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Neuropsychiatric Symptoms Predict Functional Status in Alzheimer's Disease

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Abstract

Background—Cognitive deficits are presumed to be the primary driver of functional impairment in Alzheimer's disease (AD); however, functional impairment is likely multifactorially determined.

Objective—Our objective was to determine the relative contribution of neuropsychiatric symptoms in predicting ratings of functional status.

Methods—A total of 223 patients received routine neurological and neuropsychological evaluations and met criteria of probable AD dementia based on the McKhann criteria. Demographic, cognitive, and neuropsychiatric variables were entered in a hierarchical linear regression analysis to predict functional status as measured by the Functional Activities Questionnaire (FAQ).

Results—The total model explained 29.7% of the variance ($p < 0.001$) in FAQ. Importantly, neuropsychiatric variables explained 12.7% of the unique variance, with apathy and sleep as significant contributors.

Conclusion—Two neuropsychiatric variables, apathy and changes in sleep/nighttime behaviors, predicted ratings of functional status in AD patients independent of age, global cognition, memory and executive function measures, and depressive symptoms. These results highlight the importance of neuropsychiatric symptoms in understanding and potentially treating the functional limitations so prevalent in AD.

Keywords

Alzheimer's disease; apathy; neuropsychology; sleep disorders

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INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia, affecting an estimated 35.6 million people worldwide in 2010 with the total number doubling every 20 years [1]. While deficits in executive functions, memory, and visuospatial abilities are typically associated with functional impairment in AD [2–7], functional status is likely multifactorially determined. Other factors that may influence reported decline in functional skills include neuropsychiatric symptoms and caregiver burden. The most frequent neuropsychiatric symptoms in patients with AD are apathy, anxiety, depression, irritability, and sleep disturbances [8]. For example, apathy has been strongly correlated with functional status [3, 9–13] and identified as a predictor of progression from mild cognitive impairment (MCI) to AD [14]. Other studies have found anxiety and behavioral disturbances, in conjunction with cognitive status, as prodromal markers for AD [15]. Problems with sleep are also associated with declines in cognitive and functional capacities [16, 17]. The major goal of AD treatment is to improve daily living skills, so understanding the determinants of independent functional status is vitally important. Functional status is defined as ability to independently complete typically universal activities among older adults. The purpose of the current study was to determine whether neuropsychiatric symptoms uniquely contribute to predicting ratings of functional status apart from cognition and, if so, identify these symptoms in probable AD patients.

MATERIALS AND METHODS

Subjects

This study included 223 patients seen at the UCSF Memory and Aging Center either through the clinic or the research program between 2000 and 2011. Written informed consent was obtained from each patient. Patients underwent routine neurological and neuropsychological evaluations, and additional information was gathered from a caregiver report. Data were collected from the first visit, which included Neuropsychiatric Inventory (NPI), Functional Activities Questionnaire (FAQ), Clinical Dementia Rating (CDR), and neuropsychological screening. Caregivers were identified by patients as someone who has known them for some time, knows them well, and sees them often. A cutoff score of greater than or equal to 11 on the Mini-Mental State Examination (MMSE) was utilized to ensure patients could adequately comprehend and answer questions on neuropsychological testing as scores less than 11 indicate severe dementia [18]. Patients included in this study met criteria of probable AD, based on the McKhann criteria [19], and the diagnosis of probable major neurocognitive disorder due to AD was made by a multidisciplinary consensus diagnostic team, including a neurologist and neuropsychologist. Other team members may have included a pharmacist, registered nurse, licensed clinical social worker, and genetic counselor. This study was approved by the UCSF Committee on Human Research.

Caregiver instruments

The NPI, FAQ, and CDR were administered to each patient's primary caregiver by nursing or counseling staff. The NPI examines 12 subdomains of behavioral and psychological symptoms: hallucinations, delusions, agitation, dysphoria, anxiety, irritability, disinhibition,

euphoria, apathy, aberrant motor behavior, sleep and nighttime behavior change, and eating change [20]. Changes in behavior were assessed since onset of illness. Each subdomain is evaluated for severity, frequency, total (severity × frequency), and distress to the caregiver. Severity is rated on a three-point scale from 1, mild, to 3, severe. Frequency is rated on a four-point scale as 1, rarely, to 4, very often. Caregiver distress is rated on a five-point scale from 0, not at all, to 5, very severely or extremely.

The FAQ evaluates performance of 10 typically universal activities among older adults [21]. Performance for each activity was rated on a four-point scale from 0, normal (independent), to 3, dependent. A total score of 9, with dependence in 3 or more activities, indicates impaired function and possible cognitive impairment.

The CDR is a semi-structured interview that rates impairment in six cognitive categories of memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care [22]. Each domain is rated on a five-point scale: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment. Personal care is scored on a 4-point scale without a 0.5 rating. CDR Sum of Boxes (CDR-SB) score is calculated by summing each of the individual domain scores, ranging from 0 to 18 and Global CDR is derived from all six domains, ranging from 0 to 3.

Neuropsychological assessment

Patients were administered routine neuropsychological screening as part of their multidisciplinary evaluation. For this study, the selected measures of interest assessed global cognition, verbal memory, executive functions, and depression, and were part of a larger battery given during neuropsychological evaluation. Global cognition was assessed by the MMSE, shown to be valid and reliable in populations with dementia and psychiatric disorders [23]. The MMSE is a brief screening tool that captures orientation, registration, attention, working memory, recall, language, and visuoconstruction skills. Verbal memory and learning was assessed using the California Verbal Learning Test-II Short Form (CVLT-SF) [24]. The executive function tasks used were Modified Trails, verbal fluency, digit span backward, and Stroop task [25]. Depression was assessed by the Geriatric Depression Scale (GDS), specifically designed for use in the elderly [26]. Other measures in the screening battery included tasks of nonverbal fluency, nonverbal memory, math, sequencing, word reading, verbal agility, repetition, picture vocabulary, verbal abstraction, visual confrontation naming, social cognition, and visual perception.

Measures of interest were selected based on available measures across patients in multiple ongoing longitudinal observational studies. These measures were entered into a factor analysis and generated two factors, interpreted as representing memory and executive functioning. The memory factor score comprised of CVLT-SF total correct across the learning trials, delayed recall correct, and delayed recognition (d prime). The executive function factor score was comprised of Modified Trails, D-words correct, backward digit span length, and number of correct responses on Stroop interference.

Statistical analysis

We were interested in examining whether neuropsychiatric symptoms have a unique contribution to ratings of functional status in probable AD. To assess the association between neuropsychiatric symptoms and ratings of functional status, Pearson's partial correlation analyses were performed between NPI subdomain total scores and FAQ Total, after adjusting for age and MMSE. Correlational analyses identified NPI subdomains for use as predictors in a hierarchical linear regression analysis. Demographic, cognitive, and neuropsychiatric variables were entered in three steps to better understand their relationship in predicting ratings of functional status, defined by FAQ Total score. In step 1, demographic and global cognition variables (gender, age, and MMSE total) were entered. In step 2, memory and executive function factor scores were entered to determine whether specific cognitive functions play a significant role in predicting ratings of functional status above and beyond the MMSE. In step 3, neuropsychiatric symptoms that were previously correlated with FAQ Total (total subdomain scores of anxiety, apathy, motor, and sleep) and GDS were entered to examine whether neuropsychiatric symptoms uniquely contribute to ratings of functional status in AD. GDS was entered in the third step to determine whether the neuropsychiatric symptoms that correlated with FAQ would predict FAQ independent of symptoms of depression. All statistical analyses were performed using IBM SPSS Statistics 21.0 for Mac (IBM Corp., Armonk, NY).

RESULTS

The patient sample included 103 males and 120 females, aged 70.2 years ± 11.1 and education level of 15.3 years ± 3.1 (mean ± SD). MMSE scores for our sample ranged from 12 (moderate cognitive impairment) to 29 (normal range), with mean score of 21.3 ± 4.5 (SD). Patients with high educational achievement, similar to that seen in our sample, were more likely to score within normal range on the MMSE despite significant memory impairment [27]. Caregiver report data are presented in Table 1, including NPI, FAQ, and CDR. CDR-SB scores ranged from 1 to 15.

Partial correlations for all 12 NPI subdomains with FAQ Total are presented in Table 2. NPI anxiety, apathy, motor, and sleep scores were significantly positively correlated with FAQ Total, meaning the more severe and frequent the neuropsychiatric symptom, the more dependent they were for performing general activities. The range for these four NPI subdomain scores was 1 to 12, the maximal possible score of severity and frequency of symptoms. The range of FAQ Total scores was 0 to 30. The range on GDS was 0 to 28, with a mean of 6.4 ± 5.1 (SD). Memory and Executive Functions Factor Scores are standardized to a mean of 0 and variance of 1 as they are latent variables composed of individual test scores. The mean and standard deviation of the individual tests contributing to each factor score are presented in Table 3.

The demographic, cognitive, and neuropsychiatric variables were entered in a hierarchical linear regression analysis to predict FAQ. In step one, Gender, Age, and MMSE explained 19.3% of the variance (F Change = 14.2; $p < 0.001$). Only MMSE significantly predicted FAQ score, $\beta = -0.4$, $t(182) = -6.3$, $p < 0.0001$. In step two, the memory and executive function factor scores were entered into the model, and there was no significant change from

the first model of 0.02% (F Change = 1.8; $p = 0.16$). In step three, entering GDS and NPI anxiety, apathy, motor, and sleep scores explained an additional 12.7% of FAQ variance (F Change = 6.6; $p < 0.001$). The specific NPI variables that significantly contributed to the unique variance in the third regression model were Apathy $\beta = -0.2$, $t(182) = 2.4$, $p = 0.017$ and Sleep and Nighttime Behavior Disorders $\beta = -0.2$, $t(182) = 2.8$, $p = 0.006$. Coefficient values for all variables in the regression model are presented in Table 4.

DISCUSSION

The main finding of this study is that two NPI variables, apathy and changes in sleep/nighttime behaviors, predict ratings on FAQ, a measure of functional status, in AD patients. Although apathy and changes in sleep can be related to depression, our results did not indicate that depressive symptoms predicted functional status as measured by the FAQ. The results suggest that these specific neuropsychiatric symptoms uniquely contributed to ratings of functional status independent of age, specific measures of memory and executive function, and depressive symptoms and highlight their possible role in functional status. Delusions and hallucinations have been observed to correlate with cognitive and functional decline in AD patients [28, 29]; however, the NPI subdomains of delusions or hallucinations did not significantly correlate with FAQ ratings in our sample. This may be due to only 8.5% of our sample classified as having moderate to severe dementia, with a CDR-SB score greater than 9 [30]. We found that anxiety, apathy, motor, and sleep scores correlated with ratings of functional status, but only apathy and sleep scores significantly contributed to the unique variance in the regression model.

Our results are consistent with previous studies that found correlations between apathy and functional status [9, 11–13] and between sleep and functional capacity [16, 17]. Apathy is commonly rated as a severe and frequent behavior on the NPI for individuals with AD [31] and strongly correlated to cognitive ability [32]. Elevated apathy at baseline has also been associated with decreasing functional status across the AD spectrum from normal controls to mild AD [33]. In a previous study examining neuropsychiatric and medical problems associated with functional status independent of cognitive difficulty, as defined by MMSE scores, patients with apathy were 3.5 times more likely to have difficulty independently completing activities of daily living compared to patients without apathy [10]. Only one other study used hierarchical regression analysis, but found apathy and executive function to independently contribute to instrumental activities of daily living [3]. Different measures may have led to conflicting results as apathy was assessed by the Frontal Systems Behavioral Inventory and executive function by the Initiation/Perseveration subscale of the Mattis Dementia Rating Scale. Our study adds to the literature in several ways. We separated symptoms of apathy from depressive symptoms using informant ratings, and parsed cognition into distinct, psychometrically robust measures of memory and executive function. In addition, we tested the unique contributions of neuropsychiatric symptoms using hierarchical linear regression that enabled us to fully control for cognition, in contrast to prior studies utilizing correlational analysis.

Changes in sleep are common in AD and have been described as one of the core non-cognitive symptoms in MCI, which may be a precursor to AD [34, 35]. Prior studies have

also associated higher frequency and severity of sleep disturbances with depression, disinhibition, or aberrant motor behavior [16]. In a previous study of AD patients with reported sleep disturbance on the NPI, better objective sleep was shown to be associated with better cognitive performance and functional status [36]. Further, objective measures of nighttime behaviors showed that greater sleep disturbance was again associated with impaired function in dementia [37]. The sleep disturbance captured by the NPI can describe any combination of nighttime agitation, insomnia, sleep disturbance, and/or daytime sleeping. Though the measure itself is not specific to the type of sleep disturbance, it has been shown that disturbed sleep, ranging from mild disturbances to more severe sleep disorders, can impair cognition, which in turn could impact functionality [38–42]. When controlling for cognition, sleep is still related to daily functioning. Therefore, though sleep disturbance may contribute to impaired cognition, our study indicates that the effect of reported sleep disturbance on patient function may be due to sleep-related factors independent of cognitive effects.

Additional directions for future research include measuring distress to caregiver to assess the impact of caregiver perception and distress, as discrepancies in caregiver versus clinician reports have been shown on the NPI for AD patients [43]. Differentiating symptoms of apathy from symptoms of depression and how they may independently affect functional status using instruments that focus solely on apathy, such as the Apathy Evaluation Scale, would provide further information regarding the type of apathy (behavioral, cognitive, or emotional) affecting functional status [8]. Similar elevations in neuropsychiatric symptoms of depression, sleep disturbance, and apathy were found in another study assessing patients with MCI and cerebrospinal fluid markers for AD [44]. Furthermore, cholinesterase inhibitors have been shown to improve behavioral and psychological symptoms in patients with AD [45], and psychotropic medication can certainly impact neuropsychiatric symptoms, cognition, and functioning [46]. This is a limitation of the current study, as results may have differed if medications of patients were included in analyses. Lastly, tracking the severity of AD and neuropathologic correlates as well as differentiating between neuropsychiatric symptoms will help us further understand the progression of AD and provide more sensitive, effective markers for clinical trials. Our study suggests that neuropsychiatric symptoms, in addition to cognitive factors, could be sensitive targets for clinical trials tracking longitudinal change.

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Table 1

Caregiver instrument scores

Measure	No. (%)	Mean (SD)
NPI Delusions		0.5 (1.6)
Any symptom (NPI > 0)	30 (13.8)	
NPI Hallucinations		0.07 (0.4)
Any symptom (NPI > 0)	11 (5.0)	
NPI Agitation/Aggression		1.1 (2.2)
Any symptom (NPI > 0)	62 (29)	
NPI Depression/Dysphoria		1.7 (2.7)
Any symptom (NPI > 0)	98 (46.9)	
NPI Anxiety		1.7 (2.7)
Any symptom (NPI > 0)	94 (44.5)	
NPI Elation/Euphoria		0.2 (1.2)
Any symptom (NPI > 0)	11 (5.0)	
NPI Apathy/Indifference		2.2 (3.1)
Any symptom (NPI > 0)	113 (50.7)	
NPI Disinhibition		0.4 (1.4)
Any symptom (NPI > 0)	35 (16.0)	
NPI Irritability/Lability		1.3 (2.4)
Any symptom (NPI > 0)	74 (34.4)	
NPI Aberrant motor behavior		1.1 (2.3)
Any symptom (NPI > 0)	49 (22.5)	
NPI Sleep and Nighttime Behavior Disorders		1.0 (2.1)
Any symptom (NPI > 0)	53 (25.0)	
NPI Appetite and Eating Disorders		1.4 (2.6)
Any symptom (NPI > 0)	68 (32.1)	
FAQ		15.2 (7.4)
CDR-SB		5.3 (2.7)
CDR Score		0.9 (0.5)
0.5	89 (40.5)	
1	108 (49.1)	
2	22 (10.0)	
3	1 (0.5)	

NPI subdomain scores represent Frequency × Severity.

Table 2

NPI subdomain correlations with FAQ

	Del	Hal	Ag	Dep	Anx*	Eup	Apth*	Dis	Irr	Mot*	Sle*	Eat
Correlation with FAQ	0.1	−0.04	0.1	0.08	0.2	0.04	0.3	0.1	0.05	0.2	0.3	0.1
p	0.06	0.6	0.1	0.3	0.01	0.6	0.00	0.04	0.5	0.01	0.00	0.3

* NPI subdomains included in multiple regression analysis with *p*-values ≤0.01.

Del, Delusions; Hal, Hallucinations; Ag, Agitation/Aggression; Dep, Depression/Dysphoria; Anx, Anxiety; Eup, Elation/Euphoria; Apth, Apathy/Indifference; Dis, Disinhibition; Irr, Irritability/Lability; Mot, Aberrant motor behavior; Sle, Sleep and Nighttime Behavior Disorders; Eat, Appetite and Eating Disorders.

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Table 3

Factor scores and contributing variables

Memory Factor Score Contributing Variables	Description of Score	Mean (SD)
CVLT-SF Total	Total number of words recalled across learning trials	15.4 (5.7)
CVLT-SF Recall	Total number of words recalled after 10 minute delay	1.4 (1.9)
CVLT-SF d prime	Recognition discriminability reflecting hit rate relative to false-positive rate	1.3 (0.9)
Executive Functions Factor Score Contributing Variables	**Description of Score**	**Mean (SD)**
Modified Trails	Seconds to complete modified Trails B	1.6 (0.9)
D-Words	Total number of D-words completed in one minute	9.2 (4.7)
Digit Span Backward	Longest digit span able to accurately recite backward	3.4 (1.0)
Stroop	Number of correct responses on Stroop interference	18.8 (12.8)

Scores represent mean (standard deviation). CVLT-SF, California Verbal Learning Test-II, Short Form.

Table 4

Coefficient values of variables in regression analysis in third model

Variable	B	Standard Error	β	*p*
Gender	0.4	0.9	0.03	0.6
Age	0.05	0.05	0.08	0.2
MMSE Total*	−0.6	0.1	−0.3	<0.01
Memory Factor Score	−0.7	0.6	−0.09	0.2
Executive Function Factor Score	−0.3	0.6	−0.04	0.7
Anxiety	0.3	0.2	0.1	0.1
Apathy/Indifference*	0.4	0.2	0.2	0.017
Aberrant motor behavior	0.2	0.2	0.06	0.4
Sleep and Nighttime Behavior Disorders*	0.6	0.2	0.2	0.006
GDS	−0.1	0.1	−0.1	0.2

* $p \leq 0.01$. B, unstandardized coefficient, β, standardized coefficient.