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Association Between Neuropsychiatric Symptoms and Functional Change in Older Non-Demented Adults: Mayo Clinic Study of Aging

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Abstract

We examined the associations between baseline neuropsychiatric symptoms (NPS) and longitudinal changes in functional performance among 5,394 non-demented individuals aged 50 years (2,729 males; median age 74.2 years; 4,716 cognitively unimpaired, 678 mild cognitive impairment). After adjusting for age, sex, education, and medical comorbidities, NPS assessed by the Neuropsychiatric Inventory Questionnaire, clinical depression (Beck Depression Inventory score 13) and anxiety (Beck Anxiety Inventory score 10) were significantly associated with an increase in the Functional Activities Questionnaire score, indicating functional decline over time. This association may vary depending on the degree of cognitive impairment at baseline.

Keywords

Anxiety; depression; functional performance

INTRODUCTION

Neuropsychiatric symptoms (NPS) such as depression or anxiety have a high prevalence even in older adults who are free of dementia [1] and are well-established risk factors for cognitive decline [2]. Furthermore, deficits in functional activities have been reported in non-demented persons [3], and these deficits may also be predictive of progression to dementia [4] and are associated with Alzheimer's disease (AD) neuroimaging biomarkers [5].

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Cross-sectional associations between NPS and impaired functional performance in older adults free of dementia [6–10] as well as patients with dementia [6–8, 11–13] have been reported. However, little is known about the longitudinal associations between NPS and change in functional performance among non-demented older adults. For example, one study showed an association between NPS, particularly affective syndrome, and decline in functional status in persons with AD [14], and another found that NPS, particularly apathy, predict difficulties with instrumental and advanced activities of daily living in patients with mild AD [15].

The aim of this study was thus to examine the associations between NPS at baseline and change in functional activity over time in a sample of individuals aged 50 years who were either cognitively unimpaired (CU) or had mild cognitive impairment (MCI). We hypothesized that presence of NPS at baseline would be associated with decline in functional performance over time.

METHODS

Study setting and sample

The study was conducted in the setting of the population-based Mayo Clinic Study of Aging (MCSA) in Olmsted County, Minnesota. We included persons aged 50 years and free of dementia (i.e., CU or having MCI), and on who information on NPS and functional activity was available. MCSA study protocols have been approved by the IRB of the Mayo Clinic and Olmsted Medical Center in Rochester, Minnesota. All participants provided written informed consent.

Cognitive evaluation

The MCSA study protocol is described elsewhere [16]. Briefly, all participants underwent a face-to-face evaluation including a neurological examination performed by a physician, a risk factor ascertainment conducted by a study coordinator, and standardized neuropsychological testing administered by a psychometrist to assess four cognitive domains (i.e., memory, language, visuospatial skills, executive functions). An expert consensus panel consisting of physicians, study coordinators, and neuropsychologists evaluated the results and classified each participant as being CU (based on normative data developed on a separate sample in this community) or having MCI based on published criteria.

Measurement of neuropsychiatric symptoms

NPS were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q), Beck Depression Inventory (BDI-II), and Beck Anxiety Inventory (BAI). The NPI-Q [17] was administered as a structured interview to an informant by a study coordinator, and assesses the presence/absence of 12 emotional behaviors (i.e., depression, anxiety, apathy, agitation, delusion, hallucination, euphoria, disinhibition, irritability, aberrant motor behavior, sleep, and eating/appetite). The BDI-II and BAI are validated, self-administered inventories [18, 19] consisting of 21 items that measure symptoms of depression (such as loss of interest) over the last 2 weeks, or symptoms of anxiety (such as fear of losing control) over the last 7 days, respectively. The severity of each symptom is rated on an ordinal scale ranging from 0

(low) to 3 (high). The total score for both BDI-II and BAI ranges from 0 to 63, with a higher score indicating a higher severity of symptoms.

Measurement of functional status

Functional performance was measured by the Functional Activities Questionnaire (FAQ) [20], a 10-item questionnaire designed to assess activities of daily living such as writing checks, shopping alone for clothes, preparing a balanced meal, or remembering appointments. The FAQ was administered by a study coordinator to an informant who was asked to rate the participant's abilities on an ordinal scale ranging from 3 (dependent) to 0 (normal). FAQ total score was calculated for each participant by summing the scores for all items (range 0 to 30), with higher scores indicating higher degrees of functional impairment. At least 70% of FAQ items had to be answered in order to be considered in the analysis.

Statistical analysis

We compared presence of NPS between persons with FAQ scores = 0 (no functional impairment) versus 1 (some degree of functional impairment), using Chi-square tests for categorical variables (e.g., frequency of NPS) and Kruskal-Wallis tests for continuous variables (e.g., mean BDI-II score). We then ran linear mixed effects models with random subject-specific slopes for time and intercepts to examine the association between NPS at baseline and change in FAQ score over time. In our models, NPS at baseline were considered as predictor variables, and the trajectories for individual yearly change in FAQ scores over time were considered the outcomes. All models were adjusted for age at baseline, sex, education, and medical comorbidities (Charlson index). We conducted analyses for all 12 NPS as assessed by the NPI-Q, and also included clinical depression (BDI-II score 13) and clinical anxiety (BAI score 10) in the models. We ran the analyses for the overall sample and also stratified by CU and MCI. All statistical analyses were done using the conventional two-tailed alpha level of 0.05 and performed with SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

The sample consisted of 5,394 participants (2,729 males; 50.6%), of whom 4,716 were CU and 678 had MCI. The median (interquartile range, IQR) age was 74.2 (66.4, 81.1) years, and the median (IQR) years of education were 14.0 (12.0, 16.0). 973 persons (18.0%) had a FAQ score 1. Participants with a FAQ score 1 were significantly older, had less years of education, more medical comorbidities as indicated by a higher Charlson index score, higher use of psychotropic medication, and higher frequency of cerebrovascular risk factors (i.e., hypertension, diabetes, dyslipidemia) than participants with a FAQ score = 0 (Table 1). Participants with a FAQ score 1 as compared to = 0 had a significantly higher frequency of NPI-Q-assessed presence of NPS as well as clinical depression (BDI-II score 13) and clinical anxiety (BAI score 10; Table 1).

The median (IQR) follow-up time for the longitudinal analyses was 3.97 (1.27, 6.27) years. 1,007 individuals progressed from FAQ = 0 at baseline to FAQ 1 in the follow-up. Furthermore, over the follow-up, 3,936 persons remained CU, 661 progressed from CU to

MCI, 119 progressed from CU to dementia, 524 remained at MCI stage, and 154 persons progressed from MCI to dementia. The analyses revealed multiple significant associations between NPS at baseline and change in FAQ score over time (Table 2). For agitation in the overall sample as an example, the coefficient for time indicates that each one-year increase in time is associated with an increase in FAQ score of 0.32 for participants without agitation. The interaction coefficient suggests the difference in slopes over time for those without and with agitation. Thus, each one-year increase in time is associated with an increase in FAQ score of $0.32 + 0.40 = 0.72$ for participants with agitation. In the overall sample, the interaction was significant for all NPI-Q-assessed NPS except for hallucinations, euphoria, disinhibition, motor behavior, and eating change. Furthermore, the interaction was significant for clinical depression (BDI-II score ≥ 13) and clinical anxiety (BAI score ≥ 10). In the CU subsample, there were significant associations between delusions, agitation, depression, apathy, and nighttime behavior with change in FAQ score over time; whereas for the MCI subsample, there were no significant associations (Table 2).

DISCUSSION

Here we report associations between the presence of NPS at baseline and change in functional performance in a population-based sample of non-demented older adults. As hypothesized, presence of NPS as assessed by the NPI-Q (except for hallucinations, euphoria, disinhibition, motor behavior, and appetite change), as well as clinical depression (BDI-II score ≥ 13) and clinical anxiety (BAI score ≥ 10) were significantly associated with an increase in FAQ score over time which is indicating greater functional deficits. Of note, the association between NPS and longitudinal functional deficits was present for both informant-based (NPI-Q) and self-report instruments (BDI-II and BAI). Additional adjustment for psychotropic medication intake did not alter the results (data not shown). When we stratified the sample, we observed that in CU participants, delusions, agitation, depression, apathy, and nighttime behavior were associated with change in functional performance; whereas in MCI participants, no significant association between NPS at baseline and functional decline over time was observed. We hypothesize that in persons with MCI, NPS are part of the manifestation of cognitive impairment, and functional decline may primarily be attributed to decreased cognitive performance in participants with MCI. This may explain the lack of an association between NPS and functional decline in persons with MCI. Finally, in cross-sectional analyses, we found that persons with functional impairment had a significantly higher frequency of NPI-Q-assessed presence of NPS as well as clinical depression and anxiety than persons without functional impairment.

Only few studies have investigated associations between NPS and longitudinal functional decline. For example, Italian researchers reported that NPS, particularly affective syndrome, were associated with functional decline in patients with AD [14]. A study from Chile found that NPS, particularly apathy, predict activities of daily living in patients with very mild AD; whereas in more advanced AD stages cognitive impairment is a better predictor of functional decline [15]. Interestingly, this study reported results similar to ours, i.e., NPS appear to be associated with functional decline in persons that have less or no cognitive impairment rather than in those with more pronounced cognitive impairment. However, both previous studies had small sample sizes of <200 participants and included participants with AD.

Therefore, our study expands on this research by providing preliminary evidence of an association between NPS and a worsening in daily functioning over time in a large population-based sample of non-demented individuals. Furthermore, we observed that this association may vary depending on the degree of cognitive impairment, i.e., the associations were only found in the overall sample and in the CU but not MCI subsample. More research is needed to examine potential mechanisms that may explain this difference. Finally, our observations of varying results depending on level of cognitive function may be particularly interesting in the context of Mild Behavioral Impairment (MBI) as an early marker of dementia risk [21]. For example, a recent longitudinal study found that MBI is associated with faster decline in attention and working memory in cognitively normal individuals, and may be an earlier marker of neurodegenerative disease than MCI [22].

Strengths of our study include the large sample of over 5,000 community-dwelling older individuals, and the rigorous assessment of both informant-based and self-reported NPS using validated instruments. More importantly, we confirmed our previously reported cross-sectional observations [10] by conducting longitudinal analyses in the same population. A major limitation pertains to the observational study nature which does not allow for drawing any conclusions about cause and effect. Additionally, due to our sampling procedure, a large number of participants had missing information on the NPI-Q; and we observed that those with missing NPI-Q information had, on average, lower age at baseline, lower percentage of males, higher years of education, and lower medical comorbidities than participants with NPI-Q information (data not shown). Furthermore, there may be a content overlap of tools used to assess NPS, i.e., presence/absence of depression and anxiety assessed using the NPI-Q, and severity of depression and anxiety assessed using the BDI-II and BAI. Also, as expected given the sample of non-demented older adults, the frequency of NPS was low, particularly for psychotic symptoms such as hallucinations, delusions, and euphoria. Thus, one should be careful not to over-interpret a lack of associations between FAQ and rare NPS. Finally, we did not adjust for multiple comparisons. However, if we apply a Bonferroni correction and consider an alpha level of 0.003 (0.05/14 since we have 14 interaction terms in each model), then many of the interactions for the whole sample still remain significant. Without the correction, the interactions are significant for delusions, agitation, depression, anxiety, apathy, irritability, nighttime behavior, BDI-II 13, and BAI 10 (please refer to Table 2), and after applying the correction only irritability and BAI 10 would no longer remain significant. However, with regard to the CU subsample, without the correction we observed significant interactions for delusions, agitation, depression, apathy and nighttime behavior, and none of them would remain significant after the correction.

In conclusion, we observed that NPS are associated with functional decline over time in non-demented older adults. More research is needed to further examine the associations between NPS and functional impairment in old age, and to untangle any neurobiological mechanisms that may underlie this association.

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Table 1

Demographics of study participants by FAQ group

Variable	FAQ=0 N= 4421	FAQ 1 N= 973	Total N= 5394	p
Age, years				<0.0001 ^f
Mean (SD)	71.9 (9.9)	79.1 (7.8)	73.2 (9.9)	
Median (IQR)	73.0 (64.6, 79.3)	80.7 (74.8, 84.4)	74.2 (66.4, 81.1)	
Male sex, N (%)	2201 (49.8)	528 (54.3)	2729 (50.6)	0.0114 ²
Education, years ^a				<0.0001 ^f
Mean (SD)	14.4 (2.7)	13.7 (3.0)	14.3 (2.8)	
Median (IQR)	14.0 (12.0, 16.0)	13.0 (12.0, 16.0)	14.0 (12.0, 16.0)	
MCI, N (%)	336 (7.6)	342 (35.1)	678 (12.6)	<0.0001 ²
Charlson index ^b				<0.0001 ^f
Mean (SD)	2.9 (2.9)	4.4 (3.5)	3.1 (3.1)	
Median (IQR)	2.0 (1.0, 4.0)	4.0 (2.0, 6.0)	2.0 (1.0, 4.0)	
Psychotropic medication, N (%)	735 (16.6)	209 (21.5)	944 (17.5)	0.0003 ²
Hypertension, N (%) ^c	2850 (64.9)	793 (81.8)	3643 (68.0)	<0.0001 ²
Diabetes, N (%) ^c	723 (16.5)	226 (23.3)	949 (17.7)	<0.0001 ²
Dyslipidemia, N (%) ^c	3501 (79.8)	803 (82.8)	4304 (80.3)	0.0335 ²
Smoking ever, N (%)	2060 (46.6)	467 (48.0)	2527 (46.8)	0.4282 ²
FAQ total score				<0.01 ^f
Mean (SD)	0.0 (0.0)	3.1 (3.6)	0.6 (2.0)	
Median (IQR)	0.0 (0.0, 0.0)	2.0 (1.0, 4.0)	0.0 (0.0, 0.0)	
Delusions, N (%) ^d	3 (0.1)	24 (2.6)	27 (0.6)	<0.0001 ²
Hallucinations, N (%) ^d	1 (0.0)	12 (1.3)	13 (0.3)	<0.0001 ³
Agitation, N (%) ^d	76 (1.9)	81 (8.9)	157 (3.2)	<0.0001 ²
Depression, N (%) ^d	374 (9.4)	238 (26.1)	612 (12.5)	<0.0001 ²

Variable	FAQ=0 N= 4421	FAQ 1 N= 973	Total N= 5394	p
Anxiety, N (%) ^d	203 (5.1)	128 (14.0)	331 (6.8)	<0.0001 ²
Euphoria, N (%) ^d	10 (0.3)	19 (2.1)	29 (0.6)	<0.0001 ²
Apathy, N (%) ^d	128 (3.2)	155 (17.0)	283 (5.8)	<0.0001 ²
Disinhibition, N (%) ^d	24 (0.6)	52 (5.7)	76 (1.6)	<0.0001 ²
Irritability, N (%) ^d	259 (6.5)	189 (20.7)	448 (9.1)	<0.0001 ²
Motor behavior, N (%) ^d	19 (0.5)	22 (2.4)	41 (0.8)	<0.0001 ²
Nighttime behavior, N (%) ^e	189 (5.6)	179 (22.4)	368 (8.8)	<0.0001 ²
Appetite change, N (%) ^d	129 (3.2)	112 (12.3)	241 (4.9)	<0.0001 ²
BDI-II score ^f				<0.0001 ¹
Mean (SD)	4.5 (4.6)	6.8 (6.2)	4.9 (5.0)	
Median (IQR)	3.0 (1.0, 7.0)	5.0 (2.0, 9.0)	4.0 (1.0, 7.0)	
BDI-II score 13, N (%) ^f	271 (6.2)	144 (15.3)	415 (7.8)	<0.0001 ²
BAI score ^g				<0.0001 ¹
Mean (SD)	2.7 (4.1)	4.1 (5.4)	3.0 (4.4)	
Median (IQR)	1.0 (0.0, 4.0)	2.0 (0.0, 6.0)	1.0 (0.0, 4.0)	
BAI score 10, N (%) ^g	272 (6.2)	120 (12.4)	392 (7.3)	<0.0001 ²

FAQ, Functional Activities Questionnaire; SD, standard deviation; IQR, interquartile range; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory.

^aInformation missing on 5 participants

^bInformation missing on 1 participant

^cInformation missing on 36 participants

^dInformation missing on 491 participants

^eInformation missing on 1199 participants

^fInformation missing on 102 participants

^gInformation missing on 12 participants. p-value based on

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J Kruskal-Wallis test
 2 Chi-square test
 3 Fisher Exact test.

Longitudinal association between neuropsychiatric symptoms at baseline (predictors) and change in FAQ score (outcome)

Table 2

	Predictor β (SE)		Time β (SE)		Interaction β (SE)	
	p		p		p	
<i>Whole sample</i>						
Delusions	<0.0001	4.74 (0.38)	<0.0001	0.33 (0.02)	<0.0001	1.00 (0.25)
Hallucinations	<0.0001	4.39 (0.57)	<0.0001	0.33 (0.02)	<0.0001	0.53 (0.40)
Agitation	<0.0001	1.70 (0.16)	<0.0001	0.32 (0.02)	<0.0001	0.40 (0.10)
Depression	<0.0001	0.97 (0.08)	<0.0001	0.30 (0.02)	<0.0001	0.26 (0.05)
Anxiety	<0.0001	1.01 (0.11)	<0.0001	0.31 (0.02)	<0.0001	0.33 (0.07)
Euphoria	<0.0001	1.60 (0.36)	<0.0001	0.33 (0.02)	<0.0001	0.09 (0.22)
Apathy	<0.0001	2.07 (0.12)	<0.0001	0.31 (0.02)	<0.0001	0.46 (0.08)
Disinhibition	<0.0001	3.24 (0.23)	<0.0001	0.33 (0.02)	<0.0001	0.18 (0.15)
Irritability	<0.0001	1.15 (0.10)	<0.0001	0.32 (0.02)	<0.0001	0.14 (0.06)
Motor behavior	<0.0001	1.93 (0.31)	<0.0001	0.33 (0.02)	<0.0001	0.36 (0.20)
Nighttime behavior	<0.0001	1.21 (0.10)	<0.0001	0.30 (0.02)	<0.0001	0.26 (0.07)
Appetite change	<0.0001	1.42 (0.13)	<0.0001	0.33 (0.02)	<0.0001	0.12 (0.08)
BDI-II score 13	<0.0001	0.71 (0.10)	<0.0001	0.30 (0.02)	<0.0001	0.23 (0.06)
BAI score 10	<0.0001	0.59 (0.10)	<0.0001	0.31 (0.02)	<0.0001	0.14 (0.06)
<i>Cognitively unimpaired</i>						
Delusions	<0.0001	2.39 (0.39)	<0.0001	0.20 (0.01)	<0.0001	-0.73 (0.28)
Hallucinations	0.0243	1.16 (0.51)	<0.0001	0.20 (0.01)	<0.0001	0.67 (0.36)
Agitation	<0.0001	0.88 (0.12)	<0.0001	0.19 (0.01)	<0.0001	0.24 (0.09)
Depression	<0.0001	0.47 (0.06)	<0.0001	0.19 (0.01)	<0.0001	0.10 (0.04)
Anxiety	<0.0001	0.52 (0.08)	<0.0001	0.19 (0.01)	<0.0001	0.08 (0.06)
Euphoria	<0.0001	1.16 (0.29)	<0.0001	0.20 (0.01)	<0.0001	0.12 (0.19)
Apathy	<0.0001	0.89 (0.10)	<0.0001	0.19 (0.01)	<0.0001	0.16 (0.07)
Disinhibition	<0.0001	1.50 (0.18)	<0.0001	0.20 (0.01)	<0.0001	-0.08 (0.13)
Irritability	<0.0001	0.63 (0.07)	<0.0001	0.20 (0.01)	<0.0001	0.03 (0.05)
Motor behavior	0.3540	0.22 (0.23)	<0.0001	0.20 (0.01)	<0.0001	0.11 (0.16)
Nighttime behavior	<0.0001	0.43 (0.07)	<0.0001	0.17 (0.01)	<0.0001	0.11 (0.05)
Appetite change	<0.0001	0.65 (0.09)	<0.0001	0.20 (0.01)	<0.0001	0.00 (0.07)

	Predictor β (SE)	p	Time β (SE)	p	Interaction β (SE)	p
BDI-II score 13	0.31 (0.07)	<0.0001	0.19 (0.01)	<0.0001	0.07 (0.05)	0.1946
BAI score 10	0.26 (0.07)	0.0004	0.19 (0.01)	<0.0001	0.09 (0.05)	0.0784
<i>Mild cognitive impairment</i>						
Delusions	4.67 (1.08)	<0.0001	1.32 (0.11)	<0.0001	1.18 (0.67)	0.0798
Hallucination	7.03 (1.80)	<0.0001	1.35 (0.10)	<0.0001	0.22 (1.35)	0.8699
Agitation	2.54 (0.64)	<0.0001	1.35 (0.11)	<0.0001	0.00 (0.40)	0.9962
Depression	1.69 (0.39)	<0.0001	1.34 (0.12)	<0.0001	0.03 (0.24)	0.8884
Anxiety	1.28 (0.48)	0.0080	1.31 (0.11)	<0.0001	0.29 (0.29)	0.3183
Euphoria	2.14 (1.33)	0.1075	1.36 (0.10)	<0.0001	-0.61 (0.82)	0.4573
Apathy	3.42 (0.44)	<0.0001	1.35 (0.11)	<0.0001	0.02 (0.28)	0.9549
Disinhibition	5.75 (0.82)	<0.0001	1.35 (0.11)	<0.0001	-0.03 (0.57)	0.9635
Irritability	1.89 (0.43)	<0.0001	1.43 (0.12)	<0.0001	-0.39 (0.27)	0.1392
Motor behavior	5.05 (1.21)	<0.0001	1.35 (0.11)	<0.0001	0.33 (0.88)	0.7097
Nighttime behavior	2.99 (0.45)	<0.0001	1.43 (0.13)	<0.0001	0.00 (0.31)	0.9959
Appetite change	3.23 (0.59)	<0.0001	1.37 (0.11)	<0.0001	-0.23 (0.41)	0.5725
BDI-II score 13	1.31 (0.45)	0.0038	1.30 (0.11)	<0.0001	0.30 (0.30)	0.3207
BAI score 10	1.32 (0.48)	0.0055	1.41 (0.11)	<0.0001	-0.45 (0.29)	0.1246

FAQ, Functional Activities Questionnaire; β , coefficient; SE, standard error; Time, indicates annual change in FAQ score for participants without presence of NPS; interaction, indicates difference in slopes over time for participants without and with presence of NPS; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory. Models adjusted for age at baseline, sex, education, and medical comorbidities (Charlson index).