ORIGINAL CONTRIBUTION

Behavioral Disorders in Alzheimer Disease: A Transcultural Perspective

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Objectives: To compare 2 samples of patients with Alzheimer disease (AD), from Italy and the United States, in order to determine transcultural differences in the manifestation of noncognitive symptoms. To analyze the concurrent validity, internal consistency reliability, between-rater reliability, and test-retest reliability of the Neuropsychiatric Inventory Scale (NPI).

Methods: The NPI was given to 50 Italian and 50 US patients with AD. To demonstrate the validity and reliability of the Italian version of the instrument, several different methods of analysis were used. The total score on the NPI and the score of single items in the different stages of the disease were compared in the 2 samples of patients.

Results: A high level of internal consistency reliability was confirmed, the between-rater reliability was very high, and the test-retest reliability was significantly correlated. Apathy was the most frequently recorded behavior in the Italian sample. Five of 10 NPI item scores showed a significant relation with the Mini-Mental State Examination scores in both samples. The Italian patients showed an increasing and significantly higher mean NPI total score at all levels of dementia severity when compared with the US patients. The scores on some NPI subscales, such as apathy, aberrant motor behavior, disinhibition, and agitation, were significant higher in Italian patients at different levels of severity covarying with educational level.

Conclusions: These results indicate that NPI is a reliable instrument with which to study transcultural differences in the presentation of neuropsychiatric disturbances in patients with AD. The described similar pattern of behaviors between Italians and US patients with AD suggests a biological origin of the disorders. However, cultural influences must be taken in account when the focus of the study is on psychopathological aspects of dementia.

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ALZHEIMER disease (AD) is a neurodegenerative disease manifested by progressive intellectual decline.[1] It has been found to be present in all ethnic groups and most countries in which it has been sought. In view of the aging of the global population[2] and the marked rise of the prevalence of AD with increasing age,[3] studies of AD in different world populations are imperative.

The cognitive abnormalities of AD include loss of memory, language, visuospatial skills, and executive function. In addition to the neuropsychological impairment produced by AD, the disease causes marked behavioral changes, including apathy, agitation, delusions, depressive symptoms, anxiety, irritability, and disturbances of sleep and appetite (for an extensive review of the literature, see reference 4). The behavioral changes are the source of caregiver distress, may lead to elder abuse,[5] and are the most common cause of patient institutionalization in the United States.[6] Behavioral alterations are a major factor in the cost of AD because of the expense of nursing home residence, the cost of psychotropic medications, and the expenditures associated with adverse effects of psychotropic agents. Information concerning the consistency of behavioral manifestations of AD in different cultures is critical to anticipating the impact of the disease on caregivers, the use of medications, and the potential need for behaviorally oriented resources for patients with AD. Such studies would also provide preliminary insight into which behaviors are more culturally determined and which are more determined by underlying biological changes of the disease.

A number of instruments have been developed for either the global assessment of neuropsychiatric symptoms or the investigation of specific disorders, such as

PATIENTS AND METHODS

PATIENTS

The study included 50 outpatients with dementia who were examined at the outpatient clinic of the Alzheimer's Disease Unit of the Sacro Cuore Institute in Brescia, Italy, and 50 outpatients with dementia attending the Veterans Affairs Memory Disorders Clinic or the UCLA Geriatric Behavioral Neurology Clinic in Los Angeles, Calif.

All patients underwent thorough mental status testing, neurological examination, laboratory testing, and neuroimaging with computed tomography or magnetic resonance imaging. Patients met criteria of probable AD established by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders.[13] Exclusion criteria included (1) a history of head injury with loss of consciousness; (2) substance abuse or dependence; and (3) a history of psychiatric disturbances prior to the onset of dementia. Each patient had a full-time caregiver willing to report observations about the patient. Overall dementia severity of the patients with AD was evaluated with the Mini-Mental Status Examination (MMSE).[14] After a complete description of the study, written informed consent was obtained from each patient.

NEUROPSYCHIATRIC INVENTORY

The caregivers were interviewed using the NPI, providing data pertaining to the patients. Ten behavioral domains are evaluated by the NPI: delusions, hallucinations, agitation and aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability and lability, and aberrant motor activity. The NPI is based on screening questions that provide an overview of each specific domain. The screening questions are used to ask the caregiver whether the patient's behavior changed after the onset of the dementia and, if so, whether the altered behavior was present during the preceding month. If the caregiver indicates that the abnormal behavior was present, that domain is explored with structured subquestions that provide more detailed information about the specific features of the behavioral disturbances. After the subquestions, the caregiver is asked to rate the severity (1 indicates mild; 2, moderate; and 3, severe) and the frequency (1 indicates occasionally, less than once per week; 2, often, about once per week; 3, frequently, several times per week but less than every day; and 4, very frequently, once or more per day or continuously) of the neuropsychiatric disturbances. Defined anchor points for severity and frequency allow caregivers to provide ratable answers. Thus, the NPI provides frequency and severity scores for 10 subscales. A total subscale score is calculated by multiplying frequency and severity (for a maximum score of 12; eg, if the score of frequency is 3 and the severity is 3, then the total subscale score is 9). A global score for the NPI is generated by summing the total scores of the individual subscales (maximum score, 120).

Content validity, concurrent validity, between-rater reliability, and test-retest reliability of the NPI have been demonstrated.[12] Concurrent validity with the BEHAVE-AD and the Hamilton Depression Rating Scale was established.[12] Furthermore, 78% of the items showed no significant relationships, indicating that they were independent of each other and were assessing different behaviors.

TRANSLATION OF THE NPI

The NPI was translated from English into Italian and then back-translated from Italian into English to ensure the fidelity of the translation. The translation and back-translations were done by 2 independent individuals who were native to the northern Italy area where the NPI was used and who were familiar with linguistic and cultural nuances that could affect the interpretation of the NPI questions.

BETWEEN-RATER RELIABILITY

Between-rater reliability was determined by having 2 raters score the NPI responses of the caregiver. The scored interview was conducted by 1 of the raters; the 2 raters were not the same in each interview. Each rater was blind to the rating chosen by the other. Fifty NPI assessments were included in the interrater reliability study and all caregivers participated in the test-retest reliability study.

TEST-RETEST RELIABILITY

Test-retest reliability was determined by conducting a second NPI interview with the caregivers. The second interview was accomplished within 3 weeks of an initial interview. Fifty caregivers participated in the test-retest reliability assessment of the NPI.

STATISTICAL ANALYSIS

The psychometric properties of the NPI were studied with several approaches. The Cronbach α coefficient was determined to assess internal consistency reliability. Pearson correlations were calculated for the item-independence study. Percent-agreement analyses were used for between-rater reliability, and correlation coefficients were generated for test-retest reliability calculations. Spearman correlation coefficients were used to explore the relationship between NPI subscale scores and demographic factors or MMSE scores. The Student t test was used to compare demographic variables of the US and Italian samples. All data in the text are presented as mean ± SD. An analysis of the covariance was performed to compare the 2 samples on the subscale score of the NPI in the different phases of the disease.

depression.[7-11] Most of these tools, however, assess a relatively restricted range of behavior, lack differential diagnostic capability, or use direct patient observation, possibly underestimating neuropsychiatric symptoms not evident during the examination. Cummings et al[12] have developed a new scale, the Neuropsychiatric Inventory (NPI), to evaluate, on the basis of information provided by the caregiver, a wide range of behaviors encountered in patients with dementia. The NPI provides a means of distinguishing frequency and severity of behavioral changes and facilitates rapid behavioral assessment through the use of screening questions.

Table 1. Frequency and Severity Scores and Interrater Reliability (Percent-Agreement Approach) on the 10 Subscales of the Neuropsychiatric Inventory Scale Subscales in 50 Italian Patients With Alzheimer Disease

	Mean ± SD		Between-Rater Agreement	
Behavior	Frequency	Severity	Frequency	Severity
Delusions	1.2 ± 1.6	0.9 ± 1.2	95.5	88.6
Hallucinations	1.0 ± 1.6	0.7 ± 1.0	97.7	100
Agitation/aggression	1.8 ± 1.7	1.2 ± 1.1	88.6	88.6
Dysphoria	2.3 ± 1.7	1.5 ± 1.2	88.6	84.1
Anxiety	2.0 ± 1.7	1.2 ± 1.2	90.9	84.1
Euphoria	0.08 ± 0.3	0.06 ± 0.2	97.7	100
Apathy	3.2 ± 1.4	1.9 ± 1.1	90.9	88.6
Disinhibition	0.7 ± 1.4	0.5 ± 1.0	93.0	93.0
Irritability/liability	1.4 ± 1.6	1.0 ± 1.1	93.2	93.2
Aberrant motor activity	2.2 ± 1.8	1.5 ± 1.2	95.5	88.6

To our knowledge, assessment of the prevalence and nature of behavioral changes in AD in US patients compared with matched patients in other countries and studied using the same instruments has not been accomplished previously. To better understand the behavioral manifestations of AD and to assess the possible influences of different cultural settings on the behavior of patients with AD, we compared patients in southern California with patients in northern Italy.

RESULTS

NPI PROFILE IN ITALIAN PATIENTS

Caregivers providing behavioral information were all family members of the Italian patients with AD. Fifty caregivers participated in the validity study. The patients varied in age from 55 to 90 years (75.8 ± 7.8 years); there were 19 men and 31 women. The patients had from 2 to 16 years of education (6.0 ± 2.9 years). The duration of dementia ranged from 6 to 156 months (37.7 ± 31.2 months), and the MMSE scores ranged from 0 to 28 (12.1 ± 7.7).

Table 1 shows the scores of the 10 subscales of the NPI for the 50 Italian patients with AD in the validity study. These data show that a wide range of neuropsychiatric disturbances were present in the study subjects, although the mean scores tended to be relatively low. Apathy was the most commonly recorded behavior; dysphoria, anxiety, and aberrant motor behavior were also frequently described by the caregivers. Euphoria and disinhibition were the behaviors least often reported and had the most restricted range of expression.

Five of the 10 subscale scores of the NPI had significant relationships with MMSE scores: apathy (r = –0.23, P = .05), agitation (r = –0.22, P = .05), abnormal motor behavior (r = -0.21, P = .05), hallucinations (r = –0.34, P = .01), and euphoria (r = 0.28, P = .01). Only abnormal motor behavior showed a significant relationship with duration of illness (r = 0.24, P = .05). No significant correlations between NPI items and demographic variables, such as age, sex, and education, were found.

Table 2. Demographic Variables of the US and Italian Patients With Alzheimer Disease With Mild, Moderate, and Severe Dementia*

	Dementia		
Variables	Mild	Moderate	Severe
Age, y			
US patients	75.1 (56-88)	76.5 (60-88)	72.6 (63-81)
Italian patients	77.7 (69-87)	74.4 (55-92)	75.7 (59-85)
Education, y			
US patients	14.7 (12-18)	14.4 (12-20)	13.4 (8-20)
Italian patients	7.1 (3-12)†	5.4 (2-16)†	6.0 (3-13)†
Sex			
US patients	9/11	10/8	6/6
Italian patients	3/9	11/12	5/10
MMSE score			
US patients	23.5 (20-29)	15.9 (10-19)	5.3 (0-9)
Italian patients	21.8 (20-28)	15.5 (10-19)	3.1 (0-8)

**Mild dementia is defined by Mini-Mental State Examination (MMSE) scores of 21 through 30; moderate dementia, by MMSE scores of 11 through 20; and severe dementia, by MMSE scores of 0 through 10. All values are expressed as mean (range) unless otherwise indicated.*

†Student t test, P<.001.

RELIABILITY STUDY

The Cronbach coefficient α was calculated to determine the internal consistency (internal consistency reliability) among the items from the 50 NPIs. The Cronbach α for overall reliability was 0.76. The Cronbach α varied between 0.68 and 0.74 for both severity and frequency of individual items, establishing a high level of internal consistency reliability.

Between-rater reliability was determined using a percent-agreement approach. Between-rater agreement was very high (Table 1). Overall, this analysis demonstrates that the NPI is highly reliable when used by different examiners. The test-retest score for all scored measures was significantly correlated; the overall correlation for the total NPI score was 0.78 (P<.001).

COMPARISON OF ITALIAN AND US PATIENTS WITH AD

One hundred NPI assessments were included in the comparative study: 50 from Italian patients with AD and 50 from US patients with AD. The characteristics of the US patients with AD have been previously reported.[4] The participants were caregivers of outpatients with AD. **Table 2** shows demographic features of the Italian and US samples subdivided in terms of dementia severity according to MMSE scores (mild, 21-30; moderate, 11-20; and severe, 0-10).

The 2 samples did not differ significantly in terms of age or male-female ratio (although the Italian sample consisted of a relatively higher number of women), but there was a significant difference in years of education (P<.001), with lower levels among the Italian patients.

As can be seen in **Table 3**, the NPI total scores (Frequency × Severity × 10 Subscales; range of the NPI total score, 0-120) increased with increased severity of dementia, but the Italian sample displayed significantly higher mean NPI total scores (*P*s, <.005-<.01), at all levels of severity of dementia.

With respect to the NPI subscale scores, Italian patients displayed higher scores than US patients on all behaviors and at all levels of dementia severity, and, in some cases, the differences were significant (**Figure**). Italian patients with mild dementia showed significantly higher NPI scores on euphoria ($P<.005$), apathy ($P<.005$), and aberrant motor behavior subscores ($P<.005$); Italian patients with moderate dementia showed significantly higher NPI scores on dysphoria ($P<.001$), apathy ($P<.05$), irritability ($P<.05$), and aberrant motor behavior subscores ($P<.005$); and Italian patients with severe dementia showed significantly higher NPI scores on hallucination ($P<.05$), apathy ($P<.005$), and aberrant motor behavior subscales ($P<.05$) (**Table 4**).

Education was significantly different between the 2 national samples, and we performed a covariant analysis with education as a covariate. Significant differences remained for agitation ($P<.05$), apathy ($P = .001$), disinhibition ($P<.05$), and aberrant motor behavior ($P<.01$) between the 2 samples. To determine what behaviors were independent of the cognitive impairment, as measured by the MMSE, we analyzed the data with the MMSE as a covariate. Significant differences continued for dysphoria ($P<.001$), anxiety ($P<.05$), apathy ($P<.001$), irritability ($P<.05$), and aberrant motor behavior ($P<.001$).

Table 3. Neuropsychiatric Inventory Scale Total Scores of the US and Italian Patients With Alzheimer Disease With Mild, Moderate, and Severe Dementia*

	Dementia, Mean ± SEM		
Patients	**Mild**	**Moderate**	**Severe**
US	9.1 ± 2.1	15.9 ± 2.6	22.9 ± 2.5
Italian	26.0 ± 7.0†	35.6 ± 4.2‡	43.7 ± 6.0‡

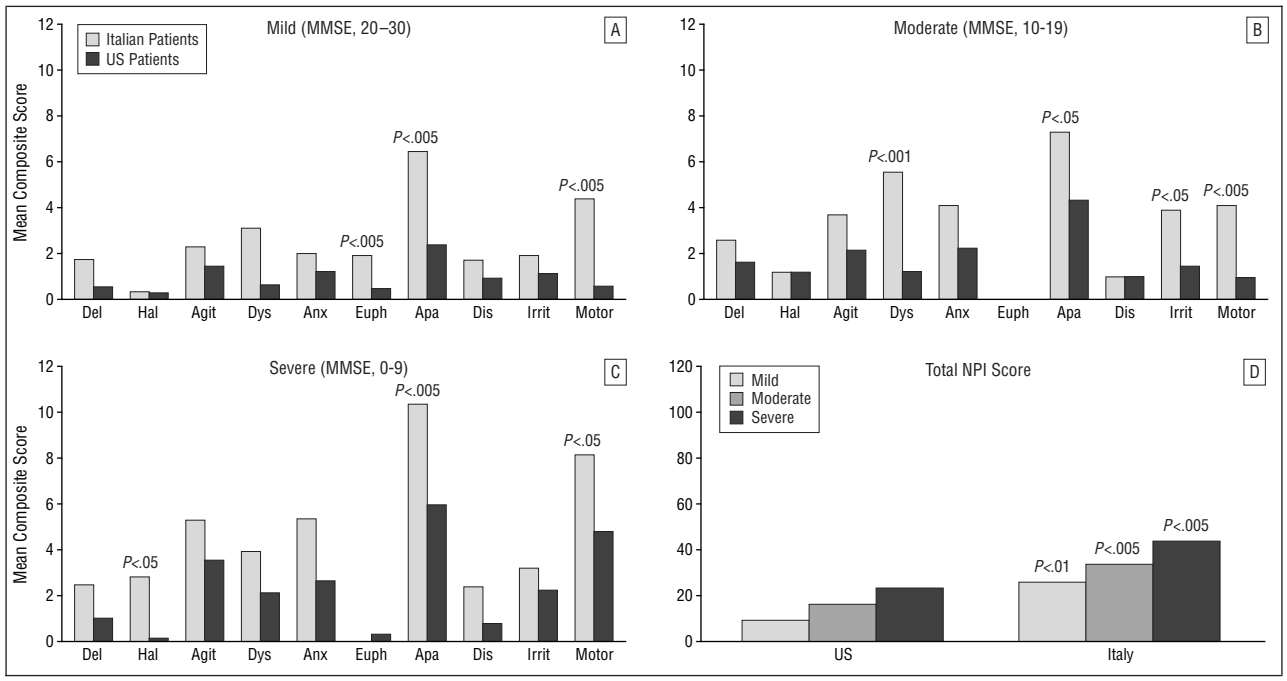
**The maximum total score is 120 (Frequency× Severity× 10 Subscales).*
†Student t test, P<.01.
‡Student t test, P<.005.

COMMENT

This study established the reliability of the NPI when applied to an Italian population of patients with AD. Our results confirmed that there is high internal consistency reliability, between-rater reliability, and test-retest reliability. To our knowledge, it is the first study to directly compare noncognitive disturbances in patients with AD from different cultural backgrounds.

There were several important findings. First, patients with AD display a wide range of behavioral disturbances. Second, dementia severity, as measured by the MMSE, was found to be related to the presence of neuropsychiatric symptoms, with more cognitively impaired patients exhibiting more neuropsychiatric disturbances. In particular, MMSE scores were significantly associated with NPI subscale scores for apathy, agitation, and abnormal motor behavior, while the euphoria score was higher on the NPI in patients with mild dementia. Psychotic symptoms as well as dysphoria showed a relatively constant frequency across dementia severity stages.

There were many similarities observed between the NPI scores of the Italian and the US patients with



Comparison of subscale scores (A, B, and C) on the Neuropsychiatric Inventory Scale (NPI) and the total NPI score (D) for Italian and US patients with Alzheimer disease with mild, moderate, and severe levels of dementia. MMSE indicates Mini-Mental State Examination; Del, delusions; Hal, hallucinations; Agit, agitation/aggression; Dys, dysphoria; Anx, anxiety, Euph, euphoria; Apa, apathy; Dis, disinhibition; Irrit, irritability/lability; and Motor, aberrant motor activity.

AD. Apathy, agitation, and abnormal motor behavior were most frequent in both patient samples. Disinhibition and euphoria were the least frequently endorsed items in both patient samples. In both groups, neuropsychiatric symptoms tended to increase with the severity of the dementia. Subscale scores for apathy, agitation, and abnormal motor behavior were inversely correlated with the MMSE scores (more severe dementia and more severe noncognitive disturbances), whereas the euphoria subscale scores were directly correlated with the MMSE scores (more euphoria in less severe dementia) in both patient samples. Thus, the overall profile of behavioral changes, as well as the relationships of the behavioral changes to dementia severity, was similar in the Italian and US cohorts.

There were also differences between the Italian and US patients. The mean NPI total scores and the NPI subscale scores were higher in the Italian sample, regardless of the severity of the dementia. The 2 samples were relatively homogeneous, as both included outpatients with AD and did not differ significantly in terms of years of age or sex distribution. There was a significant difference of years of education. It has been reported previously that, in patients with dementia, education is a significant determinant of psychosis[10,15] and is associated with a higher level of depression.[16] Lower education levels in the Italian sample might have played a role in the global increase in NPI scores compared with the US sample, but when a covariant analysis with education as a covariate was performed, a significant difference between the 2 samples was still obtained for agitation, apathy, disinhibition, and aberrant motor behavior.

An alternative hypothesis is that cultural differences contributed to the findings. Caregivers in Italy, most of whom come from small cities or rural locations, may be less sensitized to the problem of dementia. Consequently, they minimize and passively accept the cognitive deterioration associated with dementia, and seek clinical interventions when psychiatric disturbances occur. This hypothesis would constitute a culturally based selection bias emphasizing the presence of psychopathological changes.

A third possibility is that there was a lack of interrater reliability across the 2 populations studied. The NPIs were administered by US investigators to the US population and by Italian investigators to the Italian population. However, the scripted nature of the questions, the standardized method of administration, and the strict scoring criteria of the NPI minimize the opportunity for interrater discrepancies; and use of culturally syntonic interviewers improves the validity of the information. Interrater studies conducted both in the current study and by Cummings et al[12] showed high levels of interrater reliability for the NPI.

Some limitations of our study need to be considered. The investigation was based on information gathered from caregivers and, therefore, may be biased by limitations of caregivers' insight as well as their emotional states. There is currently little consensus regarding whether the source of the information may affect the reported rate of psychiatric changes in AD. Cohen and Eisdorfer[17] pointed out that caregivers may tend to report higher frequencies of psychopathological changes than clinical observers as a consequence of the high rate of depression among caregivers. Conversely, no evidence of such a confounding effect of caregiver mood was found by Cummings et al,[18] who studied caregivers' depression scale scores in relation to their reports of depression in their family members. Finally, no validity studies were performed in the current investigation to study the relationship of the NPI responses and the instruments previously used to study neuropsychiatric symptoms in Italian patients with AD. The lack of highly developed instruments for the study of Italian patients with AD, the secure validity of the English-version NPI, and the relationships between Italian and US patients observed in the current study, as well as the concurrence between the Italian investigators' clinical impression and the results of the NPI, all suggest that the results are valid.

Similarities between the Italian and US patients with AD suggest that the observed behaviors are neurobiologically determined. Their uniformity across cultures supports the hypothesis that they are of biological

Table 4. Neuropsychiatric Inventory Scale Subscale Scores of Italian and US Patients With Mild, Moderate, and Severe Dementia as Measured by the MMSE*

	Dementia, Mean ± SEM		
Subscales	**Mild**	**Moderate**	**Severe**
Delusions			
Italian patients	1.8 ± 1.1	2.6 ± 0.8	2.5 ± 1.1
US patients	0.5 ± 0.4	1.6 ± 0.8	1.0 ± 0.5
Hallucinations			
Italian patients	0.3 ± 0.3	1.2 ± 0.6	2.8 ± 1.2
US patients	0.2 ± 0.2	1.2 ± 0.8	0.1 ± 0.1†
Agitation/aggression			
Italian patients	2.3 ± 1.1	3.7 ± 0.8	5.3 ± 1.2
US patients	1.4 ± 0.5	2.1 ± 0.7	3.5 ± 0.7
Dysphoria			
Italian patients	3.1 ± 1.2	5.6 ± 0.9	3.9 ± 1.3
US patients	0.6 ± 0.4‡	1.2 ± 0.4	2.1 ± 0.6
Anxiety			
Italian patients	2.0 ± 1.1	4.1 ± 0.9	5.3 ± 1.4
US patients	1.2 ± 0.5	2.2 ± 0.7	2.6 ± 0.9
Euphoria			
Italian patients	1.9 ± 1.1	0	0
US patients	0.4 ± 0.2§	0	0.3 ± 0.3
Apathy			
Italian patients	6.5 ± 1.0	7.3 ± 1.0	10.3 ± 1.0
US patients	2.4 ± 0.7§	4.3 ± 0.6†	5.9 ± 0.9§
Disinhibition			
Italian patients	1.7 ± 1.2	1.0 ± 0.5	2.3 ± 1.1
US patients	0.9 ± 0.3	1.0 ± 0.4	0.7 ± 0.4
Irritability			
Italian patients	1.9 ± 1.1	3.9 ± 0.7	3.2 ± 1.3
US patients	1.1 ± 0.5	1.4 ± 0.6†	2.2 ± 0.7
Aberrant motor activity			
Italian patients	4.4 ± 1.4	4.1 ± 1.0	8.1 ± 1.2
US patients	0.6 ± 0.3§	0.9 ± 0.4§	4.7 ± 0.8§

*The maximum score is 12 (Frequency × Severity). MMSE indicates Mini-Mental State Examination.
†*Student* t *test,* P<.05.
‡*Student* t *test,* P<.001.
§*Student* t *test,* P<.005.

origin.[19] On the other hand, the differences observed between the 2 samples indicate that there are cultural influences that also must be taken into account when psychopathological changes are being investigated in patients with dementia.

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