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Neuropsychiatric Symptoms in Severe Dementia: Associations with Specific Cognitive Domains The Cache County Dementia Progression Study

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Abstract

Objectives—To examine the prevalence of neuropsychiatric symptoms (NPS) and cognitive correlates in severe dementia.

Methods—A population-based sample of 56 individuals with severe dementia (85.7% Alzheimer's type; 67.9% female) were assessed with the Severe Cognitive Impairment Profile (SCIP) and the Neuropsychiatric Inventory (NPI). Descriptive statistics displayed the frequency of NPS and bivariate and multiple regression analyses examined the associations between cognitive domains on the SCIP and NPS total, domain and cluster scores.

Results—NPS were common in severe dementia with 98% of the sample exhibiting at least one symptom. Most common were delusions, apathy, agitation/aggression and aberrant motor behavior, affecting 50% or more of participants. SCIP Comportment was significantly associated with NPI total score and apathy ($r = -.350$ and $-.292$, respectively). All SCIP domains except for arithmetic, visuospatial, comportment and motor behavior were significantly associated with agitation/aggression ($r = -.285$ to $-.350$). These associations remained in individual multiple regression models.

Conclusion—In severe dementia, impairment in specific cognitive domains was associated with more severe neuropsychiatric symptoms. Environmental manipulations to reduce processing demands in persons with severe dementia may be a useful strategy to target agitation and aggressive behaviors.

Keywords

dementia; severe dementia; neuropsychiatric symptoms; cognition; Alzheimer's disease

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Introduction:

There is a high prevalence of neuropsychiatric symptoms (NPS) in Alzheimer's disease and related dementias (ADRD) with nearly all individuals experiencing some type of symptom over the course of dementia[1–3]. NPS have been shown to fluctuate in severity[2] and vary in presentation over time[2,4–5]. Depression, which occurs most commonly in early or mid-course, decreases with increasing anosognosia[6]. Agitation and anxiety remain relatively common in the early stages and increase in frequency with the progression of dementia. Hallucinations and euphoria are somewhat less common, but their occurrence generally remains stable over the course of dementia[6].

Severe dementia, characterized by substantial disability in daily living activities, places significant burden on caregivers[7]. The occurrence of NPS in general has been found to predict degree of caregiver burden[8–10] as well as nursing home placement[11]. NPS are difficult to treat[12], and some pharmacological approaches have been discouraged[13]. In particular, treatment with antipsychotic medications has variable efficacy and has been associated with increased adverse events, prompting non-pharmacological approaches as a recommended first-line treatment strategy[14]. Non-pharmacological approaches to NPS include multi-sensory behavior therapy such as "Snoezelen" experiences, cognitive rehabilitation therapy, music therapy, and reminiscence therapy[15]. In advanced dementia, sensory-focused strategies (aroma, music, or multisensory therapy) with limited language demands show some evidence of reducing NPS[16].

Advanced dementia presents significant challenges to caregivers owing to the severity of cognitive and functional deficits. NPS may present further challenges. While several studies have examined NPS in mild-to-moderate dementia, few studies have focused on NPS in advanced/severe dementia, particularly in community dwelling individuals. In order to develop interventions for NPS in advanced dementia, an understanding of their correlates is important to inform possible environmental manipulations. In this exploratory study, we described the prevalence of NPS in severe dementia and participant factors (e.g., cognitive ability and overall health) as correlates of symptom type.

Methods

Participants were persons with dementia identified from the Cache County Study on Memory in Aging (CCSMA)[17] who were also followed in the Dementia Progression Study (DPS)[2]. Details of dementia screening and assessment in the CCSMA have been described elsewhere[17,18]. Briefly, the population of 5,092 residents of Cache County, Utah underwent four triennial waves of dementia screening and assessment (1995–1996; 1998–1999; 2002–2003; 2005–2007) in which, 942 persons with dementia were identified across all waves. Diagnoses were based on information gathered from a clinical assessment conducted by a nurse and neuropsychological technician in which the participant completed a brief physical exam, neurological exam, and neuropsychological assessment. A caregiver or knowledgeable informant provided information about clinical symptoms of memory loss and impairments in other cognitive domains and activities of daily living (ADLs)[19]. The results of the clinical assessment were reviewed by a study physician, neuropsychologist and

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clinical assessment team where preliminary diagnoses of dementia were assigned using criteria from the Diagnostic and Statistical Manual III-Revised (DSMIII-R)[20]. Individuals with suspected dementia or its prodrome were asked to complete a physician examination by a geropsychiatrist or neurologist, a brain MRI scan and standard laboratory tests to rule out other causes of dementia[17]. The results of clinical studies (clinical assessment, physician exam, MRI scan and laboratory tests) were reviewed by an expert panel consisting of geropsychiatrists, neurologists, neuropsychologists and a cognitive neuroscientist, who assigned final diagnoses of dementia and type of dementia. Diagnostic criteria for dementia type followed standard research protocol at the time, for example, criteria for Alzheimer's disease followed NINCDS-ADRDA criteria[21] and vascular dementia followed NINDS-AIREN criteria[22].

In 2002, surviving persons identified with dementia in Waves 2, 3 and 4 along with their caregivers, were invited to participate in the DPS (2002 through 2012). Three hundred twenty-eight persons with dementia (PWD) and their caregivers were enrolled and were followed semi-annually through the duration of the study. At each visit, PWDs completed a battery of neuropsychological tests including the Mini-Mental State Exam (MMSE), a brief neurological and physical exam (height, weight, blood pressure, check of reflexes, review of symptoms) and caregivers completed questions regarding the PWD's cognitive status, functional (ADL) status, NPS, health and medication history, nutritional status and cognitive and physical activities. Demographic information was obtained from the CCMS, and overall health and place of residence (private home, assisted living facility and nursing home) were updated at each visit[2]. When the PWD's MMSE score reached 15 points or below, the Severe Cognitive Impairment Profile (SCIP) was administered along with other neuropsychological tests in the battery. Once initiated, the SCIP was continued at each follow-up. We identified persons with severe dementia as those with an MMSE score less than or equal to 10 or a Clinical Dementia Rating of "severe"[23]. To be included in the current analyses, those with severe dementia had to have the NPI and SCIP at the visit in which they met criteria for severe dementia or at a subsequent visit. Figure 1 displays the number of participants that were included in the final sample. Procedures of the DPS were approved by the Institutional Review Boards of Utah State University and the Johns Hopkins University.

Severe Cognitive Impairment Profile (SCIP).

The SCIP was developed to assess cognitive abilities that extend beyond the lower range of other traditional cognitive measures (e.g., floor effect)[24]. The SCIP assesses the following domains: Comportment (appearance and behavioral response to social stimuli), Attention, Language, Memory, Motor, Conceptualization, Arithmetic, and Visuospatial abilities. Interpretation of ability level for domain raw scores and subscale conversion to standard scores (range 1 – 19) are based on the standardization sample[24]. Interrater reliability has been reported as r=.99 and test-retest reliability as r=.96. Construct validity has been examined in correlation with other measures of dementia severity [e.g., (r= .91) with the Dementia Rating Scale (r= .91) and .84 with the MMSE (r= .84)][24]. We used raw scores for descriptive purposes and standard scores in inferential statistical models.

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Neuropsychiatric symptoms (NPS).

NPS were assessed by caregiver report using the 12-domain Neuropsychiatric Inventory (NPI) which assesses delusions, hallucinations, agitation/aggression, depression, apathy, irritability, anxiety, euphoria, aberrant motor behavior, disinhibition, sleep and appetite disturbance[25]. If a symptom was endorsed, the caregiver rated the frequency and severity of each symptom, which were multiplied to yield a domain score (maximum = 12). Scores across each domain were summed to yield a total NPI-12 score (maximum = 144). In addition to the single domain score, we also examined total NPI-12 score and symptom clusters of affective symptoms (depression and anxiety, maximum, affective score = 24), psychosis (hallucinations and delusions, maximum psychosis score = 24) as previously published in this population[26, 27].

General Medical Health Rating (GMHR).

The GMHR[28] was used as an indicator of overall health. At each visit, a nurse conducted a physical and neurological exam and review of health conditions and medications as noted above. Based on these data, the nurse assigned a rating of the participant's overall health (4 - excellent, 3 - good, 2 - fair or 1 - poor), based on the number of chronic, acute and controlled or uncontrolled conditions. The GMHR has been used in previous studies of dementia (kappa = .91)[28], and in the Cache County population in persons with AD, the GMHR has been found to correspond with indicators of progression.[29]

Data Analysis.

Descriptive statistics were used to characterize the sample. To examine differences in demographics between those who were included or excluded in analyses, we used independent samples t-tests for continuous variables and chi square tests for categorical variables. Bivariate correlations (Pearson correlation coefficient) between SCIP domain scores and Total NPI-12 and NPI domain scores and clusters were examined in exploratory analyses. Owing to the large number of variables, we selected only those SCIP domain scores that were significantly correlated ($p < .05$) with NPI total score or domain/cluster scores in bivariate correlations to enter into multiple linear regression models. However, we examined SCIP total score as an indicator of global cognitive status in the regression models, regardless of the significance level of the bivariate associations. Covariates examined included the age at assessment, gender, overall health and years of education. Variables were retained at $p < .05$; recognizing that our small sample size may have resulted in limited power, we retained the covariates regardless of the α level. Statistical software used was SPSS version 24.

Results:

There were 89 participants in DPS who met criteria for severe dementia. Of those, fifty-six (63%) had completed a SCIP once they met criteria for severe dementia. Table 1 displays sample characteristics of those included and excluded in the analyses. The majority of participants in both groups were female. Compared to those excluded from the analyses, a greater percentage of those in the sample had Alzheimer's dementia (85.7 vs. 66.7%) and were residing in a private residence (37.5% vs. 15.2%). As a group, those included in the

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analyses did not differ in NPI-12 total score than those excluded from analyses. However, those excluded were slightly worse in their overall health.

Sample characteristics with respect to severity of cognitive abilities and neuropsychiatric symptoms are displayed in Tables 2 and 3, respectively. A majority of the sample (60.7%) was "moderately severe" or "severe" as indicated by the SCIP total score. In all SCIP domains, an overwhelming majority performed in the "low" category, with the exception of motor dexterity and speed (21.4%) and conceptualization or problem solving (64.3%). NPS were common, affecting 98% of the sample (Table 3). The most common symptoms were delusions, agitation/aggression, apathy, and aberrant motor behavior with at least 50% of participants exhibiting these symptoms. Very rare was elation/euphoria with a frequency of 3.6%, followed by disinhibition (21.4%), appetite disturbance (23.2%), and irritability (25%). Altogether, at least 64.3% of the sample exhibited one of the symptoms making up the affective cluster and 55.4% in the psychosis cluster, though mean severity scores were low.

Several significant correlations were observed between NPI scores and domains on the SCIP. As displayed in Table 4, Comportment was significantly correlated with total NPI-12 score ($r = -.350$, $p < .01$), and negatively correlated with apathy ($r = -.292$, $p < .05$). Total SCIP score and several cognitive domains were negatively associated with agitation/aggression: Total SCIP ($r = -.278$, $p < .05$), Memory ($r = -.329$, $p < .05$), Attention ($r = -.285$, $p < .05$), Conceptualization ($r = -.312$, $p < .05$), and Language ($r = -.350$, $p < .01$). The SCIP domains of arithmetic, visuospatial, and motor abilities were not significantly correlated with any NPI scores.

In multiple regression models with SCIP subdomain scores as correlates of NPI outcomes (NPI total-12 score, apathy, and agitation/aggression), none of the covariates (age, gender, overall health and years of education) were statistically significant at $p < .05$. However, these variables were retained in the models as theoretically relevant to NPS. Table 5 displays the results of each of the multiple regression models. For each unit decrease in Comportment, there was a .15-point increase in NPI-12 total score. For the NPI domains, each unit decrease in Comportment was associated with a 0.58-point increase in apathy. Regarding Memory and Language, there was a 0.35- and 0.38-point increase in agitation/aggression for each unit decrease in Memory and Language scores, respectively. Smaller effects were noted for Conceptualization and Attention, with βs of 0.15 and 0.29 points, respectively. SCIP total score was significantly associated only with NPI agitation/aggression score.

Discussion

In this community-based sample of persons with severe dementia, we found several associations between cognitive domains and NPS. Our results support the notion that poorer cognitive abilities are associated with more severe NPS, with comportment being associated with total NPI score. We found specificity of cognitive abilities that were associated with some but not other NPS. Poorer comportment was associated with apathy, whereas memory, language, attention, and conceptualization were associated with more severe agitation and aggression, though SCIP total score was also associated with the latter NPS. One implication

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of our findings is that in severe dementia, environments that place undue processing demands may place PWD at greater risk for exhibiting agitation and aggressive behavior. Thus, environmental manipulations aimed at decreasing cognitive demands in the aforementioned domains (e.g., reducing sensory stimuli, breaking down communication into simple phrases, scheduling quiet time, etc.) may be a strategy to prevent agitation or reduce its severity. Creating and maintaining an environment better suited to the PWD's level of cognitive abilities may decrease NPS, which would be a significant contribution given the higher caregiver burden[8–10] and increased rates of nursing home placement associated with NPS in care recipients[11]. The fluctuating nature of agitation/aggression and other NPS would be consistent with the notion that varying environmental demands elicit such behaviors in persons with increasingly compromised cognitive status and behavioral control.

Of interest, we found few if any cognitive scores that were predictive of other NPS such as psychosis or affective behavior. While these domains were not uncommon in this sample of severe dementia, their severity was low, with mean scores approaching 4 out of a maximum possible of 24 and 36, respectively. Several NPS were not common in this sample, notably euphoria, disinhibition, and appetite disturbances. These NPS were also rare in our sample of persons in milder stages of dementia, though there was a tendency for most NPS to increase in severity over time. Among persons with dementia in the PRIME (Prospective Research in Memory Clinics) study in Australia[6], disinhibition and euphoria were relatively uncommon, similar to our report here and our report in the broader DPS AD sample[2]. However, other NPS occurred in greater frequency in the PRIME study (e.g., irritability, apathy, and agitation/aggression in follow-up year 3), likely reflecting the differences in sample characteristics between community-based vs. memory clinic samples. Even amongst our sample of individuals with severe dementia, the most common NPS (delusions, apathy, agitation/aggression and aberrant motor behaviors) were present in about half of the sample. In the PRIME study, 50% or more experienced agitation, apathy and irritability at baseline and throughout the 3-year observation period[6]. We note the pattern of NPS differed in the Cache DPS at milder stages of severity where none of the NPS (with the exception of apathy) affected half or more of the sample over the follow-up period (mean 3.8 years; range 0.07 – 12.9 years[2]).

Notable in the present study is that none of the covariates assessed, including age and overall health, were associated with NPS in severe dementia. This is in contrast to our previous work in persons with mild to moderate dementia[29]. Sex differences were also not observed in the present analyses. Thus, our findings highlight the relationship between severity of cognitive impairments and specific NPS in late stage dementia where demographic and other factors appear less relevant.

Limitations of the current study include the small sample size, though sizeable given the requirement of being in advanced/severe stages of dementia and completion of the SCIP. Nonetheless, the sample size may have resulted in low statistical power to detect significant associations. Additionally, the large number of variables examined in separate multiple regression models may have increased the possibility of a Type 1 error. The sample was primarily White and demographically homogeneous with respect to being comprised mostly of persons of middle-class socioeconomic status, which may limit the generalizability of

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findings. Nonetheless, the sample was community-based, with over one third residing in private homes. While we did not select participants based on dementia type, the majority (85.7%) were diagnosed with Alzheimer's dementia. The high participation rate of the Cache County Dementia Progression Study and careful characterization of the sample are strengths that reduce concerns of a biased sample.

In conclusion, our results suggest that in severe dementia, certain cognitive impairments are associated with greater severity of apathy, agitation and aggression. Educating caregivers on care management strategies that reduce processing demands (particularly in the domains identified) could prove useful to reduce NPS, caregiver burden and rates of institutionalization. Additionally, conducting brief, periodic cognitive assessments may be helpful to aid in treatment planning of dementia residents in long-term care facilities. Such assessments may help inform more effective non-pharmacological interventions to reduce NPS.

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Key points:

1. Neuropsychiatric symptoms are common in severe dementia
2. Most common in severe dementia are apathy, delusions, agitation/aggression and aberrant motor behavior
3. Impairment in specific cognitive domains are associated with neuropsychiatric symptoms
4. Overall health status is not a strong correlate of neuropsychiatric symptoms in severe dementia

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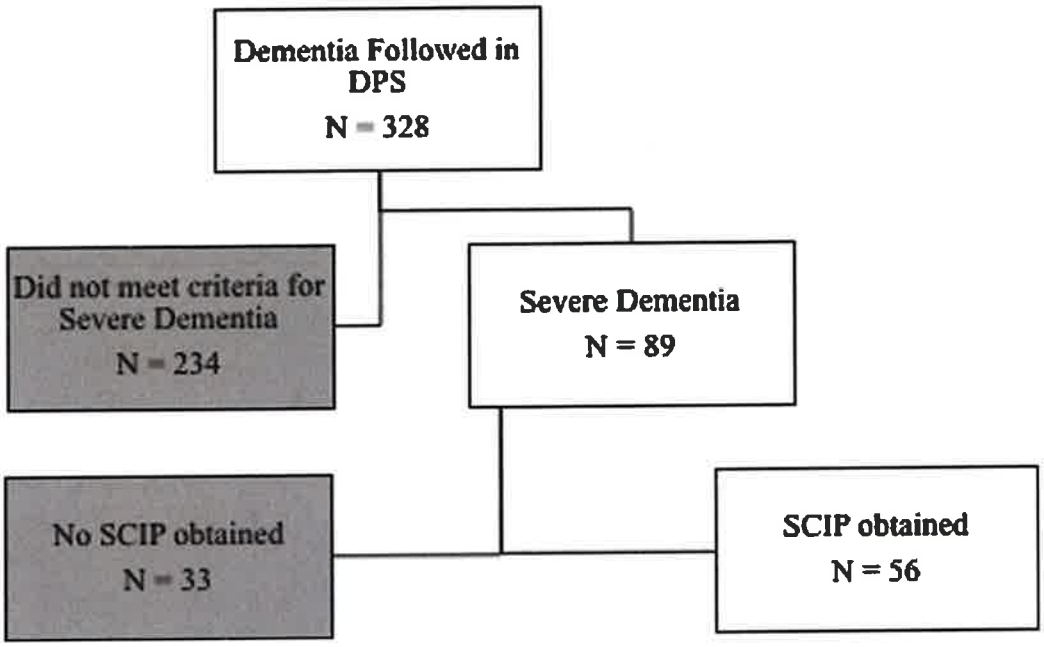

Figure 1.
Display of a flow chart depicting those participants included and excluded in the study sample

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Table 1.

Demographic Characteristics of those Included and those Excluded in Analyses

	Included in Analyses (N = 56)				Excluded (N = 33)				T-Test	Chi Square
Variables	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**		
Age at severe dementia	85.68	6.23			86.69	6.27			0.741	
Age of onset	79.61	6.31			80.68	6.15			0.783	
Education	13.54	2.88			13.41	3.25			−0.194	
GMHR	2.93	0.60			2.55	0.91			−2.17*	
NPI-12 total score	19.16	10.84			22.58	12.73			1.22	
Female Sex			38	67.9			25	75.8		0.627
Alzheimer's dementia			48	85.7			22	66.7		4.49*
Place of Residence										1.39
- Private home			21	37.5			5	15.2		
- Assisted Living			14	25.0			6	18.2		
- Locked Assisted Living/Nursing facility			21	37.5			22	66.6		

*
$p < .05$;

**
$p < .01$;

GMHR = General Medical Health Rating; NPI = Neuropsychiatric Inventory.

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Table 2.

Severe Cognitive Impairment Profile Severity Classification

Measure	N (%)	M (SD)	Min, Max
SCIP Raw Score Total [1] (range 0 – 245)		154.77 (57.66)	27, 232
- Moderately Severe	18 (32.1)		
- Severe	16 (28.6)		
- Very Severe	16 (28.6)		
- Profound	6 (10.7)		
SCIP Comportment (range 0 – 34)		28.02 (3.94)	15, 34
- Low (Failure to respond, unintelligible)	48 (85.7)		
SCIP Attention (range 0 – 44)		19.25 (13.69)	0, 44
- Low (Poor attention/concentration, distractible)	47 (83.9)		
SCIP Language (range 0 – 88)		64.36 (22.03)	4, 86
- Low (Impaired repetition, fluency, comprehension, etc.)	43 (76.8)		
SCIP Memory (range 0 – 17)		9.57 (3.53)	1, 17
- Low (Impaired remote memory, memory for simple or autobiographical information	48 (85.7)		
SCIP Motor (range 0 – 10)		7.95 (3.96)	0, 10
- Low (Impaired motor dexterity, speed, motor manipulation)	12 (21.4)		
SCIP Conceptualization (range 0 – 26)		14.30 (11.25)	0, 26
- Low (Deficits in reasoning, problem solving, concrete, perseverative)	36 (64.3)		
SCIP Arithmetic (range 0 – 10)		3.98 (3.09)	0, 10
- Low (Significant impairment counting, simple calculations, working with currency)	51 (91.1)		
SCIP Visuospatial (range 0 – 16)		7.39 (6.06)	0, 16
- Low (Impaired basic visuospatial/perceptual abilities)	47 (83.9)		

SCIP – Severe Cognitive Impairment Profile.

[1] Interpretations are based on the Severe Cognitive Impairment Profile manual, Peavey (1998).

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Table 3.

Neuropsychiatric Inventory Scores

	Symptom Present N (%)	Symptom M (SD)	Symptom Min, Max
NPI-12 Total Score (range 0 – 144)	55 (98.2)	19.55 (11.37)	0, 48
- Delusions (range 0 – 12)	28 (50.0)	1.98 (2.54)	0, 9
- Hallucinations (range 0 – 12)	17 (30.4)	1.18 (2.14)	0, 9
- Agitation/Aggression (range 0 – 12)	28 (50.0)	1.88 (2.41)	0, 9
- Depression (range 0 – 12)	20 (35.7)	1.27 (2.12)	0, 8
- Apathy/Indifference (range 0 – 12)	35 (62.5)	4.16 (3.86)	0, 12
- Elation/Euphoria (range 0 – 12)	2 (3.6)	0.13 (0.81)	0, 6
- Anxiety (range 0 – 12)	21 (37.5)	1.50 (2.16)	0, 8
- Disinhibition (range 0 – 12)	12 (21.4)	0.68 (1.71)	0, 9
- Irritability (range 0 – 12)	14 (25.0)	0.75 (1.55)	0, 6
- Aberrant Motor Behavior (range 0 – 12)	30 (53.6)	2.54 (3.04)	0, 12
- Sleep (range 0 – 12)	20 (35.7)	2.05 (3.20)	0, 12
- Appetite (range 0 – 12)	13 (23.2)	1.45 (2.97)	0, 12
- NPI Affective (range 0 – 36)	36 (64.3)	3.52 (3.65)	0, 15
- NPI Psychotic (range 0 – 24)	31 (55.4)	3.16 (4.21)	0, 18

NPI = Neuropsychiatric Inventory

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Table 4.

ıd SCIP Standard Scores

np	SCIP Mem	SCIP Vis	SCIP Attn	SCIP Conc	SCIP Mot	SCIP Lang	SCIP Arth	NPI Apa	NPI Aff	NPI Ag/Ag	NPI Psy	NPI Dis	NPI Ab/Mtr	NPI Sleep	NPI App	NPI Total-12
	-															
	.387**	-														
	.499**	.634**	-													
	.526**	.512**	.669**	-												
	.342**	.464**	.484**	.385**	-											
	.484**	.528**	.683**	.676**	.520**	-										
	.395**	.586**	.539**	.557**	.526**	.698**	-									
	−.249	−.150	−.088	.091	−.103	.002	−.064	-								
	−.146	−.199	−.226	−.089	.104	−.053	−.133	.141	-							
	−.329*	−.131	−.285*	−.312*	−.079	−.350**	−.147	.051	.090	-						
	−.101	−.030	.007	−.025	.004	−.085	−.007	−.069	.155	.380**	-					
	−.045	.038	.140	−.001	.117	−.007	−.040	−.219	.036	.264*	.134	-				
	−.226	.058	−.102	.021	.019	−.095	−.030	.228	.096	.230	.219	−.026	-			
	.205	−.191	−.170	−.090	−.182	−.127	−.174	.262	−.105	−.112	−.056	−.233	−.158	-		
	.069	−.017	−.086	.172	.069	−.037	−.020	−.008	.029	−.033	.215	.165	.190	.080	-	
*	−.231	−.189	−.234	−.098	−.021	−.191	−.167	.468**	.464**	.455**	.607**	.180	.523**	.091	.459**	-

The shaded area displays the correlations between SCIP and NPI scores. SCIP = Severe Cognitive Impairment Profile; Comp = Comportment, Mem = Memory; Vis = Visuospatial; Attn = Attention; Conc = Conceptualization; Mot = metic; NPI = Neuropsychiatric Inventory; Apa = apathy; Aff = affective; Ag/Ag = Agitation/Aggression; Psy = Psychosis; Dis = Disinhibiton; Ab/Mtr = Aberrant Motor; App = Appetite

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Table 5.

Results of Multiple Regression Analyses for Various NPI Outcomes

	ß	Standard Error	Standard ß	P value
NPI-12 Total Score				
- Model 1: SCIP Total Score	−.127	.076	−.227	.102
- Model 2: SCIP Comportment	−.151	.706	−.292	*.037*
NPI Apathy				
- Model 1: SCIP Total Score	−.034	.027	−.179	.218
- Model 2: SCIP Comportment	−.580	.247	−.330	*.023*
NPI Agitation/Aggression				
- Model 1: SCIP Total Score	−.037	.017	−.310	*.033*
- Model 2: SCIP Memory	−.348	.138	−.339	*.015*
- Model 3: SCIP Attention	−.292	.132	−.312	*.031*
- Model 4: SCIP Conceptualization	−.153	.065	−.320	*.023*
- Model 5: SCIP Language	−.379	.131	−.402	*.006*

NPI = Neuropsychiatric Inventory. Individual multiple regression models for NPI outcomes. All models include covariates: age, gender, General Medical Health Rating, and education.