q total or factor scores. See Table 8 for results of regression analyses utilizing total NPI-Q scores. The change in R^2 resulting from the addition of NPI-Q total or factor scores to the model containing the covariates is also presented in Table 8. Total

NPI-Q was significantly associated with measures of dementia severity, the ADAS-Cog (overall model $F = 5.15$, $p = .024$) $p = .024$, and MMSE (overall model $F = 10.03$, $p < .001$), $p = .003$. Higher total NPI-Q was associated with poorer performance on these measures. Higher total NPI-Q was also significantly associated with poorer performance on a measure of immediate verbal recall (LM I; overall model $F = 6.17$, $p = .002$), $p = .022$. Total NPI-Q was not related to performance on any other neuropsychological measures. Regression analyses were also conducted using NPI-Q quartiles and were not found to differ from the above results.

See Table 9 for regression analyses utilizing factor scores. Negative/Oppositional scores were not significantly associated with performance on any neuropsychological measures. Anxiety/Restlessness scores, however, were significantly associated with performance on measures of dementia severity, the ADAS-Cog (overall model $F = 4.36$, $p = .014$), $p = .005$, and MMSE (overall model $F = 7.88$, $p < .001$), $p = .001$. Anxiety/Restlessness was also associated with a measure of executive functioning (VSAT; overall model $F = 4.55$, $p = .004$), $p = .02$. These factor scores were also significantly associated with two measures of visuospatial skills: immediate visual recall (VR I; overall model $F = 9.49$, $p < .001$), $p < .001$, and visuospatial construction (Block Design; overall model $F = 8.25$, $p < .001$), $p = .001$. When regressions were conducted with NPI-Q domain quartiles, the pattern of results did not differ.

Initial NPI-Q associations with functional performance (Hypothesis 3)

See Table 8 for regression analyses utilizing the NPI-Q total score. NPI-Q total was significantly associated with performance on basic ADLs (overall model $F = 19.55$, $p <$

.001), $p < .001$ and the IADL ratio (overall model $F = 24.32$, $p < .001$), $p < .001$. Higher total NPI-Q scores were associated with poorer performance on these measures.

See Table 9 for regression analyses utilizing NPI-Q factor scores. Negative/Oppositional scores were not significantly associated with performance on basic or instrumental ADLs. Anxiety/Restlessness was significantly associated with basic ADLs (overall model $F = 16.72$, $p < .001$), $p < .001$, as well as the IADL ratio (overall model $F = 18.16$, $p < .001$), $p < .001$, with higher factor scores being related to worse functional status.

ANCOVA examining association between APOE ε4 and NPI-Q scores (Hypothesis 4)

See Tables 10-12 for results of ANCOVA examining the association between NPI-Q scores and APOE ε4 status. Number of APOE ε4 alleles was not significantly associated with NPI-Q total or factor scores.

Longitudinal analyses involving NPI-Q initial scores (Hypothesis 5)

Mixed model analyses were conducted with time and time-squared included in the first model. For those models with either significant time or time-squared effects, demographic variables and interactions with time or time-squared were added to the second model. The time-squared variable was included as a measure of acceleration or deceleration of change over time (Shek & Ma, 2011). The third, complete model included initial NPI-Q total or factor scores in addition to those demographic variables that were significantly associated with the dependent measure (and their interactions with time). The following neuropsychological measures were not found to vary over time: Animals, COWAT, Similarities, VSAT, VR I, Rey-O, and BD (see Tables 13-19). Thus, further models (including demographic, dementia severity, and NPI-Q variables) involving these dependent variables were not examined. Of note, there was a significant effect of time-squared for

ADAS-Cog indicating a deceleration in decline of ADAS-Cog score over time. As shown in Table 20 (Model 3; overall model AIC = 5147.97), initial total NPI-Q scores were associated with changes in ADAS-Cog, $p < .02$ for the NPI-Q X Time interaction. Higher initial total NPI-Q score was associated with worsening performance on ADAS-Cog over time. There was a significant decrease in AIC with the addition of NPI-Q and the NPI-Q X Time interaction to the model, indicating that this model was a better fit for the data than the model containing just the covariates. There were no other significant NPI-Q X Time interactions, though this interaction was nearly significant ($p = .03$) for basic ADLs.

Initial total NPI-Q score was also associated with both ADLs ($p < .001$) and IADL ratio ($p < .001$), such that higher baseline total NPI-Q score was associated with poorer performance on both (e.g., a significant effect of NPI-Q in Tables 21 and 22; overall model AIC =-1206.67 and -756.34, respectively). A significant decrease in AIC for the model containing NPI-Q indicated that these models were a better fit for the data than the model containing only the covariates. There was no significant association of NPI-Q with BNT or LM I (see Tables 23 and 24). Analyses were re-conducted using NPI-Q quartiles and results did not differ.

Results of mixed model analyses utilizing NPI-Q factor scores indicated that initial Anxiety/Restlessness score was associated with overall performance on ADLs, $p < .001$ (see Table 21; overall model AIC = -1212.70) and the IADL ratio, $p < .001$ (see Table 22; overall model AIC = -755.72). Higher baseline Anxiety/Restlessness score was associated with poorer performance on these measures. Comparison of AIC values indicate that the model containing NPI-Q factor scores was a better fit for the data than the model containing only NPI-Q total score for basic ADLs, but not for IADL ratio. However, both models were a

better fit than the model containing only the covariates. Neither factor score was associated significantly with change in performance on these measures over time. Analyses were re-conducted using NPI-Q factor score quartiles and the pattern of results did not differ.

Longitudinal analyses involving changes in NPI-Q scores over time (Hypothesis 6)

Mixed model analyses were completed using a similar procedure described in hypothesis 5. However, for the third model, NPI-Q total and factor scores over time (instead of just initial scores) were added to the model. Animals, COWAT, Similarities, VSAT, VR I, Rey-O, and BD scores did not vary over time (see Tables 25-31), and thus additional modeling involving these dependent variables was not conducted. A significant effect of time-squared for ADAS-Cog indicated a deceleration in decline of ADAS-Cog score over time. Results of mixed model analyses indicated that increases in total NPI-Q score over time was associated with increases (worsening) in ADAS-Cog score over time, $p < .001$ (e.g., a significant effect of NPI-Q X Time in Table 32; overall model AIC = 4918.79). Additionally, increases in total NPI-Q score over time was associated with acceleration in ADAS-Cog declines over time, $p = .01$ (e.g., a significant effect of NPI-Q X Time-sq in Table 32). Worsening NPI-Q scores over time were related to poorer overall IADL ratio, $p < .001$ (e.g., a significant effect of NPI-Q in Table 33; overall model AIC = -695.92). For both of these variables, lower AIC values indicated that the model containing the NPI-Q variables was a better fit for the data than the model containing only covariates. Change in NPI-Q score over time was not related to change in basic ADLs, BNT, or LM I over time (see Tables 34-36). When analyses were conducted with log-transformed total NPI-Q scores, results did not differ except for a significant effect of change in NPI-Q score over time found for basic ADLs (e.g., a significant NPI-Q X Time interaction).

Change in Anxiety/Restlessness score over time was significantly associated with ADAS-Cog change, $p = .001$ (e.g., a significant effect of Anxiety/Restlessness X time in Table 32; overall model AIC = 4909.85). Anxiety/Restlessness was also significantly associated with overall IADL ratio, $p < .001$ (e.g., a significant effect of Anxiety/Restlessness in Table 33; overall model AIC = -707.61). An increase in symptoms of Anxiety/Restlessness over time was associated with overall poorer functioning. For both of these variables, AIC values indicated that the model containing NPI-Q factor scores provided a better fit than the model containing only the covariates, as well as a better fit than the model containing the NPI-Q total score. Results from analyses conducted with log-transformed NPI-Q factor did not differ except that Anxiety/Restlessness over time was associated with basic ADLs (e.g., a significant effect of Anxiety/Restlessness).

Discussion

Psychiatric and behavioral symptoms frequently occur in Alzheimer's disease, along with cognitive and functional deterioration. Previous research has identified a link between greater severity of psychiatric and behavioral symptoms with greater severity of cognitive and functional deficits. The present study sought to identify associations between neuropsychiatric symptoms and cognitive and functional performance, both at initial visit, and changes over time. Neuropsychiatric symptoms may be associated with cognitive and functional decline due to a bidirectional influence between cognition/functioning and emotional/behavioral problems. As patients notice a decline in their cognition and functioning due to the progression of the disease, they may experience more emotional or behavioral symptoms, such as depression, apathy, or anxiety, in response to these observed changes. Likewise, the presence of these symptoms may interfere with functioning in

everyday settings and with performance on neuropsychological testing. It is also possible that these results are due to more severe neuropathological abnormalities that are associated with more rapid cognitive and functional decline as well as the presence of neuropsychiatric symptoms.

The first hypothesis was that results of exploratory factor analysis would demonstrate a three-factor structure of the NPI-Q consisting of mood, frontal, and psychosis symptoms, consistent with the results of previous research. However, this hypothesis was not supported, as a two factor structure consisting of Negative/Oppositional symptoms (agitation, irritability, apathy, depression, disinhibition, and delusions) and Anxiety/Restlessness symptoms (nighttime behavior disturbance, anxiety, hallucinations, and appetite changes) was identified. These results differ from previously presented factor structures of the NPI-Q (Johnson et al., 2011; Trzepacz, et al. 2013), which consisted of three factors, perhaps due to the mild nature of the initial dementia presentation in the current sample. Furthermore, the two factors identified in the current study differed from previously identified factors. A psychosis factor consisting of delusions and hallucinations has typically been presented in the previous literature, but in the current sample, delusions and hallucinations contributed to two different factors. Again, this likely is due to the mild, homogeneous nature of the current sample, particularly when compared to the samples utilized by Johnson et al. (2011) and Trzepacz et al. (2013).

The second hypothesis, that greater neuropsychiatric symptom severity at the initial evaluation would be associated with greater cognitive impairment at initial evaluation, and that differences would emerge between the factors, was partially supported. Greater total severity of neuropsychiatric symptoms was significantly associated with poorer performance

on measures of dementia severity (ADAS-Cog and MMSE) at the initial NPI-Q visit, consistent with the results of Yener et al. (2009), who also demonstrated an association between NPI-Q total score and dementia severity. Greater total severity of neuropsychiatric symptoms at the initial NPI-Q visit was also associated with poorer performance on a measure of immediate verbal recall (LM I), consistent with the association between NPI score and impairments in memory reported by Garcia-Alberca and colleagues (2011).

The identified NPI-Q factors differed in their associations with cognitive and functional variables at the initial NPI-Q visit. Negative/Oppositional scores were not significantly associated with performance on any cognitive or functional measures. However, Anxiety/Restlessness scores were significantly associated with two measures of dementia severity (ADAS-Cog and MMSE), a measure of executive functioning (VSAT time), immediate visual recall (VR I), and visuospatial construction (Block Design). Higher severity of Anxiety/Restlessness symptoms was associated with poorer performance on these measures.

The third hypothesis, that greater neuropsychiatric symptom severity at the initial NPI-Q visit would be associated with greater functional impairment, was supported. Higher initial NPI-Q total scores were associated with poorer performance on basic and instrumental ADLs. These results are consistent with previous literature suggesting an association between neuropsychiatric symptoms and functional impairment (Tun et al., 2007; Rapoport et al., 2001; Wadsworth et al., 2012). Consistent with the results involving cognitive functioning, higher severity of Anxiety/Restlessness symptoms was associated with poorer performance on basic and instrumental ADLs, while Negative/Oppositional symptoms were not related to functional performance.

The hypothesis that greater neuropsychiatric symptom severity would be associated with having more APOE ε4 alleles (Hypothesis four) was not supported. Total NPI-Q score and NPI-Q factor scores were not found to be related to APOE ε4 allele status. These results support those of D'Onofrio et al. (2011), who also found no association between neuropsychiatric symptoms and APOE ε4 allele status in a group of patients with more moderate to severe AD.

The fifth hypothesis was that initial neuropsychiatric symptom severity would be associated with greater declines in cognitive and functional performance over time. Higher initial NPI-Q total scores were associated with change over time on a dementia severity measure (ADAS-Cog), consistent with the finding of Serra et al. (2010), who also found an association between disease progression and behavior at baseline. Higher initial scores on the two NPI-Q factors were not significantly associated with change over time on any of the neuropsychological or functional measures. These results differed from those of Palmer and colleagues (2011), who found differences in disease progression between patients with differing neuropsychiatric profiles; however, these neuropsychiatric profiles were affective and manic syndromes. Therefore, the neuropsychiatric profiles in Palmer et al. (2011)'s study differed from those presented in the current study.

The final hypothesis, that worsening of neuropsychiatric symptoms over time would be related to cognitive and functional declines over time, was partially supported. Changes in NPI-Q total scores over time were found to be related to changes in cognition, specifically to worsening of overall dementia severity and acceleration of decline over time (ADAS-Cog). Changes in symptoms of Anxiety/Restlessness in particular were also related to worsening of

overall dementia severity (ADAS-Cog). Few studies to date have examined the relationship between changes in neuropsychiatric symptoms and disease progression over time.

Limitations

One limitation is that follow-up visit data with the NPI-Q scores was limited to a smaller portion of the sample, as not all participants had follow-up data available. Therefore, longitudinal analyses were restricted to this smaller subset of the sample. It may be that this subset of participants differed from the overall sample. Participants who did not return for a follow-up visit may have had a faster disease progression, died, or been unable to complete a neuropsychological testing session. Of the 288 participants in the current sample, 28 did not return for any follow-up visits. A comparison of those who did not return with those who did return for follow-up visits revealed no significant differences in demographics. However, those who did not return for follow-up had significantly lower initial MMSE scores (mean of 17.00 compared to a mean of 19.54 for those who did return), higher initial ADAS-Cog score (mean of 25.25 compared to a mean of 20.73 for those who did return), and higher initial NPI-Q score (mean of 9.67 compared to a mean of 6.19 for those who did return). This suggests that those who did not return for follow-up may have done so due to a faster disease progression or a greater burden of neuropsychiatric symptom severity. A second limitation of this study is the lack of a significant change over time found for several of the cognitive variables (specifically, Animals, COWAT, Similarities, VSAT, VR I, Rey-O, and BD). It is possible that as the patients were initially in the very mild/mild stages of dementia that performance on these variables was declining at a relatively slow rate, and that this mild rate of decline was not detected. As the participants developed more moderate to severe dementia, it is possible that this rate of decline would increase. Another possibility is that

decline on these measures was impacted by the use of medications to slow the progression of AD, which the majority of participants were taking at the time of their participation in this study.

Another possible limitation is that this study sample may not be representative of the population of AD patients. The sample was highly educated (on average) and mostly Caucasian. Also of note is that the NPI-Q is a measure completed by the caregiver and may be subject to bias. As evaluation of basic and instrumental ADLs was also completed by the caregiver, the noted associations between NPI-Q score and ADLs could be at least partly due to this methodological similarity. Psychotropic medication usage information for all visits was not available, but the fact that significant associations between neuropsychiatric symptoms and cognitive and functional abilities were found initially and over time indicates that any medication effects did not 'wash out' all these relationships. A final limitation for the analysis of the association between APOE genotype and neuropsychiatric symptoms was the small number of participants with two APOE ε4 alleles (only 35 participants, or 12% of the sample, had two ε4 alleles).

Implications

These results support the validity and utility of the NPI-Q in clinical settings, particularly as the measure is straightforward to administer and score, takes only a few minutes for the caregiver to complete and may provide valuable information for the clinician. Findings indicated that, within a relatively mildly demented sample, greater severity of neuropsychiatric symptoms is associated with cognitive and functional deficits, and that changes in these symptoms over time is also related to cognitive and functional decline. The majority of the current sample was very mildly or mildly demented, indicating that the

association between cognitive and functional deficits and neuropsychiatric symptoms may be particularly important to detect at this mild stage, before much of the cognitive and functional decline has occurred.

The identified syndromes of Negative/Oppositional behaviors and Anxiety/Restlessness differ in their associations with cognition and everyday functioning. Negative/Oppositional symptoms were not related to any cognitive or functional deficits, while Anxiety/Restlessness symptoms *were* associated with poorer performance on some measures of cognition and functioning. This indicates that symptoms of Anxiety/Restlessness (nighttime behavior disturbance, anxiety, hallucinations, and appetite changes) may be more indicative of greater disease progression and greater severity of deficits. Of note, the Anxiety/Restlessness factor consisted of many symptoms (hallucinations, appetite changes, and nighttime behaviors) that are commonly associated with later-stage AD. This may account for the associations between symptoms of Anxiety/Restlessness and greater cognitive and functional impairment, both at baseline and over time. The use of the NPI-Q factor scores in the mixed models often provided a better fit for the data than the use of the NPI-Q total score, indicating that the use of the factor scores may better explain changes in cognition and functioning over time. Given the particular association between symptoms of Anxiety/Restlessness and greater disease progression, clinicians may find it helpful to utilize this score in addition to the total NPI-Q score. Scores about 1 standard deviation about the means presented in Table 5 (a total NPI-Q score of 12 or greater and an Anxiety/Restlessness score of 5 or greater) may prove to be useful indicators of poorer prognosis, particularly related to dementia severity and functioning. Future research should investigate the clinical utility of such scores for predicting greater declines over time.

Both baseline NPI-Q and changes in NPI-Q over time were found to predict decline in cognition, and baseline NPI-Q additionally predicted decline in everyday functioning. This finding highlights the importance of assessing for psychiatric and behavioral changes as well as cognitive changes in AD. A greater number of neuropsychiatric symptoms at baseline, and particularly a greater number of Anxiety/Restlessness symptoms, may indicate a greater decline in functioning and cognition over time. When possible, patients and caregivers should be offered options for treatment and management of these difficult symptoms to reduce the impact of psychiatric and behavioral problems on daily functioning. As this sample was relatively mildly demented, early detection of these symptoms could be especially important for intervening before the disease progresses. Additionally, providing feedback to caregivers and family members could be useful for those patients who are not experiencing significant neuropsychiatric symptoms, as this may be a positive indicator of a less severe course of the disease. Further research is needed on treatment options for neuropsychiatric symptoms in AD, as management of these symptoms could ameliorate declines in functioning over time for patients with AD and improve quality of life for both the patient and their caregivers.

Appendix 1. Questions on the Neuropsychiatric Inventory-Questionnaire.
The caregiver is asked to indicate yes or no for each of the following questions. For those questions that are answered "yes", the caregiver is to rate the patient on severity of the symptom from 1 to 3 and caregiver distress from 0 to 5.

1. Delusions: Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?
2. Hallucinations: Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear or see things that are not present?
3. Agitation/Aggression: Is the patient resistive to help from others at times, or hard to handle?
4. Depression/Dysphoria: Does the patient seem sad or say that he/she is depressed?
5. Anxiety: Does the patient become upset when separated from you? Does he/she have any other signs of nervousness such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?
6. Elation/Euphora: Does the patient appear to feel too good or act excessively happy?
7. Apathy/Indifference: Does the patient seem less interested in his/her usual activities or in the activities and plans of others?
8. Disinhibition: Does the patient seem to act impulsively, for example, talking to strangers as if he/she knows them, or saying things that may hurt people's feelings?
9. Irritability/Lability: Is the patient impatient and cranky? Does he/she have difficulty coping with delays or waiting for planned activities?
10. Motor Disturbance: Does the patient engage in repetitive activities such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?

11. Nighttime Behaviors: Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?
12. Appetite/Eating: Has the patient lost or gained weight, or had a change in the type of food he/she likes?

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Table 1. Previous literature identifying neuropsychiatric syndromes using versions of the NPI.

Study	*N*	NPI version	Factors Identified
Johnson, et al. 2011	2,963 dementia	NPI-Q	Mood Psychotic Frontal
Trzepacz, et al. 2013	5,158 MCI and AD	NPI-Q	Frontal Agitation/aggression Mood
Garre-Olmo, et al. 2010	491 AD	10 item NPI	Psychotic Affective Behavior
Spalletta, et al. 2010	1,015 AD	10 item NPI	Apathetic Affective Psychomotor Psychosis Manic
Lyketsos, et al. 2001	198 AD	10 item NPI	Those with one or no symptoms Predominantly affective Predominantly psychotic
Frisoni, et al. 1999	162 AD	10 item NPI	Mood Psychotic Frontal
Tun, et al. 2007	122 AD	10 item NPI	Minimally symptomatic Highly symptomatic Affective/apathetic
Starr & Lonie 2007	556 AD	10 item NPI	Mood Psychotic Frontal
Hollingworth, et al. 2006	1,120 AD	12 item NPI	Behavioral Psychotic Mood Agitation
Cheng, et al. 2012	224 AD	12 item NPI	Behavioral Psychotic Mood Euphoria
Chen, et al. 2012	96 AD	12 item NPI	Agitation/aggression-delusion

			Euphoria-disinhibition Depression-apathy Hallucination-nighttime behavior Appetite
Mirakhur, et al. 2004	435 AD	12 item NPI	Affect Physical behavior Psychosis Hypomania
Aalten, et al. 2008	2,808 dementia	12 item NPI	Hyperactivity Psychosis Affective Apathy

Table 2. Previous literature on the association of the APOE ε4 allele with neuropsychiatric symptoms (in order presented in text)

Study	*N*	Relationship of ε4 to NPS
Chen, et al. 2012	96	Higher risk of agitation/aggression
Craig, et al. 2004	400 moderate-severe AD	Higher frequency of aggressive symptoms
Xing, et al. 2012	86 male, 87 female	Modified effects of sex hormones on aggression
Zdanys, et al. 2007	266	Associated with presence of psychotic symptoms
Spalletta, et al. 2006	171	Associated with delusions
Del Prete, et al. 2009	53 (24 followed for one year)	More NPS More hallucinations and aberrant motor behavior
Christie, et al. 2012	790	Less hallucinations
Michels, et al. 2012	659	Homozygous- more anxiety and hallucinations Carrier- More depression
Van der Flier, et al. 2007	110	Homozygous- more delusions and agitation/aggression
Levy, et al. 1999	605	None
D'Onofrio, et al. 2011	201 AD; 121 controls	None
Lyketsos, et al. 1997	120	None
Hirono, et al. 1999	175	None

Table 3. Demographic and clinical characteristics of the sample (*N* = 288)

	Mean	SD
Age	73.67	8.53
Education	14.66	2.97
% Female	63.2% (*N* = 182)	
% Caucasian	92.5% (*N* = 267)	
% with 1 or more APOE ε4 alleles	57.7% (*N* =166)	
N with 2 or more NPI-Q visits	*N* = 260	
N with 3 or more NPI-Q visits	*N* = 179	
N with 4 or more NPI-Q visits	*N* = 99	
N with 5 or more NPI-Q visits	*N* = 45	
Follow-up time from first to last neuropsych visit	3.10	1.79
Follow-up time from first to last NPI-Q visit (in years)	2.56	1.27

Table 4. Initial Performance on Neuropsychological Testing.

Neuropsychological Test	*N*	Mean	SD	Range
ADAS-Cog	283	21.16	9.77	5-52
MMSE	287	19.30	5.27	3-30
COWAT	263	24.67	12.08	0-61
Animals	280	8.68	4.12	0-23
BNT	278	40.18	14.12	4-60
Similarities	265	8.07	3.14	0-17
LM I	280	7.46	5.28	0-23
VR I	279	16.29	8.45	0-38
VSAT	276	194.40	83.52	57-446
Rey-O	146	18.47	11.05	0-36
Block Design	262	7.29	2.94	1-16
ADLs	283	7.53	2.49	6-16
IADL Ratio	280	0.51	0.20	0.25-1.00

Table 5. Initial NPI-Q severity scores (*N* = 288)

	Mean	SD
NPI-Q total score	6.52	5.75
Negative/Oppositional	3.74	3.61
Anxiety/Restlessness	2.23	2.35
Delusions	0.31	0.71
Hallucinations	0.10	0.43
Agitation	0.75	0.94
Depression	0.70	0.85
Anxiety	0.77	0.95
Euphoria	0.14	0.47
Apathy	0.75	0.96
Disinhibition	0.49	0.83
Irritability	0.74	0.94
Motor Behavior	0.41	0.76
Nighttime Behavior	0.69	0.96
Appetite Change	0.67	0.96

Table 6. Correlations between NPI-Q total and factor scores and neuropsychological test performance at initial NPI-Q visit.

Neuropsychological measure	NPI-Q Total	Negative/Oppositional	Anxiety/Restlessness
Age	.01	.02	.002
Education	-.01	.01	-.01
ADAS-Cog	.13	.05	.17
MMSE	-.18	-.08	-.20
COWAT	-.06	-.02	-.08
Animals	-.07	-.02	-.09
BNT	-.10	-.06	-.11
Similarities	-.12	-.09	-.10
LM I	-.13	-.08	-.13
VR I	-.10	.01	-.18
VSAT	.12	.06	.15
Rey-O	-.05	-.02	-.06
Block Design	-.09	.01	-.18
ADLs	.27	.15	.32
IADL Ratio	.33	.21	.35

Table 7. Rotated Factor Matrix for initial NPI-Q severity scores

	Factor	
	Negative/Oppositional	Anxiety/Restlessness
Agitation	.73	.09
Irritability	.60	.24
Apathy	.55	.20
Depression	.54	.25
Disinhibition	.52	.33
Delusions	.48	.11
Nighttime behavior	.30	.57
Anxiety	.32	.52
Hallucinations	-.01	.49
Appetite	.27	.47

Table 8. Results of regression analyses utilizing total NPI-Q scores

	Total NPI-Q score			
Dependent Measures	ΔR^2	Covariates retained in final model	Beta (β)	t
ADAS-Cog	.02	none	.13*	2.27
MMSE (serial 7s)	.03	Sex	-.17**	-3.00
Animals	.004	Age	-.06	-1.04
COWAT	.003	Education	-.06	-.96
BNT	.01	Age	-.10	-1.65
Similarities	.01	Age Education	-.12	-2.05
VSAT Time	.01	Education	.12	2.01
LM I	.02	Education	-.14*	-2.30
VR I	.01	Education	-.10	-1.64
ROCFT	.001	Sex	-.03	-0.36
Block Design	.01	Age Education	-.09	-1.53
Basic ADLs	.08	Age	.29**	5.17
IADL Ratio	.10	Age	.32**	5.80

*$p < .025$; **$p < .01$

Table 9. Results of regression analyses utilizing factor NPI-Q scores

			Negative/Oppositional		Anxiety/Restlessness	
Dependent Measures	ΔR^2	Covariates retained	Beta (β)	t	Beta (β)	t
ADAS-Cog	.03	None	-.05	-.78	.19**	2.85
MMSE (serial 7s)	.04	Sex	.03	.48	-.22**	-3.26
Animals	.01	Age	.05	.66	-.11	-1.57
COWAT	.01	Education	.02	.22	-.09	-1.22
BNT	.01	Age	-.01	-.08	-.10	-1.48
Similarities	.01	Age Education	-.06	-.93	-.06	-.98
VSAT Time	.02	Education	-.02	-.31	.16*	2.34
LM I	.02	Education	-.02	-.33	-.13	-1.84
VR I	.04	Education	.13	1.92	-.24**	-3.58
ROCFT	.003	Sex	.03	.32	-.07	-.68
Block Design	.04	Age Education	.12	1.80	-.24**	-3.50
Basic ADLs	.11	Age	-.01	-.12	.34**	5.34
IADL Ratio	.12	Age	.04	.68	.32**	5.03

*$p < .025$; **$p < .01$

Table 10. Results of ANCOVA examining association between APOE ε4 and total NPI-Q score.

	df	*F*	*p*
Age	1, 270	.00	.99
Sex	1, 270	.53	.47
Education	1, 270	.00	.99
Number of APOE ε4 alleles	2, 270	.26	.78

Table 11. Results of ANCOVA examining association between APOE ε4 and Negative/Oppositional factor.

	df	*F*	*p*
Age	1, 270	.13	.72
Sex	1, 270	.51	.48
Education	1, 270	.08	.78
Number of APOE ε4 alleles	2, 270	.04	.97

Table 12. Results of ANCOVA examining association between APOE ε4 and Anxiety/Restlessness factor.

	Df	*F*	*p*
Age	1, 270	.03	.87
Sex	1, 270	.05	.82
Education	1, 270	.09	.77
Number of APOE ε4 alleles	2, 270	1.29	.28

Table 13. Mixed effects models predicting rate of change in Animals score.

	Animals score	
	β	p
Model 1		
Time in years	-.22	.52
Time-squared	-.07	.48
Intercept	8.64	<.001
AIC: 4,044.46		

Table 14. Mixed effects models predicting rate of change in COWAT score.

	COWAT score	
	β	p
Model 1		
Time in years	-.57	.59
Time-squared	-.23	.51
Intercept	24.52	<.001
AIC: 5,022.58		

Table 15. Mixed effects models predicting rate of change in Similarities score.

	Similarities score	
	β	P
Model 1		
Time in years	-.03	.90
Time-squared	.-.07	.44
Intercept	8.08	<.001
AIC: 3,249.04		

Table 16. Mixed effects models predicting rate of change in VSAT score.

	VSAT score	
	β	p
Model 1		
Time in years	2.86	.64
Time-squared	9.37	.05
Intercept	194.47	<.001
AIC: 8,467.88		

Table 17. Mixed effects models predicting rate of change in VR I score.

	VR I score	
	β	p
Model 1		
Time in years	-.21	.77
Time-squared	-.41	.06
Intercept	16.36	<.001
AIC: 5,112.01		

Table 18. Mixed effects models predicting rate of change in Rey-O score.

	Rey-O score	
	β	p
Model 1		
Time in years	.87	.50
Time-squared	-.47	.27
Intercept	18.75	<.001
AIC: 2,758.19		

Table 19. Mixed effects models predicting rate of change in BD score.

	BD score	
	β	p
Model 1		
Time in years	.24	.39
Time-squared	-.20	.03
Intercept	7.29	<.001
AIC: 3,211.89		

Table 20. Mixed effects models predicting rate of change in ADAS-Cog score.

	ADAS-cog score	
	β	P
Model 1		
Time in years	1.72	.04
Time-squared	.95	.001
Intercept	21.33	<.001
AIC: 5,690.39		
Model 2		
Time in years	1.97	.46
Time-squared	2.40	.03
Age (centered)	-.07	.07
Sex	1.75	.025
Education in years (centered)	.34	.01
Baseline MMSE	-1.63	<.001
Age x time interaction	.03	.63
Age × time- sq interaction	-0.05	.06
Sex × time interaction	-1.23	.33
Sex × time- sq interaction	.76	.10
Education × time interaction	-.21	.32
Education x time-sq interaction	.10	.24
MMSE x time interaction	.07	.61
MMSE x time-sq interaction	-.10	.05
Intercept	52.31	<.001
AIC: 5,150.10		
Model 3 (Total NPI-Q score)		
Time in years	1.36	.10
Time-squared	2.34	.001
Age (centered)	-.07	.03
Sex	1.49	.02
Education in years (centered)	.29	.004
Baseline MMSE	-1.61	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-.07	.03
NPIQ	-.01	.86
NPIQ x time interaction	.24	.02
NPIQ x time-sq interaction	-.06	.06
Intercept	52.07	<.001
AIC: 5,147.97		
Model 3 (NPI-Q factor scores)		
Time in years	1.40	.10
Time-squared	2.41	.001
Age (centered)	-.07	.02
Sex	1.45	.03
Education in years (centered)	.30	.003
Baseline MMSE	-1.60	<.001
Age x time interaction	-	-

	ADAS-cog score	
	β	P
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-.07	.025
Negative/Oppositional	-.07	.51
Anxiety/Restlessness	.08	.67
Negative/Oppositional x time interaction	.05	.79
Negative/Oppositional x time-sq interaction	-.02	.71
Anxiety/Restlessness x time interaction	.66	.03
Anxiety/Restlessness x time-sq interaction	-.17	.11
Intercept	51.91	<.001
AIC: 5,150.04		

Table 21. Mixed effects models predicting rate of change in log-transformed ADL score.

	ADL score	
	β	P
Model 1		
Time in years	.03	.02
Time-squared	.01	.09
Intercept	.86	<.001
AIC: -898.47		
Model 2		
Time in years	.10	<.001
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-.01	.53
Education in years (centered)	.01	.01
Baseline MMSE	-.01	<.001
Age x time interaction	.001	.66
Age × time- sq interaction	-	-
Sex × time interaction	-.01	.61
Sex × time- sq interaction	-	-
Education × time interaction	-.001	.62
Education x time-sq interaction	-	-
MMSE x time interaction	-.002	.04
MMSE x time-sq interaction	-	-
Intercept	1.05	<.001
AIC: -1,174.76		
Model 3 (Total NPI-Q score)		
Time in years	.08	.001
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-	-
Education in years (centered)	.01	.01
Baseline MMSE	-.01	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-.002	.07
MMSE x time-sq interaction	-	-
NPIQ	.01	<.001
NPIQ x time interaction	.002	.03
NPIQ x time-sq interaction	-	-
Intercept	1.00	<.001
AIC: -1,206.67		
Model 3 (NPI-Q factor scores)		
Time in years	.08	.001
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-	-
Education in years (centered)	.01	.01
Baseline MMSE	-.01	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-

	ADL score	
	β	P
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-.002	.06
MMSE x time-sq interaction	-	-
Negative/Oppositional	-.0001	.94
Anxiety/Restlessness	.01	<.001
Negative/Oppositional x time interaction	.001	.35
Negative/Oppositional x time-sq interaction	-	-
Anxiety/Restlessness x time interaction	.003	.24
Anxiety/Restlessness x time-sq interaction	-	-
Intercept	.99	<.001
AIC: -1,212.70		

Table 22. Mixed effects models predicting rate of change in IADL ratio.

	IADL ratio	
	β	P
Model 1		
Time in years	.08	<..001
Time-squared	.004	.70
Intercept	.51	<.001
AIC: -170.45		
Model 2		
Time in years	.08	.03
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-.01	.73
Education in years (centered)	.01	.002
Baseline MMSE	-.02	<.001
Age x time interaction	-.001	.16
Age × time- sq interaction	-	-
Sex × time interaction	.01	.61
Sex × time- sq interaction	-	-
Education × time interaction	-.004	.19
Education x time-sq interaction	-	-
MMSE x time interaction	.0002	.87
MMSE x time-sq interaction	-	-
Intercept	.94	<.001
AIC: -705.12		
Model 3 (Total NPI-Q score)		
Time in years	.09	<.001
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-	-
Education in years (centered)	.01	.003
Baseline MMSE	-.02	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
NPIQ	.01	<.001
NPIQ x time interaction	-.001	.71
NPIQ x time-sq interaction	-	-
Intercept	.84	<.001
AIC: -756.34		
Model 3 (NPI-Q factor scores)		
Time in years	.09	<.001
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-	-
Education in years (centered)	.01	.004
Baseline MMSE	-.02	<.001
Age x time interaction	-	-

	IADL ratio	
	β	P
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
Negative/Oppositional	.01	.05
Anxiety/Restlessness	.02	<.001
Negative/Oppositional x time interaction	-.001	.60
Negative/Oppositional x time-sq interaction	-	-
Anxiety/Restlessness x time interaction	.0001	.97
Anxiety/Restlessness x time-sq interaction	-	-
Intercept	.84	<.001
AIC: -755.72		

Table 23. Mixed effects models predicting rate of change in BNT score.

	BNT score	
	β	P
Model 1		
Time in years	-2.70	.003
Time-squared	-.50	.53
Intercept	40.26	<.001
AIC: 5,804.62		
Model 2		
Time in years	-12.43	<.001
Time-squared	-	-
Age (centered)	-.31	<.001
Sex	-1.57	.20
Education in years (centered)	.26	.18
Baseline MMSE	1.50	<.001
Age x time interaction	.16	.03
Age × time- sq interaction	-	-
Sex × time interaction	.68	.62
Sex × time- sq interaction	-	-
Education × time interaction	-.13	.56
Education x time-sq interaction	-	-
MMSE x time interaction	.40	.004
MMSE x time-sq interaction	-	-
Intercept	11.72	<.001
AIC: 5,270.06		
Model 3 (Total NPI-Q score)		
Time in years	-12.12	<.001
Time-squared	-	-
Age (centered)	-.30	<.001
Sex	-	-
Education in years (centered)	-	-
Baseline MMSE	1.49	<.001
Age x time interaction	.16	.03
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	.40	.004
NPIQ	-.01	.90
NPIQ x time interaction	.01	.97
NPIQ x time-sq interaction	-	-
Intercept	52.07	<.001
AIC: 5,268.92		
Model 3 (NPI-Q factor scores)		
Time in years	-12.02	<.001
Time-squared	-	-
Age (centered)	-.30	<.001
Sex	-	-
Education in years (centered)	-	-
Baseline MMSE	-1.50	<.001
Age x time interaction	.15	.03
Age × time- sq interaction	-	-

	BNT score	
	β	P
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	.39	.01
MMSE x time-sq interaction	-	-
Negative/Oppositional	-.04	.80
Anxiety/Restlessness	.03	.91
Negative/Oppositional x time interaction	.14	.48
Negative/Oppositional x time-sq interaction	-	-
Anxiety/Restlessness x time interaction	-.19	.56
Anxiety/Restlessness x time-sq interaction	-	-
Intercept	11.41	<.001
AIC: 5,272.30		

Table 24. Mixed effects models predicting rate of change in LM I score.

	LM I score	
	β	P
Model 1		
Time in years	-1.17	<.001
Time-squared	-.04	.55
Intercept	7.54	<.001
AIC: 4,051.67		
Model 2		
Time in years	-.70	.41
Time-squared	-	-
Age (centered)	.01	.80
Sex	-.28	.52
Education in years (centered)	.14	.034
Baseline MMSE	.57	<.001
Age x time interaction	.001	.97
Age × time- sq interaction	-	-
Sex × time interaction	-.20	.58
Sex × time- sq interaction	-	-
Education × time interaction	-.05	.48
Education x time-sq interaction	-	-
MMSE x time interaction	-.03	.44
MMSE x time-sq interaction	-	-
Intercept	-3.26	<.001
AIC: 4,102.30		
Model 3 (Total NPI-Q score)		
Time in years	-1.55	<.001
Time-squared	-	-
Age (centered)	-	-
Sex	-	-
Education in years (centered)	-	-
Baseline MMSE	.55	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
NPIQ	-.07	.06
NPIQ x time interaction	.02	.43
NPIQ x time-sq interaction	-	-
Intercept	-2.80	.001
AIC: 4,095.30		
Model 3 (NPI-Q factor scores)		
Time in years	-1.63	<.001
Time-squared	-	-
Age (centered)	-	-
Sex	-	-
Education in years (centered)	-	-
Baseline MMSE	.56	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-

	LM I score	
	β	P
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
Negative/Oppositional	-.08	.22
Anxiety/Restlessness	-.04	.69
Negative/Oppositional x time interaction	.04	.39
Negative/Oppositional x time-sq interaction	-	-
Anxiety/Restlessness x time interaction	.03	.76
Anxiety/Restlessness x time-sq interaction	-	-
Intercept	-2.94	.001
AIC: 4,099.41		

Table 25. Mixed effects models predicting rate of change in Animal score with NPI-Q change over time.

	Animals score	
	β	p
Model 1		
Time in years	-.24	.49
Time-squared	-.07	.51
Intercept	8.68	<.001
AIC: 3,878.59		

Table 26. Mixed effects models predicting rate of change in COWAT score with NPI-Q change over time.

	COWAT score	
	β	P
Model 1		
Time in years	-.34	.74
Time-squared	-.29	.42
Intercept	24.47	<.001
AIC: 4,808.04		

Table 27. Mixed effects models predicting rate of change in Similarities score with NPI-Q change over time.

	Similarities score	
	β	p
Model 1		
Time in years	-.09	.75
Time-squared	-.06	.55
Intercept	8.12	<.001
AIC: 3,119.32		

Table 28. Mixed effects models predicting rate of change in VSAT with NPI-Q change over time.

	VSAT score	
	β	P
Model 1		
Time in years	.58	.94
Time-squared	4.68	.05
Intercept	195.07	<.001
AIC: 8,085.40		

Table 29. Mixed effects models predicting rate of change in VR I score with NPI-Q change over time.

	VR I score	
	β	P
Model 1		
Time in years	-.19	.80
Time-squared	-.43	.05
Intercept	16.45	<.001
AIC: 4,892.57		

Table 30. Mixed effects models predicting rate of change in Rey-O score with NPI-Q change over time.

	Rey-O score	
	β	p
Model 1		
Time in years	1.06	.42
Time-squared	-.51	.24
Intercept	18.55	<.001
AIC: 2,671.35		

Table 31. Mixed effects models predicting rate of change in BD score with NPI-Q change over time.

	BD score	
	β	P
Model 1		
Time in years	.22	.43
Time-squared	-.19	.05
Intercept	7.29	<.001
AIC: 3,089.18		

Table 32. Mixed effects models predicting rate of change in ADAS-Cog score with NPI-Q change over time.

	ADAS-cog score	
	β	p
Model 1		
Time in years	1.83	.02
Time-squared	1.06	<.001
Intercept	20.98	<.001
AIC: 5,409.92		
Model 2		
Time in years	4.15	.13
Time-squared	1.89	.09
Age (centered)	-.08	.05
Sex	1.30	.10
Education in years (centered)	.40	.001
Baseline MMSE	-1.53	<.001
Age x time interaction	.04	.57
Age × time- sq interaction	-.05	.06
Sex × time interaction	-1.04	.40
Sex × time- sq interaction	.71	.12
Education × time interaction	-.23	.28
Education x time-sq interaction	.10	.21
MMSE x time interaction	-.04	.75
MMSE x time-sq interaction	-.08	.15
Intercept	50.37	<.001
AIC: 4,925.25		
Model 3 (Total NPI-Q score)		
Time in years	1.12	.15
Time-squared	.79	.001
Age (centered)	-.05	.19
Sex	.90	.22
Education in years (centered)	.28	.02
Baseline MMSE	-1.52	<.001
Age x time interaction	-	-
Age × time- sq interaction	-.03	.004
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
NPIQ	.01	.93
NPIQ x time interaction	.33	<.001
NPIQ x time-sq interaction	-.07	.01
Intercept	51.30	<.001
AIC: 4,918.79		
Model 3 (NPI-Q factor scores)		
Time in years	1.02	.19
Time-squared	.82	.001
Age (centered)	-.06	.12
Sex	.85	.24
Education in years (centered)	.29	.01

	ADAS-cog score	
	β	p
Baseline MMSE	-1.54	<.001
Age x time interaction	-	-
Age × time- sq interaction	-.03	.004
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
Negative/Oppositional	.10	.46
Anxiety/Restlessness	-.16	.44
Negative/Oppositional x time interaction	.04	.83
Negative/Oppositional x time-sq interaction	-.01	.83
Anxiety/Restlessness x time interaction	.95	.001
Anxiety/Restlessness x time-sq interaction	-.18	.03
Intercept	50.60	<.001
AIC: 4,909.85		

Table 33. Mixed effects models predicting rate of change in IADL ratio with NPI-Q change over time.

	IADL ratio	
	β	p
Model 1		
Time in years	.08	<.001
Time-squared	.01	.63
Intercept	.51	<.001
AIC: -189.14		
Model 2		
Time in years	.09	.01
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-.01	.42
Education in years (centered)	.01	.001
Baseline MMSE	-.02	<.001
Age x time interaction	-.001	.16
Age × time- sq interaction	-	-
Sex × time interaction	.004	.79
Sex × time- sq interaction	-	-
Education × time interaction	-.003	.24
Education x time-sq interaction	-	-
MMSE x time interaction	.00	.93
MMSE x time-sq interaction	-	-
Intercept	.91	<.001
AIC: -684.08		
Model 3 (Total NPI-Q score)		
Time in years	.07	<.001
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-	-
Education in years (centered)	.01	.04
Baseline MMSE	-.02	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
NPIQ	.01	<.001
NPIQ x time interaction	.001	.26
NPIQ x time-sq interaction	-	-
Intercept	.82	<.001
AIC: -695.92		
Model 3 (NPI-Q factor scores)		
Time in years	.08	<.001
Time-squared	-	-
Age (centered)	.01	<.001
Sex	-	-
Education in years (centered)	.01	.03
Baseline MMSE	-.02	<.001

	IADL ratio	
	β	p
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
Negative/Oppositional	.01	.04
Anxiety/Restlessness	.02	<.001
Negative/Oppositional x time interaction	.002	.13
Negative/Oppositional x time-sq interaction	-	-
Anxiety/Restlessness x time interaction	-.002	.47
Anxiety/Restlessness x time-sq interaction	-	-
Intercept	.83	<.001
AIC: -707.61		

Table 34. Mixed effects models predicting rate of change in log-transformed ADL score with NPI-Q change over time.

	ADL score	
	β	P
Model 1		
Time in years	.03	.006
Time-squared	.01	.10
Intercept	.86	<.001
AIC: -888.32		
Model 2		
Time in years	.11	<.001
Time-squared	-	-
Age (centered)	.004	<.001
Sex	-.01	.23
Education in years (centered)	.01	.004
Baseline MMSE	-.01	<.001
Age x time interaction	.001	.71
Age × time- sq interaction	-	-
Sex × time interaction	-.01	.49
Sex × time- sq interaction	-	-
Education × time interaction	-.001	.67
Education x time-sq interaction	-	-
MMSE x time interaction	-.002	.02
MMSE x time-sq interaction	-	-
Intercept	1.01	<.001
AIC: -1,145.54		
Model 3 (Total NPI-Q score)		
Time in years	.06	<.001
Time-squared	-	-
Age (centered)	.004	<.001
Sex	-	-
Education in years (centered)	.001	.66
Baseline MMSE	-.01	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-.01	.14
MMSE x time-sq interaction	-	-
NPIQ	.004	.002
NPIQ x time interaction	.002	<.001
NPIQ x time-sq interaction	-	-
Intercept	.93	<.001
AIC: -1,126.84		
Model 3 (NPI-Q factor scores)		
Time in years	.06	<.001
Time-squared	-	-
Age (centered)	.003	<.001
Sex	-	-
Education in years (centered)	.001	.41
Baseline MMSE	-.01	<.001

	ADL score	
	β	P
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-.001	.08
MMSE x time-sq interaction	-	-
Negative/Oppositional	.001	.49
Anxiety/Restlessness	.01	<.001
Negative/Oppositional x time interaction	.002	.05
Negative/Oppositional x time-sq interaction	-	-
Anxiety/Restlessness x time interaction	.002	.29
Anxiety/Restlessness x time-sq interaction	-	-
Intercept	.93	<.001
AIC: -1,139.47		

Table 35. Mixed effects models predicting rate of change in BNT score with NPI-Q change over time.

	BNT score	
	β	P
Model 1		
Time in years	-2.59	.003
Time-squared	-.62	.419
Intercept	40.70	<.001
AIC: 5,547.67		
Model 2		
Time in years	-12.79	<.001
Time-squared	-	-
Age (centered)	-.30	<.001
Sex	-1.59	.21
Education in years (centered)	.22	.27
Baseline MMSE	1.40	<.001
Age x time interaction	.15	.03
Age × time- sq interaction	-	-
Sex × time interaction	1.03	.45
Sex × time- sq interaction	-	-
Education × time interaction	-.15	.49
Education x time-sq interaction	-	-
MMSE x time interaction	.42	.003
MMSE x time-sq interaction	-	-
Intercept	14.24	<.001
AIC: 5,038.68		
Model 3 (Total NPI-Q score)		
Time in years	-7.77	<.001
Time-squared	-	-
Age (centered)	-.27	<.001
Sex	-	-
Education in years (centered)	-	-
Baseline MMSE	1.53	<.001
Age x time interaction	.07	.07
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	.23	.002
MMSE x time-sq interaction	-	-
NPIQ	-.07	.60
NPIQ x time interaction	-.10	.05
NPIQ x time-sq interaction	-	-
Intercept	11.40	<.001
AIC: 5,227.05		
Model 3 (NPI-Q factor scores)		
Time in years	-12.52	<.001
Time-squared	-	-
Age (centered)	-.29	<.001
Sex	-	-
Education in years (centered)	-	-
Baseline MMSE	1.39	<.001

	BNT score	
	β	P
Age x time interaction	.15	.04
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	.41	.003
MMSE x time-sq interaction	-	-
Negative/Oppositional	-.19	.15
Anxiety/Restlessness	.18	.40
Negative/Oppositional x time interaction	.05	.52
Negative/Oppositional x time-sq interaction	-	-
Anxiety/Restlessness x time interaction	-.02	.87
Anxiety/Restlessness x time-sq interaction	-	-
Intercept	14.11	<.001
AIC: 5,038.93		

Table 36. Mixed effects models predicting rate of change in LM I score with NPI-Q change over time.

	LM I	
	β	p
Model 1		
Time in years	-.93	.03
Time-squared	-.04	.74
Intercept	7.57	<.001
AIC: 4,189.03		
Model 2		
Time in years	-.73	.34
Time-squared	-	-
Age (centered)	.01	.84
Sex	-.10	.82
Education in years (centered)	.12	.09
Baseline MMSE	.56	<.001
Age x time interaction	.001	.96
Age × time- sq interaction	-	-
Sex × time interaction	-.25	.49
Sex × time- sq interaction	-	-
Education × time interaction	-.04	.49
Education x time-sq interaction	-	-
MMSE x time interaction	-.03	.47
MMSE x time-sq interaction	-	-
Intercept	-3.21	<.001
AIC: 3,936.85		
Model 3 (Total NPI-Q score)		
Time in years	-1.20	<.001
Time-squared	-	-
Age (centered)	-	-
Sex	-	-
Education in years (centered)	.12	.07
Baseline MMSE	.50	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
NPIQ	-.06	.22
NPIQ x time interaction	-.01	.69
NPIQ x time-sq interaction	-	-
Intercept	-1.67	.075
AIC: 3,988.94		
Model 3 (NPI-Q factor scores)		
Time in years	-1.22	<.001
Time-squared	-	-
Age (centered)	-	-
Sex	-	-
Education in years (centered)	.13	.06

	LM I	
	β	p
Baseline MMSE	.50	<.001
Age x time interaction	-	-
Age × time- sq interaction	-	-
Sex × time interaction	-	-
Sex × time- sq interaction	-	-
Education × time interaction	-	-
Education x time-sq interaction	-	-
MMSE x time interaction	-	-
MMSE x time-sq interaction	-	-
Negative/Oppositional	-.06	.43
Anxiety/Restlessness	-.07	.56
Negative/Oppositional x time interaction	.02	.73
Negative/Oppositional x time-sq interaction	-	-
Anxiety/Restlessness x time interaction	-.05	.48
Anxiety/Restlessness x time-sq interaction	-	-
Intercept	-1.70	.07
AIC: 3,986.69		