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Insight in Alzheimer's Disease and its Relation to Psychiatric and Behavioral Disturbances

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Abstract

Objective—Individuals suffering from Alzheimer's disease (AD) often have impaired awareness or a lack of insight into their cognitive deficits and functional abilities, especially in the later stages of the disease. Previous research has documented a relationship between depression and insight in AD, such that greater awareness of one's disease has been associated with a higher degree of depression. However, little is known about the relationship between insight, cognitive decline, and other psychiatric or behavioral problems associated with AD.

Methods—This study included 107 outpatients who met criteria for probable AD. Instruments included the Neurobehavioral Rating Scale, the Apathy Evaluation Scale, and the MMSE. A series of hierarchical regression analyses were conducted to determine the relationship between insight and depressed mood, anxiety, psychosis, apathy, agitation, and behavioral retardation in AD patients after controlling for cognitive skills.

Results—Insight was found to significantly predict depressed mood, anxiety, and apathy even after controlling for global cognition. Greater insight was found to be associated with depressed mood and anxiety. However, impaired insight was associated with higher levels of apathy.

Conclusion—Insight may be differentially related to mood symptoms and apathy within AD, such that patients with intact insight are more depressed, while patients with impaired insight are more apathetic. This suggests that assessment of insight in AD may complement the clinical evaluation of depression and apathy in AD and help guide the most appropriate interventions.

Keywords

Insight; Alzheimer's disease; Dementia; Apathy; Depression

Global and gradual cognitive decline is the hallmark of Alzheimer's disease (AD) with the progression and severity of decline eventually reducing one's ability to function independently (American Psychiatric Association, 2000; Thies & Bleiler, 2011). In addition to cognitive decline, research has demonstrated that depression, anxiety, apathy, agitation, and other psychiatric and behavioral disturbances frequently occur throughout the disease process (Landes, Sperry, Strauss, & Geldmatcher, 2001; Levy, Cummings, Fairbanks, Bravi, Calvani, & Carta, 1998; Lyketsos, & Olin, 2002; Mega, Cummings, Fiorello, & Gornbein, 1996; Teri et al., 1999). In addition to cognitive impairment and reduction in ability to care for oneself, behavior and psychiatric disturbances are a large factor in a caregiver's decision to place a patient with AD into a structured living environment, such as an assisted-living facility or other long-term care setting (Haupt & Kurz, 1993; Steele, Rovner, Chase, &

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Folstein, 1990). Therefore, better understanding of the underlying causes for the psychiatric and behavioral disturbances in AD may assist in finding adequate treatments for these symptoms, as well as potentially reduce caregiver burden.

An impaired awareness of cognitive deficits among patients with AD, or rather a lack of insight, is also common, especially in later stages of the disease process (Cummings & Cole, 2002; Kashiwa et al., 2005; Mullen, Howard, David, & Levy, 1996). As the severity of an AD patient's cognitive dysfunction increases, so does their inaccurate insight (Ott et al., 1996; Harwood, Sultzer, & Wheatley, 2000). Impaired insight in AD has been associated with frontal lobe functioning, particularly the right lateral frontal area of the brain (Harwood et al., 2005). In addition to disease severity and cognitive functioning, insight in AD has also been found to be associated with psychiatric symptoms and behavioral disturbances (Harwood et al., 2000; Kashiwa et al., 2005; Landes et al., Sevush & Leves, 1993; Smith, Henderson, McCleary, Murdock, & Buckwalker, 2000). For example, Harwood et al. explored the association between impaired insight in AD patients and mood disturbances, as well as other commonly occurring psychiatric and behavioral symptoms associated with dementia. The authors found that AD patients who had greater awareness of their disease state experienced more depressed mood and anxiety after accounting for cognitive impairment (Harwood et al.). Sevush & Leves (1993) also reported similar findings, such that AD patients with greater awareness of their memory loss tended to express more depression.

Despite several studies which have documented a relationship between impaired insight, as well as a lack of awareness of deficits, to depression (Harwood et al., 2005; Kashiwa et al, 2005; Sevush & Leves, 1993), several studies have failed to find a significant relationship (Arkin & Mahendraw, 2001; Cummings, Ross, Absher, Gornbeing, & Hadjiaghai, 1995; Verhey, Rozendaal, Ponds, & Jolles, 1993). The discrepancies across the literature are likely due to the vast differences in how insight has been defined and measured. Also, limited research exists on the relationship between insight in AD to other psychiatric and behavioral disturbances, although recent findings have documented a positive relationship between anosognosia and apathy in AD (Vogel, Waldorff, Waldemar, 2010; Starkstein, Brockman, Bruce, & Petracca, 2010). Apathy commonly occurs in AD, and has been defined as a loss of motivation, accompanied by low interest, inactivity, emotional unresponsiveness, and also poor insight (Landes et al., 2001; Marin, 1990). Although apathy and depression present similarly in AD patients, the literature suggests a differential relationship. Insight may remain intact among depressed patients (Harwood et al., 2005; Kashiwa et al, 2005; Sevush & Leves, 1993) and impaired among those experiencing apathy (Vogel et al., 2010; Starkestein et al., 2010), despite similarities in the clinical presentation of both syndromes. The present study aimed to expand on previous findings, and to explore impaired insight in AD patients and its relationship to psychiatric symptoms and behavioral disturbances, particularly depressed mood, apathy, anxiety, psychosis, agitation, and behavioral retardation.

Methods

Participants

Data from $N = 107$ participants with probable AD were included in the study. Patients were recruited from the Greater Los Angeles VA Healthcare System Geropsychiatry Outpatient Program and from the UCLA Alzheimer's Disease clinics and met criteria for probable AD (McKhann et al., 1984; McKhann et al., 2011). Diagnosis was confirmed by a board certified geriatric psychiatrist (David Sultzer) based on a clinical evaluation that included a complete history, cognitive assessment, psychiatric assessment, neurological examination, and structural neuroimaging with magnetic resonance imaging (MRI) or computed

tomography (CT). Patients were excluded from the study if they had a history of premorbid psychotic disorder, history of head trauma resulting in a loss of consciousness, a psychoactive substance use disorder, or a systemic illness or other neurological condition accounting for cognitive impairment. The study was approved by the local IRB, and consent to participate was documented according to IRB guidelines.

Measures

Mini-Mental State Exam (MMSE)—Global level of cognitive functioning was assessed using the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975). The MMSE is a 30-point, clinician administered measure that broadly assesses orientation, memory, attention, language, and visuospatial functioning.

Neurobehavioral Rating Scale—The Neurobehavioral Rating Scale (NRS) is a clinician-rated scale originally developed by Levin et al. (1987) to assess the cognitive and behavioral symptoms typically associated with head trauma. The NRS has been found to be useful and reliable in assessing these symptoms among patients with AD (Sultzer, Levin, Mahler, High, & Cummings, 1992; Sultzer, Berisford, Gunay, 1995). The 28-item scale measures common neurocognitive, behavioral, and psychiatric disturbances often manifested by individuals with brain damage or neurodegeneration. Each item assesses a particular symptom, such as anxiety, depressed mood, and motor retardation, which is rated on scale from 0 to 6, whereas 0 = *not present* to 6 = *extremely severe*. Using principal components analysis, the NRS has six factors among patients with dementia, defined as follows: Cognition/Insight, Agitation/Disinhibition, Behavioral Retardation, Anxiety/Depression, Verbal Output Disturbance, and Psychosis (Sultzer et al., 1992). For the present study, the NRS item measuring level of impaired insight was utilized to assess overall insight. After a 30 minute structured interview, trained clinician-researchers rated a patient's level of insight. The insight rating was based on the observed relationship between how the patient views their current difficulties, level of disability, future plans and challenges, and the reality of those plans given the patient's cognitive functioning, functional abilities, and caregiver's report. Additionally, NRS items assessing depressed mood and anxiety, as well as NRS factor scores, including anxiety/depression, agitation/disinhibition, behavioral retardation, and psychosis, were used to measure the behavioral and psychiatric symptoms among AD patients.

Apathy Evaluation Scale

The Apathy Evaluation Scale (AES) was created to assess apathy as both a clinical state, as well as a symptom of a disease, such as dementia (Marin, Biedrzycki, & Firinciogullari, 1991). The AES consists of 18-items with responses measured on a 4-point Likert scale, ranging from *Not at all True* to *Very True*. Participants' caregivers completed the AES. The AES was used in the present study to measure AD patients' levels of apathy. Only a subset of the participants received the AES (n = 52), as it was added later to the study's initial protocol.

Results

Participant Information

The sample was 81.1% male with a mean age of 82.4 (SD = 6.6) at the time of enrollment. The mean years of education was 14.1 (SD = 3.6). The racial/ethnic breakdown of the sample was as follows: 67.6 % White/Anglo, 23.8% African-American, 4.8% Asian/Pacific Islander, and 3.8% Hispanic

Data Analysis

In order to determine the influence of insight to psychiatric and behavioral disturbances in patients with AD after controlling for cognition, a total of seven hierarchical regression analyses were conducted. For each of the regressions, a measure of global cognitive functioning (i.e., MMSE) was entered into the first step of the hierarchical regression to first account for the contribution of cognition. Next, the measure of insight was entered into the second step to determine if one's degree of insight predicts psychiatric or behavioral symptoms after accounting for cognitive functioning. All assumptions of the regression procedure were checked before interpretation of the results. Table 1 displays the mean and standard deviation for each variable. Please see Table 2 for a correlation matrix of all variables.

Regression Analyses

To test for statistical significance, the alpha level was set to the .05 level. Using R^2, effect sizes were defined as follows: (a) .01 is small, (b) .09 is medium, and (c) .25 is large (Cohen, 1992). Tables 3 and 4 display a summary of the results for each of the regression analyses. The first hierarchical multiple regression analysis was conducted to determine if one's level of insight predicted level of anxiety after accounting for global cognition. After accounting for MMSE scores, level of insight was found to significantly predict levels of anxiety and depressed mood in the second step of the models (F[1, 102] = 4.80, p = .03, n = 105 and F[1, 102] = 6.00, p = .02, n = 105), with 4% of additional variance in anxiety levels and 6% in depressed mood being accounted for by insight (see Table 3). Specifically, a greater degree of intact insight was associated with greater levels of anxiety and depressed mood. Level of insight was also found to significantly predict degree of apathy after controlling for MMSE scores (F[1, 49] = 6.64, p = .01, n = 52), with 11% of additional variance being accounted for in degree of apathy by insight (see Table 3). In contrast to anxiety and depression, more impaired insight was associated with greater levels of apathy.

Regarding the factors scores on the NRS, level of insight was found to significantly predict the anxiety and depression factor score (F[1, 101] = 4.84, p = .03, n = 104), with 5% of additional variance being accounted for by insight after controlling for cognition (see Table 4). Again, more intact insight was associated with greater levels of anxiety and depression. Finally, level of insight was not found to significantly predict the NRS factor scores for agitation/disinhibition (F[1, 101] = 0.49, p = .49, n = 104), behavioral retardation (F[1, 101] = 0.60, p = .44, n = 104), or psychosis (F[1, 101] = 0.78, p = .38, n = 104), after controlling for cognition (see Table 4). (Tables 3 and 4 about here)

Discussion

The results of the present study found significant relationships between insight and depressed mood, anxiety, and apathy among AD patients even after controlling for gross cognitive functioning. Specifically, more intact insight was related to anxiety and depressed mood, whereas impaired insight was related to greater apathy. In other words, patients who were more likely to show awareness and appreciation for their disease state and other circumstances were also more likely to experience depressed mood or anxiety. Conversely, patients who were less likely to show this awareness were more likely to experience apathy. Overall, results demonstrated that per one unit increase in the NRS inaccurate insight item, there is a 3.00 unit increase in the Apathy Evaluation Scale, a .16 unit decrease both in both the NRS anxiety and depressed mood items, as well as a .45 unit decrease in the NRS factor score for depression and anxiety approximately, suggesting not only statistical, but clinically relevant findings. No relationships were found between insight and agitation/disinhibition, psychosis, or behavioral retardation after controlling for overall cognitive functioning.

Similar to the present findings, Harwood et al. (2000) also found an association between depressed mood and insight, supporting their theory that insight may allow an individual with AD to cognitively appraise declines in their overall functioning, which may contribute to feelings of sadness and hopelessness. The process of cognitive appraisal has long been understood as having a direct impact on one's emotional response (Lazarus & Folkman, 1984), and has been found to be a factor in how patients with chronic illness react to their situation, including experiencing feelings of depression (Bombardier, D'Amico, & Jordon, 1990). Accordingly, depression and also anxiety in AD may be an emotional response arising as a result of the understanding or appraisal that one will inevitably be faced with additional cognitive and functional decline (Lyketsos & Olin, 2002). Mood disturbances, such as feeling depressed or anxious, therefore, would be more likely to occur in patients who have this insight or awareness of inevitable decline, compared to patients who are unable to understand or accurately appraise the gravity of their disease state. If a patient with AD has accurate insight, they are likely to be able to apply a more accurate appraisal of their current situation, and may be at an increased risk for depression. Insight appears to play a large role in one's ability to cognitively appraise stressors, and consequently, impacts one's emotional experience or lack thereof (Harwood et al., 2000).

Other researchers have explored similar syndromes to impaired insight, including anosognosia in AD, which is usually defined as an individual's inability to recognize or be aware of their own disease state (Kashiwa et al., 2005; Smith et al., 2000; Starkstein et al., 2010; Vogel et al., 2010). Although conceptually distinct, anosognosia is a term often used interchangeably in the AD literature with insight or awareness into one's cognitive deficits. Kashiwa and colleagues explored the relationship between anosognosia in AD patients to psychiatric disturbances. The authors found that greater anosognosia (i.e., poor insight) was related to lesser degrees of self-reported depression, as well as higher levels of disinhibition (Kashiwa et al., 2005). Similar to the present study, anosognosia in AD has been found be significantly related to greater apathy (Starkstein et al., 2010; Vogel et al., 2010), further bolstering the argument that insight plays a role in the experience of mood and behavioral disturbances. Some previous reports have not found insight in AD to be related to depression or mood (Arkin & Mehendra, 2001; Cummings et al., 1995; Lyketsos & Olin, 2002; Verhey et al., 1993; Vogel, Waldorff, & Waldemar, 2010). Discrepancies across studies may be explained by the variability in how insight has been defined (i.e., denial of deficits, anosognosia, recognition of the severity of memory deficits) and measured (i.e., self-reported versus clinician-rated). Presently, there is no consensus on how to conceptualize the phenomenon. For example, Verhey et al. examined this concept as an "awareness of deficit" based on a neuropsychiatrist 4-point rating. Arkin & Mehendra (2001) attempted to assess insight in several ways, including utilizing the Geriatric Depression Scale (GDS) insight questions "Do you feel you have more problems with memory than most?" and "Is your mind as clear as it used to be?," as well as through a sentence completion task. The present study conceptualized insight as a broad phenomenon, taking into consideration not only awareness of cognitive deficits but also how patients plan for the future in light of these concerns. Therefore, this more globally defined concept of insight as measured in the present study appears to have a significant relationship to one's emotional responsiveness or lack thereof (i.e., depressed mood, anxiety, or apathy) even after accounting for the impact of cognitive decline.

Interestingly, also, is the differential relationship between insight to depressed mood and apathy. Apathy is a common behavioral disturbance in AD, but is frequently mistaken for depression due to the similarities of their presentations, particularly the shared feature of a loss of motivation (Landes et al., 2001; Marin, 1990). Although loss of motivation is observed in both, depression and apathy in AD are considered distinct symptoms, but are often difficult to distinguish (Landes et al., 2001; Levy et al., 1998). Within depression, a

cognitive appraisal of a perceived negative situation is typically followed by a negative affective state, which engenders the lack of motivation or reduced activity level observed among depressed patients (Beck, Rush, Shaw, & Emery, 1979; Lazarus & Folkman, 1984). This cognitive-emotional process requires a degree of insight or awareness of the perceived stressor which is being evaluated (e.g., disease, functional disability, cognitive decline). However, AD patients who are lacking insight into their situation may also experience a lack of motivation or inactivity, but for different reasons. Apathy, by definition, implies a lack of emotional responsiveness or concern resulting in reduced motivation or inactivity (Marin, 1990). This suggests that the lack of concern in apathy could be in part due to inaccurate insight or unawareness. Regarding the present study, AD patients who experienced apathy were more likely to have poor insight, whereas the opposite was true for patients with depressed mood. Examining the underlying etiology for the lack of motivation or inactivity typical in both syndromes, therefore, may assist a clinician in differential diagnosis between the two syndromes.

Relationships between psychiatric symptoms in AD may be related to shared neurobiological underpinnings. Impaired insight and anosognosia in AD have been associated with involvement of right lateral frontal brain regions (Harwood et al., 2005), orbitofrontal cortex, medial frontal cortex (L. Leskin, personal communication, December 28, 2012), and medial temporal cortex (Salmon et al., 2005). Apathy as a clinical syndrome in AD has been associated with greater pathology and reduction in functioning of the anterior cingulate cortex, the oribitofrontal cortex, and the ventromedial frontal regions of the brain (Guimaraes et al., 2008; Marshall, Fairbanks, Tekin, Vinters, & Cummings, 2006; Tunnard et al., 2011). Frontal lobe functioning is involved in decision-making, self-monitoring, and initiation of goal-directed behavior (Stuss & Knight, 2002). Thus, disruption in shared frontal lobe circuits that contribute to apathy, insight, and goal-directed behavior may further explain the co-occurrence of these symptoms (Starkstein et al., 2010).

Thorough assessment of an AD patient's level of insight may inform treatment planning, particularly by potentially assisting in differentiating the two syndromes (apathy versus depression), suggesting not only statistical, but clinically relevant findings. Intervention strategies are likely to differ based upon the target syndrome. For example, pharmacological treatment may be warranted in both syndromes, but the preferred treatment may vary based on whether the provider is targeting depression or apathy, such as treating apathy with methylphenidate or mood with antidepressants (Landes et al., 2001; Marin, Fogel, Hawkins, Duffy, & Krupp, 1995; Padala, Burke, Bhatia, & Petty, 2007; Thompson, Herrmann, Rapoport, & Lanctot, 2007). In addition, AD patients with intact insight who are experiencing depression may also benefit from individual or group psychotherapy. Life review/ reminiscence therapy, as well as behavior therapy, are two evidence-based psychotherapeutic approaches that have been found to be helpful in reducing depression among AD patients (Verkaik, van Weert, & Francke, 2005). Likewise, patients who are lacking in insight and experiencing apathy may benefit from more behavioral or sensory-based interventions, such as sensory stimulation (Verkaik al., 2005). Caregiver education and involvement may also be heavily emphasized in patients who are experiencing apathy in order to assist in initiating activities (Landes et al., 2001).

Limitations

This study has several limitations. First, mood symptoms and behavioral disturbances were assessed using a clinician's rating. Self-assessment of depressed mood and anxiety may provide a more accurate evaluation of a patient's emotional response, although this creates its own challenges due to cognitive deficits and the possibility for inaccurate recall of one's own mood states over time. Also, the patient population was predominantly male and Caucasian. Cultural and sex differences should be examined in future studies to determine if

these variables differentially impact the relationship between insight and psychiatric and behavioral disturbances.

Conclusions

Insight over and above cognitive functioning appears to play a role in an AD patient's experience of depressed mood, anxiety, and apathy. Although patients experiencing depression and apathy may initially present quite similarly, their overall experience is likely to be quite distinct. Therefore, assessment of an AD patient's level of insight may help the clinician to better recognize a primary depression or apathy syndrome, which in turn may inform treatment planning.

Additional research on insight in AD should continue to explore its relationship to other psychiatric and behavioral disturbances in order to improve clinical diagnostic formulations and treatment plans. Better treatment of the associated symptoms would likely improve caregivers' and AD patients' quality of life, as well as reduce the healthcare burden through avoidance of premature institutionalization (Haupt & Kurz, 1993; Steele et al., 1990). Additionally, research exploring insight as a diagnostic component within depression in AD may help to better define the clinical syndromes of depression and apathy in AD and inform treatment approaches in the future.

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Key Points

1. Impaired insight is common among patients with AD, especially as the disease progresses, and may be related to the patient's experience of depression, anxiety, and apathy.
2. Among patients with Alzheimer's disease, intact insight is related to depressed mood and anxiety, whereas impaired insight is related to greater apathy, even after controlling for cognitive functioning.
3. Although apathy and depression may present similarly in patients with AD, they are distinct syndromes. Therefore, assessment of an AD patient's level of insight may assist a clinician with greater recognition of the target syndrome (e.g., depression or apathy), which in turn may inform treatment planning.

Table 1

Means and Standard Deviations

	Mean	Minimum	Maximum
MMSE	19.4 (4.7)	9	28
NRS Impaired Insight	3.1 (1.4)	0	5
NRS Anxiety	0.9 (1.1)	0	4
NRS Depressed Mood	0.8 (1.2)	0	4
NRS Factor AG/D	3.8(4.7)	0	17
NRS Factor BR	4.3 (3.7)	0	11
NRS Factor AX/D	2.9 (3.1)	0	11
NRS Factor P	1.6 (1.9	0	6
AES	21.2 (10.9)	0	40

Note. Standard deviations are shown in parentheses. NRS = Neurobehavioral Rating Scale; AES = Apathy Evaluation Scale; NRS Factor AG/D = NRS Factor Score Agitation/ Disinhibition; NRS Factor BR = NRS Factor Score Behavioral Retardation; NRS Factor AX/D = NRS Factor Score Anxiety/ Depression; NRS Factor P = NRS Factor Score Psychosis

Table 2

Spearman Correlations between Insight and Symptom Inventories in Patients with AD

	MMSE	NRS Impaired Insight	NRS Anxiety	NRS Depressed Mood	NRS Factor AG/D	NRS Factor BR	NRS Factor AX/D	NRS Factor P	AES
MMSE	1.00	−.45**	−.12	−.02	−.38**	−.18	−.11	−.31**	−.19
NRS Impaired Insight		1.00	−.15	−.21*	.19	.12	−.17	.20*	.35**
NRS Anxiety			1.00	.39**	.46**	−.17	.77**	.35**	−.19
NRS Depressed Mood				1.00	.28**	.17	.73**	.17	.04
NRS Factor AG/D					1.00	−.01	.48**	.47**	.26
NRS Factor BR						1.00	.00	−.21*	.25
NRS Factor AX/D							1.00	.36**	−.08
NRS Factor P								1.00	.09
AES									1.00

Note. NRS = Neurobehavioral Rating Scale; AES = Apathy Evaluation Scale; NRS Factor AG/D = NRS Factor Score Agitation/ Disinhibition; NRS Factor BR = NRS Factor Score Behavioral Retardation; NRS Factor AX/D = NRS Factor Score Anxiety/ Depression; NRS Factor P = NRS Factor Score Psychosis

* $p < .05$;

** $p < .01$

Table 3

Regression Analyses Predicting Depressed Mood, Anxiety, and Apathy from Insight and MMSE

	NRS Depressed Mood		NRS Anxiety		AES	
Predictor	**ΔR^2**	**β**	**ΔR^2**	**β**	**ΔR^2**	**β**
Step 1	.00		.03		.05	
MMSE		.02		−.17		−.22
Step 2	.06*		.04*		.11**	
MMSE		−.10		−.28**		−.02
NRS						.39**
Insight		−.27*		−.24*		
Total R^2	.06*		.07*		.16	
N	105		105		52	

Note. ΔR^2 = Change in R^2; β = Standardized Beta Coefficients; *N* = Number of Participants; NRS = Neurobehavioral Rating Scale

* $p < .05$;

** $p < .01$

Table 4

Regression Analyses Predicting NRS Factor Scores from Insight and MMSE

	NRS Factor AG/D		NRS Factor BR		NRS Factor AX/D		NRS Factor P	
Predictor	**ΔR^2**	**β**	**ΔR^2**	**β**	**ΔR^2**	**β**	**ΔR^2**	**β**
Step 1	.19**		.01		.02		.13**	
MMSE		−.43**		−.12		−.14		−.36**
Step 2	.00		.01		.05*		.01	
MMSE		−.40**		−.08		−.25*		−.32**
NRS		.07		−.09		−.24*		.09
Insight								
Total R^2	.19**		.02		.07*		.14**	
N	104		104		104		52	

Note. ΔR^2 = Change in R^2; β = Standardized Beta Coefficients; *N* = Number of Participants; AES = Apathy Evaluation Scale NRS Factor AG/D = NRS Factor Score Agitation/ Disinhibition; NRS Factor BR = NRS Factor Score Behavioral Retardation; NRS Factor AX/D = NRS Factor Score Anxiety/ Depression; NRS Factor P = NRS Factor Score Psychosis

* $p < .05$;

** $p < .01$