Iran J Psychiatry Behav Sci. 2022 December; 16(4):e126596. https://doi.org/10.5812/ijpbs-126596.

Published online 2022 December 18. **Research Article**

Prediction of Cognitive Decline by Behavioral Symptoms in Neuropsychiatric Disorders

Majid Barekatain [1], Sona Sadeghpour [1], Fatemeh Rajabi [1,*] and Mohammad Reza Maracy [2]

[1] Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Epidemiology & Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran

[*] *Corresponding author*: Isfahan University of Medical Sciences, Isfahan, Iran. Email: fara860@yahoo.com

Received 2022 April 19; **Revised** 2022 October 08; **Accepted** 2022 November 19.

Abstract

Background: Neuropsychiatric disorders are described by their neurological, behavioral, and cognitive symptoms. However, behavioral symptoms may often be overlooked due to the current approach in neurology.
Objectives: This study investigated the relationship between behavioral symptoms and cognitive functioning in neurological disorders. The second aim was to predict neurocognitive patterns by behavioral symptoms as independent variables.
Methods: Behavioral symptoms were collected based on semi-structured neuropsychiatric interviews with 211 patients admitted to the neuropsychiatry department of Ayatollah Kashani hospital in Isfahan by both a neuropsychiatry fellow and an attending neuropsychiatrist. A neuropsychiatry fellow assessed all patients using the neuropsychiatry unit cognitive (NUCog) assessment tool. We used a generalized linear model (GLM) to indicate the effect of behavioral symptoms on the risk of decline in cognitive domains. Due to the use of all available samples, this study had no age limit, and the patients were 15 to 92 years old.
Results: The regression coefficient of NUCog subscale scores for behavioral symptoms using GLM revealed that education level had a positive relationship with the scores of attention ($P < 0.001$), visuoconstruction ($P < 0.001$), memory ($P < 0.001$), executive function ($P < 0.001$), language ($P < 0.001$), and the total score of NUCog ($P < 0.001$). Patients with apathy had lower scores on the memory subscale ($P = 0.002$) and total NUCog ($P = 0.021$). Similarly, patients with delusion had lower scores on memory ($P = 0.006$) and executive function ($P = 0.026$). There was a negative relationship between agitation and attention ($P = 0.049$), visuoconstruction ($P = 0.015$), memory ($P = 0.018$), executive function ($P = 0.005$), and total score of NUCog ($P = 0.007$). Sleep disturbances were accompanied by lower memory scores ($P = 0.056$) and lower mean NUCog scores ($P = 0.052$). Visual hallucination was associated with declined performance in attention ($P = 0.057$).
Conclusions: Behavioral assessment can help predict cognitive patterns in patients with neurobehavioral syndromes.

Keywords: Attention, Behavior, Cognition, Executive Function, Neuropsychiatric Disorders, Neuropsychiatry, NUCog

1. Background

Behavioral symptoms result from many neurologic conditions, including cerebrovascular disease, frontotemporal dementia (FTD), and stroke, and determine the patient's future performance (1). The evidence shows that behavioral symptoms are prevalent in neurologic diseases and negatively affect patients' function, and in many cases, they are the patient's chief complaint (2). In dementia, considering different stages of the disease, neuropsychiatric symptoms such as depression, psychosis, restlessness, aggression, apathy, sleep disorders, and disinhibition are seen in more than 90% of cases (2). In some cases, neuropsychiatric representations become apparent even before dementia and increase the burden on the caregiver (3). They also cause several behavioral and interpersonal problems for the patient, along with the underlying disease (4). Regardless of cognitive problems, neuropsychiatric symptoms such as depression, apathy, irritability, mood lability, and sleep and eating problems are associated with impaired daily function in various types of dementia.

Alzheimer's disease (AD) is associated with agitation, irritability, and mood lability. Likewise, vascular dementia is seen in association with apathy (5). Idiopathic Parkinson's disease (PD) is also one of the most common neurodegenerative disorders known as motor disease, while a significant part of the disease burden is related to neuropsychiatric symptoms. The most common psychiatric symptom in PD is depression, which has a clinical prevalence of about 35%. Another important symptom is apathy, which leads to decreased activity. Approximately one-third of Parkinson's patients suffer from anxiety disorders. Al-

though different aspects of cognition are affected in this disease, neuropsychiatric manifestations also significantly impact the patient's performance and usually appear before other disease symptoms (6). Several sleep problems are associated with AD, including fragmentation of nocturnal sleep, insomnia, diurnal drowsiness, and circadian rhythm sleep disorder (7). Psychiatric problems such as depression, anxiety, and irritability are common in patients with Huntington's disease (HD); in most cases, they precede movement symptoms (8) .In many cases, the association of brain pathology with cognitive problems has been established. Attention and memory problems could be considered the symptoms of subcortical pathology. Regarding the findings of imaging studies, brain atrophy is the most stable finding for cognitive decline in patients with multiple sclerosis (MS) (9, 10).

Likewise, some studies have shown a significant relationship between brain pathology and neuropsychiatric symptoms. MRI revealed an association between right frontal lobe atrophy and anxiety score in MS. Depressive disorders are more common in MS with lesions in the left arcuate fasciculus, prefrontal cortex, anterior temporal lobe, and parietal lobe (9).

Some behavioral symptoms may have predictive values for neurological disorders and cognitive dysfunction; for example, impulse control disorders, which constitute a wide range of presentations, are very common in PD and are associated with executive dysfunction and impaired visuospatial capacity (11). Moreover, the presence of REM sleep behavioral disorder in PD predicts mild cognitive impairment (12). In PD, apathy is associated with executive dysfunction. Moreover, apathy is related to the evaluated level of cortical amyloidopathy. Regardless of diagnosis, lesions in frontostriatal pathways, orbitofrontal cortex, ventral pallidum, and ventral tegmental area are underlying joint mechanisms of cognitive decline and apathy syndrome (13). The lesions of the prefrontal subcortical limbic regions are among the first complications of Alzheimer's disease. Depression, anxiety, irritability, aggression, apathy, vegetative symptoms, motor restlessness, hallucinations, and delusions all reflect this (3). Elderly depression is considered a prodrome of dementia and has a significant role in developing persistent cognitive disabilities. The above-mentioned problem has been linked to an increased risk of dementia, including PD and AD.

Evidence shows depressive symptoms may result in the progression of mild cognitive impairment to dementia (14). So far, several studies have investigated the relationship between behavioral symptoms and cognitive problems. In most of these studies, the aim was to assess the overall cognitive function, while the patient's performance in different cognitive domains has not been comprehensively studied. In previous studies, a limited range of behavioral symptoms has been considered simultaneously. Although there is a complex two-way association between cognitive changes and neuropsychiatric symptoms, behavioral symptoms are often considered a consequence of cognitive disorders, and their role as a precedent to cognitive disorders is ignored. In addition, some studies have sought to link behavioral symptoms to lesions in specific areas of the brain.

2. Objectives

In the present study, we aimed to indicate whether neuropsychiatric symptoms could predict concomitant cognitive impairments in patients with neurological disorders.

3. Methods

3.1. Study Design and Conduct

We performed a retrospective review of the medical records of 220 patients with neuropsychiatric disorders. This descriptive-analytical study was conducted at Ayatollah Kashani hospital in Isfahan, Iran.

3.2. Patient Population

Data used in the preparation of this article were obtained from the Ayatollah Kashani hospital database. Patients with cognitive complaints admitted to the neuropsychiatry unit of Ayatollah Kashani hospital from September 1, 2018, to August 31, 2020, were included in the study. A total of 220 hospitalized patients were included in the screening.

By evaluating patients' medical records, a neuropsychiatrist screened all 220 patient records. Patients with malingering diagnoses and those unable to perform neuropsychological tests were excluded from the study. Based on the inclusion and exclusion criteria, all eligible patient records were included, indicating that 211 patient records were finally recruited for this study.

3.3. Baseline Characteristics

First, the background data on age, education, gender, and handedness were collected according to medical records. Education was calculated as the maximum level achieved.

3.4. Behavioral Assessment

Detailed information about the patient's subjective experiences and objective behavior was collected from medical records based on the history, semi-structured clinical interviews, and discharge reports. History was obtained and documented through semi-structured interviews by the neuropsychiatry fellow and the attending neuropsychiatrist; clinical neuropsychiatric evaluation was performed and documented by the same fellow and attending neuropsychiatrist.

The following clinical symptoms were determined and recorded: Apathy, disinhibition, irritability, agitation, aggression, delusion, visual hallucination, auditory hallucination, other hallucinations, anxiety, depressed mood, talkativity, movement symptoms, and sleep-wake cycle disturbances.

3.5. Neuropsychological Assessments

The neuropsychiatry unit cognitive (NUCog) assessment tool was used to assess the cognitive function of all 211 patients. It consists of five subscales to assess cognitive domains: Attention, visuospatial, memory, executive function, and language. The maximum score for each domain is 20, and the maximum total score is 100 (15) .The NUCog tool is valid and reliable for the diagnosis of dementia. It is a quick bedside tool used by various specialists. The NUCog can identify patients with dementia at early stages when other tests, such as MMSE, are not sensitive enough to make the distinction. At a cut-off score of 80/100, the sensitivity of NUCog for distinguishing patients with dementia was 0.84, with a specificity of 0.86 (16). The Persian version of NUCog reliably differentiates the healthy group from patients with mild neurocognitive disorders (at 86.5/100 with a sensitivity of 83.3% and specificity of 87.5%) and patients with Alzheimer's dementia from a healthy group (at 75/100 with a sensitivity and specificity of 100%) (15).

3.6. Statically Analysis

Statistical analyses were performed in SPSS version 20. A comparison of cognitive scores between the two groups was made using a *t*-test concerning the presence of each behavioral/motor symptom.

The sample size was small, so we used the Shapiro-Wilk test to assess the normality of cognitive variables. The P-value for each cognitive domain was less than 0.05, so we concluded that the cognitive variables were not normally distributed. Therefore, we had to use a non-parametric version of the test, which does not assume normality. With this in mind, the Gamma distribution was used.

We used a generalized linear model to identify whether neuropsychiatric symptoms are associated with an increased risk of cognitive decline, both in general and subgroups of cognitive domains. A P-value of less than 0.05 was taken as significant.

4. Results

We enrolled 211 patients in the study. Descriptive statistics were used to describe the study population's demographic data, behavioral symptoms, and cognitive function.

Table 1 demonstrates the demographic characteristics. We found that 34.6% (n = 73) of the patients had 12 years of education, 21.5% (n = 45) had five years of education, and 12.8% (n = 27) had eight years of education. Moreover, 9% (n =19) of them were illiterate. Table 2 shows behavioral/motor symptoms. The prevalence of at least one motor/behavioral symptom in the participants was 100%.

Table 1. Demographic Characteristics of the Study Population [a]

Variables	Values
Gender	
Male	99 (46.9)
Female	112 (53.1)
Handedness	
Right-handed	201 (95.3)
Left-handed	10 (4.7)
Age	52.25 ± 16.87
Years of education	9.39 ± 4.84

[a] Values are expressed as mean ± SD or No. (%).

All details in the cognitive domains are shown in Table 3.

We also used the Shapiro-Wilk test to assess the normality of cognitive variables, showing that the distribution of cognitive variables departed significantly from normality.

The results of regression coefficients (mean difference) of NUCog subscales for clinical symptoms of patients using a generalized linear model (GLM) with gamma distribution and link function log are demonstrated in Table 4.

The correlations of total cognitive scores with behavioral/motor symptoms are demonstrated in Table 5. The cognitive scores were included as the dependent variables. Behavioral/motor symptoms were predictors of cognitive ability. All results were obtained after controlling for age, gender, education, and handedness.

Table 2. Behavioral/Motor Variables of the Study Population

Variables	No. (%)
Amotivation	63 (29.9)
Apathy	41 (19.4)
Disinhibition	95 (45)
Irritability	64 (30.3)
Aggression	45 (21.3)
Agitation	20 (9.5)
Auditory hallucination	6 (2.8)
Visual hallucination	14 (6.6)
Other hallucinations	1 (0.5)
Delusion	37 (17.5)
Sleep disturbance	69 (32.7)
Anxiety	80 (37.9)
Depression	38 (18)
Talkativeness	20 (9.5)
Movement abnormality	69 (32.7)

Table 3. Cognitive Parameters of the Study Population (NUCog Mean Score and Subscores)

Variables	N	Minimum-Maximum	Mean ± SD
Attention	211	0 - 20	9.960 ± 4.8897
Visuoconstruction	211	5 - 20	13.794 ± 3.7371
Memory	211	0 - 20	10.682 ± 4.4648
Executive function	211	0 - 20	10.908 ± 5.0934
Language	211	2 - 20	16.618 ± 3.2470
NUCog total	211	10 - 99	61.931 ± 19.1583

Table 4. Regression Coefficients (Mean Difference) of NUCog Total Score for Clinical Symptoms of Patients Using Generalized Linear Model (GLM) with Gamma Distribution and Link Function Log (n = 211)

Variables	NUCog	
	Mean Difference (95%CI)	P-Value
Gender/male (female ref.)	-0.003 (-0.086 - 0.079)	0.935
Age/year	-0.002 (-0.005 - 0.000)	0.064
Education/year	0.035 (0.026 - 0.044)	< 0.001
Handedness/right (left ref.)	0.006 (-0.179 - 0.190)	0.952
Amotivation/no (yes ref.)	0.017 (-0.069 - 0.103)	0.695
Apathy/no (yes ref.)	0.131 (0.019 - 0.243)	0.021
Disinhibition/no (yes ref.)	0.023 (-0.064 - 0.111)	0.500
Irritability/no (yes ref.)	-0.008 (-0.106 - 0.090)	0.874
Aggression/no (yes ref.)	0.038 (-0.066 - 0.143)	0.469
Agitation/no (yes ref.)	0.182 (0.050 - 0.314)	0.007
Hallucination/no (yes ref.)	-0.103 (-0.667 - 0.461)	0.721
Visual hallucination/no (yes ref.)	0.059 (-0.106 - 0.225)	0.481
Delusion/no (yes ref.)	0.082 (-0.030 - 0.194)	0.150
Sleep disorder/no (yes ref.)	0.084 (-0.169 - 0.001)	0.052
Anxiety/no (yes ref.)	0.043 (-0.134 - 0.047)	0.348
Depressed mood/no (yes ref.)	0.011 (-0.119 - 0.097)	0.839
Talkativeness/no (yes ref.)	-0.030 (-0.171 - 0.111)	0.677
Movement/no (yes ref.)	-0.001 (-0.083 - 0.081)	0.984

5. Discussion

This cross-sectional study investigated the ability of neuropsychiatric symptoms to predict concomitant cognitive impairments in patients with neurological disorders. Considering clinical symptoms, there was a statistically significant negative association between sleep disturbance, agitation, and apathy and the total score of the NUCog.

In addition, the score of the NUCog's memory subscale was correlated negatively with sleep symptoms, apathy, agitation, and delusion. We also found that visual hallucination had a significant negative association with the score of the attention subscale. Delusion and agitation were also associated with lower scores of executive function. In addition, agitation had a negative correlation with the language subscale score.

The neuropsychiatric symptoms of dementia were previously considered a complication of severe dementia and labeled as "behavioral and psychological symptoms of dementia." However, neuropsychiatric symptoms are inevitable in dementia, which may appear at any stage of the disease. One study reported that apathy is a harbinger of cognitive decline in the early stages of HD (17). This finding is consistent with our study, suggesting that behavioral symptoms are not exclusive for late-stage dementia. Although the prevalence and severity of behavioral problems increase with the increasing severity of cognitive disease, sometimes even in cases of mild cognitive impairment, depression and apathy are among the most common problems of the patient (18). In patients with language variant FTD, the inability to convey their mental concepts may lead to agitation even in the early stage. Amotivation in patients with the behavioral type of FTD may result from working memory deficits. These findings confirm the traditional belief that cognitive decline precedes behavioral symptoms (19). Apathy is associated with high levels of dysfunction in daily activities and is one of the symptoms of frontal lobe dysfunction in patients with AD and PD, so it acts as a prelude to cognitive impairment (20). Negative symptoms such as decreased emotional experience, poverty of speech, isolation, and abulia are associ-

Table 5. Regression Coefficient (Mean Difference) of NUCog Subscales for Clinical Symptoms of Patients Using Generalized Linear Model (GLM) with Gamma Distribution and Link Function Log (n = 211)

Variables	Attention		Visuoconstruction		Memory		Executive Function		Language	
	Mean Difference (95%CI)	P-Value	Mean Difference (95%CI)	P-Value	Mean Difference (95%CI)	P-Value	Mean Difference (95%CI)	P-Value	Mean Difference (95%CI)	P-Value
Gender/male (female ref.)	0.03 (-0.09 - 0.16)	0.625	0.04 (-0.03 - 0.11)	0.189	0.02 (-0.09 - 0.13)	0.738	-0.06 (-0.19 - 0.08)	0.402	-0.03 (-0.09 - 0.04)	0.413
Age/year	-0.001 (-0.005 - 0.003)	0.431	-0.002 (-0.004 - 0.001)	0.157	-0.004 (-0.08 - -0.001)	0.023	-0.005 (-0.01 - 0.0)	0.036	-0.001 (-0.003 - 0.001)	0.245
Education/year	0.06 (0.01-0.05)	< 0.001	0.031 (0.024 - 0.039)	< 0.001	-0.04 (0.03 (0.05)	< 0.001	0.04 (0.03 - 0.05)	< 0.001	0.02 (0.01 - 0.03)	< 0.001
Handedness/right (left ref.)	0.07 (-0.37 - 0.21)	0.517	-0.03 (-0.19 - 0.12)	0.708	-0.03 (-0.28 - 0.22)	0.830	0.22 (-0.09 - 0.53)	0.164	0.02 (-0.12 - 0.16)	0.774
Amotivation/no (yes ref.)	-0.01 (-0.15 - 0.12)	0.853	0.01 (-0.06 - 0.08)	0.769	0.07 (-0.04 - 0.19)	0.202	0.03 (-0.12 - 0.17)	0.706	-0.02 (-0.08 - 0.05)	0.557
Apathy/no (yes ref.)	0.16 (-0.02 - 0.34)	0.081	0.04 (-0.05 - 0.14)	0.378	0.24 (0.09 - 0.39)	0.002	0.13 (-0.06 - 0.32)	0.168	0.05 (-0.03 - 0.14)	0.214
Disinhibition/no (yes ref.)	0.07 (-0.07 - 0.21)	0.279	0.005 (-0.07 - 0.08)	0.885	0.07 (-0.05 - 0.19)	0.247	0.01 (-0.13 - 0.16)	0.856	-0.002 (-0.07 - 0.06)	0.962
Irritability/no (yes ref.)	-0.04 (-0.20 - 0.11)	0.519	0.001 (-0.08 - 0.08)	0.974	0.04 (-0.09 - 0.17)	0.601	0.001 (-0.16 - 0.16)	0.988	-0.03 (-0.10 - 0.05)	0.477
Aggression/no (yes ref.)	0.09 (-0.07 - 0.26)	0.183	0.03 (-0.06 - 0.11)	0.589	-0.02 (-0.16 - 0.13)	0.825	0.05 (-0.22 - 0.13)	0.605	0.05 (-0.03 - 0.13)	0.200
Agitation/no (yes ref.)	0.25 (0.03 - 0.45)	0.049	0.15 (0.04 - 0.26)	0.015	0.22 (0.04 - 0.40)	0.018	0.32 (0.09 - 0.54)	0.005	0.05 (-0.05 - 0.14)	0.366
Hallucination/no (yes ref.)	0.69 (-0.19 - 10.5)	0.123	0.12 (-0.39 - 0.57)	0.120	-0.49 (-10.2 - 0.26)	0.200	-0.72 (-0.17 - 0.22)	0.134	0.17 (-0.25 - 0.59)	0.430
Visual hallucination/no (yes ref.)	0.23 (-0.04 - 0.48)	0.057	0.01 (-0.13 - 0.15)	0.831	0.13 (-0.09 - 0.35)	0.247	0.02 (-0.29 - 0.26)	0.901	-0.01 (-0.13 - 0.12)	0.952
Delusion/no (yes ref.)	0.05 (-0.12 - 0.22)	0.536	0.08 (-0.02 - 0.18)	0.128	0.21 (0.06 - 0.36)	0.006	0.21 (0.03 - 0.40)	0.026	-0.02 (-0.09 - 0.07)	0.733
Sleep disorder/no (yes ref.)	-0.11 (-0.25 - 0.02)	0.080	-0.01 (-0.23 - 0.19)	0.916	-0.11 (-0.23 - 0.003)	0.056	-0.13 (-0.27 - 0.02)	0.086	-0.04 (-0.10 - 0.02)	0.227
Anxiety/no (yes ref.)	-0.15 (-0.29 - -0.01)	0.024	-0.01 (-0.09 - 0.06)	0.698	-0.03 (-0.15 - 0.09)	0.692	-0.06 (-0.21 - 0.09)	0.421	-0.04 (-0.11 - 0.03)	0.261
Depressed mood/no (yes ref.)	-0.01 (-0.16 - 0.18)	0.853	-0.03 (-0.13 - 0.06)	0.321	-0.04 (-0.11 - 0.18)	0.637	-0.03 (-0.21 - 0.15)	0.765	-0.02 (-0.10 - 0.06)	0.623
Talkativeness/no (yes ref.)	-0.05 (-0.27 - 0.17)	0.641	0.00 (-0.12 - 0.12)	0.994	-0.06 (-0.25 - 0.13)	0.549	-0.04 (-0.27 - 0.19)	0.761	-0.01 (-0.12 - 0.09)	0.796
Movement disorder/no (yes ref.)	0.04 (-0.09 - 0.17)	0.495	0.002 (-0.07 - 0.07)	0.948	0.004 (-0.11 - 0.12)	0.940	0.006 (0.13 - 0.14)	0.927	-0.01 (-0.07 - 0.05)	0.827

ated with executive function deficits. Aggression, including self-injurious behavior, as a positive symptom, is also associated with executive dysfunction (21). This shows that cognitive decline does not always occur first; sometimes, both occur together. On the other hand, behavioral symptoms accompanying cognitive problems could be considered a coping strategy for patients' adaptation to reduced mental ability. For example, patients with AD may use persecutory delusion as a compensatory mechanism to explain the reason for lost objects (due to gaps of memory that lead to misplacement) (22).

One study revealed a strong relationship between prospective memory loss and apathy, with control of global cognitive functioning, working memory, and processing speed (23). The evolving apathy may also be an adaptive mechanism administered to redistribute limited cognitive resources to overwhelming environmental stimuli; meanwhile, agitation emerges when this compensatory mechanism is not used (24). Neuroimaging investigations also revealed the co-occurrence of behavioral symptoms and neuroanatomical changes in patients with neurological disorders. Psychotic features have been repeatedly reported with increased beta-amyloid plaques in the cerebral cortex, especially in the pre-subiculum area, decreased neurons in the CA1 hippocampus and parahippocampal gyrus, and high levels of neurofibrillary tangles in the middle frontal cortex. Neuroimaging in Alzheimer's disease also demonstrated an association between apathy and hypometabolism in the anterior cingulate gyrus and orbitofrontal areas. The increased load of neurofibrillary tangles in the orbitofrontal cortex and decreased number of neurons in the locus coeruleus were associated with agitation and aggression, respectively (25). It can be said that the relationship between behavioral symptoms and specific locations in the brain has a proven role in the cognitive process. The relationship between cognitive decline and behavioral symptoms is beyond the cause-and-effect relationship; they may predict each other, which is in line with our findings. Moreover, the connection between apathy and dementia has been shown in AD. Apathy

and frontal dysfunction, especially anterior cingulate cortex (ACC) abnormalities, are seen at the same time (26).

The relationship between sleep disorders and Alzheimer's disease is multidimensional, and the interaction between sleep and Aβ plays an important role. Sleep disorders increase Aβ production and decrease Aβ removal. On the other hand, when Aβ accumulates, sleep disturbances increase (27). In the present study, a negative correlation between sleep disorders and performance in memory tasks was reported. This is in line with previous studies that reported sleep, memory, and CSF AD biomarkers were closely interrelated with dementia progression since the disease's asymptomatic and preclinical early stages (28). Persistent short sleep duration at ages 50, 60, and 70 compared to persistent normal sleep duration was also associated with a 30% increased dementia risk independently of sociodemographic, behavioral, cardiometabolic, and mental health factors (29). Therefore, AD as a proteinopathy and sleep disturbance as a homeostatic-refreshing process would predict one another. Confirming this principle, in the present study, the generalized linear model enabled us to predict cognitive ability in the presence of sleep problems.

In mild cognitive impairment, amyloid deposition is related to decreased sleep quality and satisfaction, although there is no reduction in the quantity of sleep (30). Nevertheless, even a mere decrease in sleep quality increases Aβ accumulation in the precuneus (31). On the other hand, decreased quantity of nocturnal sleep leads to elevated Aβ levels in the right hippocampus and thalamus in healthy older adults (32).

Tau pathology, another underlying mechanism in Alzheimer's disease, is associated with sleep disorders. Abnormal tau accumulation in the brainstem, thalamus, hypothalamus, midbrain, and basal forebrain, which are related to sleep regulation, occurs even before cortical amyloid proteinopathy or cortical tauopathy (33). Moreover, it has been shown that the level of interstitial fluid tau depends on the sleep-wake cycle, and CSF tau is correlated with sleep deprivation (34). Therefore, tau pathology has a pivotal role in sleep disturbance in AD (35). Even before the onset of cortical symptoms, sleep problems can be an early indicator of tauopathy, and since tauopathy is the most critical proteinopathy in Alzheimer's disease, sleep disturbances can be a predictor of cognitive problems, especially memory dysfunction. The power of this prediction increases when PET scans also show tauopathy in noncortical regions. The level of orexin, known for its crucial role in sleep-wake cycle regulation, arousal, and appetite, is increased in advanced Alzheimer's disease, which is closely related to tau protein levels (36). Since one of the most important features of AD is memory dysfunction, the increase in the orexin level in CSF is also evidence of the association between sleep regulation and cognitive performance, especially in the memory domain.

Asymmetric atrophy, especially in the right temporal and left frontal lobes, right hippocampus, and right parietal cortex, was reported in patients with delusional features in primary psychiatric disorders (37, 38). On the other hand, delusions in AD were associated with high levels of pre-subiculum neurofibrillary tangles, increased plaques, and decreased neuronal counts in the CA1 area of the hippocampus (39). Considering the cognitive function of these areas, the association of delusion with memory and executive dysfunction seems logical. In fact, our result in this study is in line with previous studies.

Pro-inflammatory cytokines induce the main symptoms of major mental disorders such as delusions of schizophrenia. Increased serum concentrations of IL-2, IL-6, and IL-8 have been reported in schizophrenia or elevated IL-1β levels in the CSF of schizophrenic patients (40). Limbic structures like the hippocampus have an essential role in memory and also contain more enzymes involved in an inflammatory response than other areas of the brain; these areas may incur the risk of damage from inflammation (41). The association of inflammatory factors with both delusions and memory problems can confirm the findings of our study.

There was lower metabolic activity in the left inferior parietal lobule in patients with multiple delusions than in those with only one type of delusion; hence parietal hypometabolism is associated with more advanced cognitive deficits in AD. It can be said that more delusions predict more cognitive deficits in AD (42). Therefore, memory impairment, the most important cognitive problem in AD, can be associated with delusions.

The presence of hallucinations, especially visual and auditory, has been shown to increase cognitive decline (43). The relationship between cognitive impairment and visual hallucinations in PD is bidirectional. Visual hallucinations may precede cognitive decline or, in the presence of dementia, lead to faster decline. Even hallucinations in patients with PD who do not have cognitive problems are associated with executive impairments, and poorer sustained attention, and visuospatial dysfunction (44). One of the most critical problems of AD is aggression, which is especially troublesome for their caregivers and leads to a poor functional state in patients. Common concepts are often used for agitation and aggression, including wandering, restlessness, and other disorganized behavior. Since the prefrontal cortex, hippocampus, and ACC play an essential role in the aggression-related circuit, the components of this circuit are probably crucial in agitation (45). Therefore, similar to our findings, various cog-

nitive deficits related to these areas of the brain can be expected in patients with agitation.

Agitation in patients with dementia is associated with structural and functional deficits in the hippocampus, posterior cingulate gyrus, anterior cingulate gyrus, insula, amygdala, and frontal areas. Volume loss in these areas results in agitation (46). SPECT studies confirmed the association between agitation and hypo-perfusion in the left anterior temporal, right parietal, and bilateral dorsal frontal cortex (47). Other functional neuroimaging studies show that agitation is associated with cingulate hypometabolism (48). Clinico-pathological studies indicate that the interactions of the dorsolateral prefrontal cortex, orbitofrontal cortex, and ACC with the sensory cortex, amygdala, and medial temporal regions have the leading role in mood regulation. Lesions in these regions lead to aggression and agitation (49). These findings may explain the association between cognitive decline and agitation.

The presence of agitation is associated with lower scores on executive performance. Neuropathologically, agitation is associated with neurofibrillary tangles deposition in the orbitofrontal cortex and ACC. In addition, patients with Alzheimer's type dementia are more likely to be agitated in the presence of frontal and temporal lobe hypometabolism (50). Given the role of ACC in attention and the role of the temporal lobe in memory, it seems to be a persuasive argument for the association between agitation and cognitive domains such as attention and memory.

Therefore, our study showed that the symptoms of apathy, agitation, delusion, visual hallucinations and sleep disturbances significantly increase the likelihood of cognitive deficits in patients with neurological disorders.

5.1. Limitations and Strengths

The present study had several strengths. Unlike previous studies that assessed the relationship of a limited number of behavioral symptoms with only one or two cognitive domains, we evaluated the association of a wide range of behavioral symptoms with five cognitive domains. Previous studies have been performed on specific diseases such as AD and MS, while we examined the relationship between these variables regardless of clinical diagnosis. We used GLM, and therefore, our results can be used to predict cognitive disturbances. The main limitation of our study is cross-sectional analysis. Future studies should conduct longitudinal research to discover the cause-and-effect relationship between neuropsychiatric symptoms and cognitive decline. All data were collected from patient's medical records at a tertiary referral hospital, so the sample may not represent patients with neurodegenerative disorders in the community. Our study had a small sample size. The authors suggest that future studies use large samples and complementary cognitive assessment tools.

5.2. Conclusions

According to our results, apathy, agitation, delusion, visual hallucination, and sleep disturbances are correlated with cognitive decline in various domains. The present findings indicate the power of behavioral symptoms for predicting cognitive patterns in evaluating neurological disorders. The results suggest using behavioral assessment to predict cognitive disturbance with considerable predictive ability. These symptoms may reflect neuronal loss and degenerative alterations caused by various neuropathological processes.

Footnotes

Authors' Contribution: Study concept and design: F. R. and M. B.; abstraction of data: S. SR.; data analysis and interpretation: S. SR. and MR. M.; drafting of the manuscript: F. R.; critical revision of the manuscript for important intellectual content: M. B., S. SR., and F. R.; re-analyzation of the clinical and statistical data: MR. M.; study supervision: F. R.

Conflict of Interests: We declare that two of our authors (Fatemeh Rajabi, corresponding author) (Mohammad Maracy, data analyst) are members of the editorial board. The journal confirmed that the mentioned authors with CoI were completely excluded from all review processes. We also introduced these authors with CoI during the submission as an opposed reviewer."

Ethical Approval: This study is approved under the ethical approval code of IR.MUI.MED.REC.1400.142. (Webpage of the ethical approval code is: ethics.research.ac.ir/IR.MUI.MED.REC.1400.142).

Funding/Support: This study is partially supported by the financial resources of Isfahan University of Medical Sciences (thesis number: 340075). Link: ethics.research.ac.ir/PortalCommittee.php?code=IR.MUI.MED.REC.

Informed Consent: As patients' identification information remained confidential and no intervention was made on patients, the requirement for written or verbal consent from the patients was waived.

References

1. Butler C, Zeman AZ. Neurological syndromes which can be mistaken for psychiatric conditions. *J Neurol Neurosurg Psychiatry*. 2005;**76 Suppl 1**(Suppl 1):i31–8. [PubMed ID: 15718219]. [PubMed Central ID: PMC1765684]. https://doi.org/10.1136/jnnp.2004.060459.

2. Tiel C, Sudo FK, Calmon AB. Neuropsychiatric symptoms and executive function impairments in Alzheimer's disease and vascular dementia: The role of subcortical circuits. *Dement Neuropsychol*. 2019;**13**(3):293–8. [PubMed ID: 31555401]. [PubMed Central ID: PMC6753905]. https://doi.org/10.1590/1980-57642018dn13-030005.
3. Jicha GA, Carr SA. Conceptual evolution in Alzheimer's disease: implications for understanding the clinical phenotype of progressive neurodegenerative disease. *J Alzheimers Dis*. 2010;**19**(1):253–72. [PubMed ID: 20061643]. [PubMed Central ID: PMC2881218]. https://doi.org/10.3233/JAD-2010-1237.
4. Phan SV, Osae S, Morgan JC, Inyang M, Fagan SC. Neuropsychiatric Symptoms in Dementia: Considerations for Pharmacotherapy in the USA. *Drugs R D*. 2019;**19**(2):93–115. [PubMed ID: 31098864]. [PubMed Central ID: PMC6544588]. https://doi.org/10.1007/s40268-019-0272-1.
5. D'Onofrio G, Sancarlo D, Panza F, Copetti M, Cascavilla L, Paris F, et al. Neuropsychiatric symptoms and functional status in Alzheimer's disease and vascular dementia patients. *Curr Alzheimer Res*. 2012;**9**(6):759–71. [PubMed ID: 22715983]. https://doi.org/10.2174/156720512801322582.
6. Jones S, Torsney KM, Scourfield L, Berryman K, Henderson EJ. Neuropsychiatric symptoms in Parkinson's disease: aetiology, diagnosis and treatment. *BJPsych Adv*. 2020;**26**(6):333–42. https://doi.org/10.1192/bja.2019.79.
7. Hinton EC, Parkinson JA, Holland AJ, Arana FS, Roberts AC, Owen AM. Neural contributions to the motivational control of appetite in humans. *Eur J Neurosci*. 2004;**20**(5):1411–8. [PubMed ID: 15341613]. https://doi.org/10.1111/j.1460-9568.2004.03589.x.
8. Pla P, Orvoen S, Saudou F, David DJ, Humbert S. Mood disorders in Huntington's disease: from behavior to cellular and molecular mechanisms. *Front Behav Neurosci*. 2014;**8**:135. [PubMed ID: 24795586]. [PubMed Central ID: PMC4005937]. https://doi.org/10.3389/fnbeh.2014.00135.
9. Silveira C, Guedes R, Maia D, Curral R, Coelho R. Neuropsychiatric Symptoms of Multiple Sclerosis: State of the Art. *Psychiatry Investig*. 2019;**16**(12):877–88. [PubMed ID: 31805761]. [PubMed Central ID: PMC6933139]. https://doi.org/10.30773/pi.2019.0106.
10. Ehrenberg AJ, Suemoto CK, Franca Resende EP, Petersen C, Leite REP, Rodriguez RD, et al. Neuropathologic Correlates of Psychiatric Symptoms in Alzheimer's Disease. *J Alzheimers Dis*. 2018;**66**(1):115–26. [PubMed ID: 30223398]. [PubMed Central ID: PMC6381997]. https://doi.org/10.3233/JAD-180688.
11. Vitale C, Santangelo G, Trojano L, Verde F, Rocco M, Grossi D, et al. Comparative neuropsychological profile of pathological gambling, hypersexuality, and compulsive eating in Parkinson's disease. *Mov Disord*. 2011;**26**(5):830–6. [PubMed ID: 21370268]. https://doi.org/10.1002/mds.23567.
12. Gagnon JF, Vendette M, Postuma RB, Desjardins C, Massicotte-Marquez J, Panisset M, et al. Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. *Ann Neurol*. 2009;**66**(1):39–47. [PubMed ID: 19670440]. https://doi.org/10.1002/ana.21680.
13. Martin GP, McDonald KR, Allsop D, Diggle PJ, Leroi I. Apathy as a behavioural marker of cognitive impairment in Parkinson's disease: a longitudinal analysis. *J Neurol*. 2020;**267**(1):214–27. [PubMed ID: 31616991]. [PubMed Central ID: PMC6954881]. https://doi.org/10.1007/s00415-019-09538-z.
14. Muhammad T, Meher T. Association of late-life depression with cognitive impairment: evidence from a cross-sectional study among older adults in India. *BMC Geriatr*. 2021;**21**(1):364. [PubMed ID: 34130632]. [PubMed Central ID: PMC8204463]. https://doi.org/10.1186/s12877-021-02314-7.
15. Barekatain M, Walterfang M, Behdad M, Tavakkoli M, Mahvari J, Maracy MR, et al. Validity and reliability of the Persian language version of the neuropsychiatry unit cognitive assessment tool. *Dement Geriatr Cogn Disord*. 2010;**29**(6):516–22. [PubMed ID: 20523051]. https://doi.org/10.1159/000313981.
16. Walterfang M, Siu R, Velakoulis D. The NUCOG: validity and reliability of a brief cognitive screening tool in neuropsychiatric patients. *Aust N Z J Psychiatry*. 2006;**40**(11-12):995–1002. [PubMed ID: 17054568]. https://doi.org/10.1080/j.1440-1614.2006.01923.x.
17. Andrews SC, Langbehn DR, Craufurd D, Durr A, Leavitt BR, Roos RA, et al. Apathy predicts rate of cognitive decline over 24 months in premanifest Huntington's disease. *Psychol Med*. 2021;**51**(8):1338–44. [PubMed ID: 32063235]. https://doi.org/10.1017/S0033291720000094.
18. Siafarikas N, Selbaek G, Fladby T, Saltyte Benth J, Auning E, Aarsland D. Frequency and subgroups of neuropsychiatric symptoms in mild cognitive impairment and different stages of dementia in Alzheimer's disease. *Int Psychogeriatr*. 2018;**30**(1):103–13. [PubMed ID: 28927477]. https://doi.org/10.1017/S1041610217001879.
19. Bergman Nutley S, Soderqvist S. How Is Working Memory Training Likely to Influence Academic Performance? Current Evidence and Methodological Considerations. *Front Psychol*. 2017;**8**:69. [PubMed ID: 28223948]. [PubMed Central ID: PMC5295142]. https://doi.org/10.3389/fpsyg.2017.00069.
20. Funes CM, Lavretsky H, Ercoli L, St Cyr N, Siddarth P. Apathy Mediates Cognitive Difficulties in Geriatric Depression. *Am J Geriatr Psychiatry*. 2018;**26**(1):100–6. [PubMed ID: 28755989]. [PubMed Central ID: PMC5725249]. https://doi.org/10.1016/j.jagp.2017.06.012.
21. Trivedi JK. Cognitive deficits in psychiatric disorders: Current status. *Indian J Psychiatry*. 2006;**48**(1):10–20. [PubMed ID: 20703409]. [PubMed Central ID: PMC2913637]. https://doi.org/10.4103/0019-5545.31613.
22. Sultzer DL, Leskin LP, Melrose RJ, Harwood DG, Narvaez TA, Ando TK, et al. Neurobiology of delusions, memory, and insight in Alzheimer disease. *Am J Geriatr Psychiatry*. 2014;**22**(11):1346–55. [PubMed ID: 24021220]. [PubMed Central ID: PMC4254898]. https://doi.org/10.1016/j.jagp.2013.06.005.
23. Esposito F, Rochat L, Juillerat Van der Linden AC, Van der Linden M. Apathy and prospective memory in aging. *Dement Geriatr Cogn Dis Extra*. 2012;**2**(1):456–67. [PubMed ID: 23277780]. [PubMed Central ID: PMC3522457]. https://doi.org/10.1159/000345037.
24. Koenig AM, Arnold SE, Streim JE. Agitation and Irritability in Alzheimer's Disease: Evidenced-Based Treatments and the Black-Box Warning. *Curr Psychiatry Rep*. 2016;**18**(1):3. [PubMed ID: 26695173]. [PubMed Central ID: PMC6483820]. https://doi.org/10.1007/s11920-015-0640-7.
25. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. *Front Neurol*. 2012;**3**:73. [PubMed ID: 22586419]. [PubMed Central ID: PMC3345875]. https://doi.org/10.3389/fneur.2012.00073.
26. Vicini Chilovi B, Conti M, Zanetti M, Mazzu I, Rozzini L, Padovani A. Differential impact of apathy and depression in the development of dementia in mild cognitive impairment patients. *Dement Geriatr Cogn Disord*. 2009;**27**(4):390–8. [PubMed ID: 19339777]. https://doi.org/10.1159/000210045.
27. Holth J, Patel T, Holtzman DM. Sleep in Alzheimer's Disease - Beyond Amyloid. *Neurobiol Sleep Circadian Rhythms*. 2017;**2**:4–14. [PubMed ID: 28217760]. [PubMed Central ID: PMC5312809]. https://doi.org/10.1016/j.nbscr.2016.08.002.
28. Liguori C, Placidi F, Izzi F, Spanetta M, Mercuri NB, Di Pucchio A. Sleep dysregulation, memory impairment, and CSF biomarkers during different levels of neurocognitive functioning in Alzheimer's disease course. *Alzheimers Res Ther*. 2020;**12**(1):5. [PubMed ID: 31901236]. [PubMed Central ID: PMC6942389]. https://doi.org/10.1186/s13195-019-0571-3.
29. Sabia S, Fayosse A, Dumurgier J, van Hees VT, Paquet C, Sommerlad A, et al. Association of sleep duration in middle and old age with incidence of dementia. *Nat Commun*. 2021;**12**(1):2289. [PubMed ID: 33879784]. [PubMed Central ID: PMC8058039]. https://doi.org/10.1038/s41467-021-22354-2.
30. Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP, et al. Sleep quality and preclinical Alzheimer disease. *JAMA Neu-*

rol. 2013;**70**(5):587–93. [PubMed ID: 23479184]. [PubMed Central ID: PMC3676720]. https://doi.org/10.1001/jamaneurol.2013.2334.
31. Spira AP, Gamaldo AA, An Y, Wu MN, Simonsick EM, Bilgel M, et al. Self-reported sleep and beta-amyloid deposition in community-dwelling older adults. *JAMA Neurol*. 2013;**70**(12):1537–43. [PubMed ID: 24145859]. [PubMed Central ID: PMC3918480]. https://doi.org/10.1001/jamaneurol.2013.4258.
32. Shokri-Kojori E, Wang GJ, Wiers CE, Demiral SB, Guo M, Kim SW, et al. Beta-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A*. 2018;**115**(17):4483–8. [PubMed ID: 29632177]. [PubMed Central ID: PMC5924922]. https://doi.org/10.1073/pnas.1721694115.
33. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol*. 2011;**70**(11):960–9. [PubMed ID: 22002422]. https://doi.org/10.1097/NEN.0b013e318232a379.
34. Holth JK, Fritschi SK, Wang C, Pedersen NP, Cirrito JR, Mahan TE, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science*. 2019;**363**(6429):880–4. [PubMed ID: 30679382]. [PubMed Central ID: PMC6410369]. https://doi.org/10.1126/science.aav2546.
35. Chen Y, Dang M, Zhang Z. Brain mechanisms underlying neuropsychiatric symptoms in Alzheimer's disease: a systematic review of symptom-general and -specific lesion patterns. *Mol Neurodegener*. 2021;**16**(1):38. [PubMed ID: 34099005]. [PubMed Central ID: PMC8186099]. https://doi.org/10.1186/s13024-021-00456-1.
36. Liguori C, Romigi A, Nuccetelli M, Zannino S, Sancesario G, Martorana A, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. *JAMA Neurol*. 2014;**71**(12):1498–505. [PubMed ID: 25322206]. https://doi.org/10.1001/jamaneurol.2014.2510.
37. Rossi R, Geroldi C, Bresciani L, Zanetti O, Frisoni GB. Delusions in ad are associated with less severe brain structural changes. *Res Pract Alzheimer's Dis*. 2003;**7**:168–73.
38. Serra L, Perri R, Cercignani M, Spano B, Fadda L, Marra C, et al. Are the behavioral symptoms of Alzheimer's disease directly associated with neurodegeneration? *J Alzheimers Dis*. 2010;**21**(2):627–39. [PubMed ID: 20555138]. https://doi.org/10.3233/JAD-2010-100048.
39. Scarmeas N, Brandt J, Albert M, Hadjigeorgiou G, Papadimitriou A, Dubois B, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol*. 2005;**62**(10):1601–8. [PubMed ID: 16216946]. [PubMed Central ID: PMC3028538]. https://doi.org/10.1001/archneur.62.10.1601.
40. Bedrossian N, Haidar M, Fares J, Kobeissy FH, Fares Y. Inflammation and Elevation of Interleukin-12p40 in Patients with Schizophrenia. *Front Mol Neurosci*. 2016;**9**:16. [PubMed ID: 27047333]. [PubMed Central ID: PMC4801873]. https://doi.org/10.3389/fnmol.2016.00016.
41. Sartori AC, Vance DE, Slater LZ, Crowe M. The impact of inflammation on cognitive function in older adults: implications for healthcare practice and research. *J Neurosci Nurs*. 2012;**44**(4):206–17. [PubMed ID: 22743812]. [PubMed Central ID: PMC3390758]. https://doi.org/10.1097/JNN.0b013e3182527690.
42. Barbey AK, Koenigs M, Grafman J. Orbitofrontal contributions to human working memory. *Cereb Cortex*. 2011;**21**(4):789–95. [PubMed ID: 20724371]. [PubMed Central ID: PMC3059885]. https://doi.org/10.1093/cercor/bhq153.
43. Wilson RS, Gilley DW, Bennett DA, Beckett LA, Evans DA. Hallucinations, delusions, and cognitive decline in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2000;**69**(2):172–7. [PubMed ID: 10896689]. [PubMed Central ID: PMC1737043]. https://doi.org/10.1136/jnnp.69.2.172.
44. Hepp DH, da Hora CC, Koene T, Uitdehaag BM, van den Heuvel OA, Klein M, et al. Cognitive correlates of visual hallucinations in non-demented Parkinson's disease patients. *Parkinsonism Relat Disord*. 2013;**19**(9):795–9. [PubMed ID: 23706540]. https://doi.org/10.1016/j.parkreldis.2013.04.026.
45. Pinto T, Lanctot KL, Herrmann N. Revisiting the cholinergic hypothesis of behavioral and psychological symptoms in dementia of the Alzheimer's type. *Ageing Res Rev*. 2011;**10**(4):404–12. [PubMed ID: 21292041]. https://doi.org/10.1016/j.arr.2011.01.003.
46. Bateman DR, Gill S, Hu S, Foster ED, Ruthirakuhan MT, Sellek AF, et al. Agitation and impulsivity in mid and late life as possible risk markers for incident dementia. *Alzheimers Dement (N Y)*. 2020;**6**(1). e12016. [PubMed ID: 32995467]. [PubMed Central ID: PMC7507499]. https://doi.org/10.1002/trc2.12016.
47. Hirono N, Mega MS, Dinov ID, Mishkin F, Cummings JL. Left frontotemporal hypoperfusion is associated with aggression in patients with dementia. *Arch Neurol*. 2000;**57**(6):861–6. [PubMed ID: 10867784]. https://doi.org/10.1001/archneur.57.6.861.
48. Weissberger GH, Melrose RJ, Narvaez TA, Harwood D, Mandelkern MA, Sultzer DL. 18F-Fluorodeoxyglucose Positron Emission Tomography Cortical Metabolic Activity Associated with Distinct Agitation Behaviors in Alzheimer Disease. *Am J Geriatr Psychiatry*. 2017;**25**(6):569–79. [PubMed ID: 28215899]. https://doi.org/10.1016/j.jagp.2017.01.017.
49. Lane SD, Kjome KL, Moeller FG. Neuropsychiatry of aggression. *Neurol Clin*. 2011;**29**(1):49–64. vii. [PubMed ID: 21172570]. [PubMed Central ID: PMC3053027]. https://doi.org/10.1016/j.ncl.2010.10.006.
50. Tascone LDS, Bottino CMC. Neurobiology of neuropsychiatric symptoms in Alzheimer's disease: A critical review with a focus on neuroimaging. *Dement Neuropsychol*. 2013;**7**(3):236–43. [PubMed ID: 29213845]. [PubMed Central ID: PMC5619193]. https://doi.org/10.1590/S1980-57642013DN70300002.