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REVIEW ARTICLE

Neuropsychiatric symptoms in Brazilians with mild cognitive impairment and dementia

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Abstract

Introduction: Knowledge is limited about behavioral and psychological symptoms of mild cognitive impairment (MCI) and dementia in racial and ethnic minorities.

Methods: As part of the Pathology, Alzheimer's and Related Dementias Study (PARDoS), we interviewed knowledgeable informants of 2319 older Brazilian decedents (67% white, 11% black, 22% mixed) using the informant portion of the Clinical Dementia Rating Scale to classify MCI and dementia and the Neuropsychiatric Inventory to assess behavioral and psychological symptoms.

Results: We identified four clusters of neuropsychiatric symptoms: agitation, affect/apathy, psychosis, and behavioral problems. On the Clinical Dementia Rating Scale, 1407 had no cognitive impairment, 180 had MCI, and 732 had dementia. Both MCI and dementia were associated with symptoms in each behavioral/psychological cluster (all P's $< .001$). There was little evidence of racial differences in the association of MCI and dementia with these neuropsychiatric symptoms.

Conclusion: MCI and dementia are associated with elevated behavioral and psychological symptoms in older black and white Brazilians.

KEYWORDS
dementia, Latinx, mild cognitive impairment, neuropsychiatric inventory, racial differences

1 | INTRODUCTION

There is longstanding interest in the burden of behavioral and psychological symptoms in older persons with mild cognitive impairment (MCI) and dementia. Behavioral and psychological symptoms are common in dementia[1] and have been associated with adverse consequences including caregiver burden,[2,3] institutionalization,[4,5] and death.[6] There is substantial heterogeneity in the nature and severity of behavioral and psychological symptoms in those with dementia, but limited knowledge of the factors contributing to this heterogeneity. A basic question is whether symptoms differ in racial or ethnic minorities. However, most prior research has been conducted on Caucasians of non-Latin descent and the few studies of minority groups have had mixed results.[7–12]

The aims of the present study are to identify behavioral and psychological symptoms associated with MCI and dementia in older Brazilians and to test whether the symptoms differ by race. As part of the Pathology, Alzheimer's and Related Dementias Study (PARDoS), a community-based post-mortem study of aging and dementia, knowledgeable informants of older decedents in the state of Sao Paolo, Brazil, underwent a structured interview to ascertain demographic data, classify MCI and dementia, and rate behavioral and psychological

symptoms. In the analyses, we identified clusters of behavioral and psychological symptoms, established the associations of MCI and dementia with each symptom cluster, and tested whether these associations differed by race.

2 | METHODS

2.1 | Decedents and informants

PARDoS enrolls deceased older adults who died from natural nonviolent causes in the state of Sao Paulo, Brazil, and includes cases originally enrolled in the Study of Ancestry and Neurodegenerative Diseases. After legal representatives of the decedent signed a consent form for brain removal and examination of the decedent, informants were asked to sign a consent form for a structured interview while waiting for completion of the post-mortem examination. The study was approved both by the institutional review board and by the Brazilian national ethics committee Commissao Nacional de Etica em Pesquisa. Because participants are deceased, the study is exempt from human subjects review in the United States.

2.2 | Clinical interview

A study nurse conducted a structured 60- to 90-minute interview with an informant of the decedent. If more than one informant was available, we considered the responses from the individual most knowledgeable about the decedent (ie, with the most frequent contact). The interview covered basic demographic information including age at death, sex, years of formal education, and race. Informants were not compensated for participating in the interview.

2.3 | Assessment of dementia

We used the informant portion of the Clinical Dementia Rating Scale[13] to classify dementia and MCI proximate to death, as described previously.[14] Function in each of six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care) was rated on a 5-point scale. An algorithm converted the six domain scores to an overall rating of no cognitive impairment (score = 0), MCI (score = 0.5), or dementia (score >0.5). In prior research, ratings of dementia based on the informant portion of the Clinical Dementia Rating Scale have been shown to have good agreement with diagnoses based on an in-person examination.[15,16]

2.4 | Assessment of behavioral and psychological symptoms

Behavioral and psychological symptoms were assessed with the Neuropsychiatric Inventory.[17] The informant was asked to rate each of 12 symptoms (eg, irritability, anxiety) as absent (score = 0), mild (score = 1), moderate (score = 2), or severe (score = 3). The inventory has been shown previously to have good psychometric properties in Brazilian[18,19] and groups of non-Latin descent.[17,20,21] Most factor analyses of the inventory have suggested that there are three[22,23] or four[24,25] symptom clusters.

2.5 | Statistical analysis

Because prior research has suggested that behavioral and psychological symptoms of dementia can be grouped into clusters,[26,27] we performed a factor analysis of the Neuropsychiatric Inventory.

RESEARCH IN CONTEXT

1. **Systematic review**: We searched PubMed with the term "neuropsychiatric symptoms" plus "dementia" or "mild cognitive impairment." We also searched the reference lists of these articles.
2. **Interpretation**: We identified four clusters of neuropsychiatric symptoms. Each cluster was elevated in Black and White persons with mild cognitive impairment (MCI) and dementia, supporting the idea that behavioral and psychological symptoms are core manifestations of dementia in racial and ethnic minorities.
3. **Future directions**: The results indicate that the associations of behavioral and psychological symptoms with MCI and dementia generalize across racial and ethnic lines. Better understanding of the neurobiological bases of neuropsychiatric symptoms in dementia could substantially reduce disease burden.

HIGHLIGHT

- A factor analysis of the Neuropsychiatric Inventory identified 4 symptom domains: agitation, affect/apathy, psychosis, behavioral problems.
- Based on structured informant interview, decedents were classified as no cognitive impairment, mild cognitive impairment, or dementia.
- Each symptom domain was elevated in those with mild cognitive impairment and dementia compared to those without cognitive impairment.
- Race did not modify the relation of diagnosis to symptom domains except for marginally fewer psychotic symptoms in black persons with dementia compared to white persons with dementia.

TABLE 1 Demographic characteristics of no cognitive impairment, mild cognitive impairment, and dementia subgroups

Characteristic	No cognitive impairment		Mild cognitive impairment		Dementia		Statistic	*P*
	Mean	SD	Mean	SD	Mean	SD		
Age at death	77.6	8.5	81.9	9.1	83.3	8.2	$F(2, 2316) = 114.9$	<.001
Education	5.1	3.9	4.7	3.8	4.4	3.6	$F(2, 2316) = 9.6$	<.001
Women, %	45.6		62.2		62.2		$X^2(2) = 61.2$	<.001
White race, %	39.8		5.4		21.6			
Black race, %	6.9		0.6		3.4		$X^2(4) = 3.8$	.434
Mixed race, %	14.1		1.7		.6			

We used a polychoric correlation-based factor analysis because the items are binary.[28] The minimal proportion criteria were used for extracting factors. The resulting factors were examined for clinical meaningfulness. To allow for intercorrelations between factors expected from the underlying disease processes driving dementia, we used a non-orthogonal rotation of the factors.[29] Because we have a Heywood case, the iterative maximum likelihood estimation method converged to less than zero boundaries; therefore, these unique variances were set to 0 and their corresponding commonalities were set to 1. Factor loadings represent the standardized regression coefficients.

To estimate the association of MCI and dementia with each behavioral/psychological factor score, we treated persons without cognitive impairment as the reference subgroup, which was separately contrasted with the MCI and dementia subgroups in a series of linear regression models. The outcome of each model was a behavioral/psychological factor score, and the model terms included the two subgroup comparisons plus age at death, sex, education, and race. To test whether the association of MCI or dementia with a given behavioral/psychological factor was modified by race, we repeated each of the original linear regression models with terms added for the interactions of each race term with each subgroup comparison.

3 | RESULTS

3.1 | Characteristics of decedents and informants

From August 28, 2017 to June 20, 2018, a total of 3013 individuals 65 years of age or older at death had a consent signed by a legal representative for brain removal and examination of the decedent, of whom 2552 (84.7%) agreed to do a clinical interview. Of these, we excluded 233 individuals missing data on education, the Clinical Dementia Rating Scale, or the Neuropsychiatric Inventory. Analyses are based on the remaining 2319 decedents. They died at a mean age of 79.5 (SD = 8.8; range: 65-110) predominantly of cardiovascular disease (62.9%), infectious diseases (21.1%), or cancer (2.2%). They had a mean of 4.9 years of education (SD = 3.9; range: 0-25); 51.3% were women; proxy-reported race was White in 66.7%, Black in 10.9%, and mixed in 22.4%. In analyses, we contrasted the White subgroup separately with the Black and mixed subgroups.

The informant interview took place a median of 28.5 days after death (interquartile range[IQR]: 1-274). The informants reported knowing the decedent for a mean of 46.7 years (SD = 12.7; range: 1-87). The relationship of the informant to the decedent was as follows: child (71.4%), grandchild (8.5%), sibling (4.9%), spouse (4.4%), other relative or in-law (1.6%), other (9.2%). In the last year of the decedent's life, 69.8% of informants reported daily contact, 28.5% reported weekly contact, and 1.7% reported monthly contact.

3.2 | Clinical classification

On the informant portion of the Clinical Dementia Rating Scale, 1407 individuals had a score of 0, consistent with no cognitive impairment; 180 individuals had a score of 0.5, consistent with MCI; and 732 had a score of 1 or greater, consistent with dementia. As shown in Table 1, individuals with MCI and dementia were older and less educated than those without cognitive impairment and were more likely to be women.

3.3 | Distribution of behavioral and psychological symptoms

Table 2 shows the frequency of individual symptoms on the Neuropsychiatric Inventory in all decedents and separately by clinical subgroup. Symptoms were not uncommon in the no cognitive impairment subgroup, with five symptoms reported in more than 10% of decedents (appetite, agitation, depression, apathy, irritability). The frequency of each symptom was higher in the MCI subgroup compared to the no cognitive impairment subgroup and higher in the dementia subgroup than the MCI subgroup. Overall, appetite, agitation, and depression were the most common symptoms in those with and without cognitive impairment.

3.4 | Behavioral and psychological symptom clusters

Previous research has shown that Neuropsychiatric Inventory symptoms can be grouped into clusters.[19–22] To identify symptom clusters, we performed a factor analysis of the item severity scores (Table 3).

TABLE 2 Frequency of individual Neuropsychiatric Inventory symptoms in the full group and the no cognitive impairment, mild cognitive impairment, and dementia subgroups

	Full group		No cognitive impairment		Mild cognitive impairment		Dementia	
Symptom	*N*	%	*N*	%	*N*	%	*N*	%
Agitation	683	29.5	248	17.6	52	28.9	383	52.3
Irritability	475	20.5	155	11.0	32	17.8	288	39.3
Disinhibition	381	16.4	115	8.2	23	12.8	243	33.2
Depression	583	25.1	217	15.4	50	27.8	316	43.2
Apathy	510	22.0	165	11.7	36	20.0	309	42.2
Appetite	936	40.4	394	28.0	75	41.7	467	63.8
Delusion	325	14.0	73	5.2	23	12.8	229	31.3
Hallucination	417	18.0	92	6.5	23	12.8	302	41.3
Anxiety	359	15.5	100	7.1	35	19.4	224	30.6
Euphoria	143	6.2	27	1.9	7	3.9	109	14.9
Motor	166	7.2	25	1.8	9	5.0	132	18.0
Sleep	436	18.8	85	6.0	29	16.1	322	44.0

TABLE 3 Psychometric information on Neuropsychiatric Inventory in the full group

				Rotated factor loading*			
Neuropsychiatric Inventory item	Mean	SD	Skewness	1 (Agitation)	2 (Affect/apathy)	3 (Psychosis)	4 (Behavioral problem)
Agitation	0.78	1.26	1.08	0.6	0.2	0.1	0.1
Irritability	0.51	1.06	1.71	0.6	0.3	0.0	0.0
Disinhibition	0.45	1.03	1.97	1.0	-0.1	0.0	0.1
Depression	0.64	1.16	1.40	0.1	0.9	0.0	0.0
Apathy	0.58	1.14	1.55	0.3	0.7	0.0	0.1
Appetite	1.05	1.35	0.63	–0.1	0.5	0.1	0.2
Delusion	0.35	0.92	2.37	0.1	0.0	1.0	-0.1
Hallucination	0.45	1.02	1.93	0.0	0.0	0.8	0.2
Anxiety	0.38	0.95	2.23	0.2	0.3	0.0	0.5
Euphoria	0.17	0.67	3.87	0.3	0.0	0.0	0.6
Motor	0.18	0.68	3.68	0.1	0.1	0.3	0.4
Sleep	0.48	1.04	1.84	0.1	0.2	0.2	0.5

*Factor analysis using Heywood method with polychromic and Promax rotation with factors chosen by the proportion method.

Because the item scores are skewed, we used the Heywood method and polychoric and Promax rotation to allow for interitem correlation. As shown in Table 3, four clusters emerged, which we labeled agitation (factor 1), affect/apathy (factor 2), psychosis (factor 3), and behavioral problems (factor 4).

To develop behavioral and psychological factor scores, we multiplied each item score by its weight for a given factor and summed the resulting products. Table 4 shows the means and SDs for these factor scores. Older age was associated with higher factor score in each domain. Higher educational attainment was associated with lower levels of two factors: psychotic symptoms and behavioral problems. Women had higher levels of affect/apathy (1.63 vs 1.36, $t[2317] = 3.1$, $P = .002$), psychosis (0.78 vs 0.64, $t[2317] = 2.0$, $P = .047$), and behavioral problems (0.70 vs 0.53, $t[2313] = 3.2$,$P = .001$) than men but did not differ in agitation.

3.5 | Behavioral and psychological symptom clusters in MCI and dementia

To determine the association of clinical diagnoses with behavioral/psychological symptom clusters, we treated those with no cognitive

TABLE 4 Psychometric information on behavioral and psychological factors in the full group

Correlation (*P*)					
Behavioral/psychological factor	**Mean**	**SD**	**Range**	**Age**	**Education**
Agitation	1.22	2.08	0-6.60	.07 (.001)	-.02 (.307)
Affect/apathy	1.50	2.08	0-6.30	.05 (.010)	-0.2 (.213)
Psychosis	0.71	1.63	0-5.40	.11 (< .001)	-.04 (.049)
Behavioral problem	0.60	1.26	0-6.00	.12 (< .001)	-.06 (.006)

TABLE 5 Association of mild cognitive impairment and dementia with behavioral and psychological symptom factors*

	No cognitive impairment vs mild cognitive impairment			No cognitive impairment vs dementia		
Behavioral/psychological factor	**Estimate**	**SE**	**p value**	**Estimate**	**SE**	***P***
Agitation	0.366	0.154	.018	1.789	0.092	<.001
Affect/apathy	0.631	0.153	<.001	1.871	0.092	<.001
Psychosis	0.313	0.120	.009	1.400	0.072	<.001
Behavioral problem	0.316	0.091	<.001	1.216	0.054	<.001

*From four separate linear regression models adjusted for age at death, education, sex, and race.

impairment as the reference subgroup, which we contrasted with the MCI subgroup and the dementia subgroup. Each factor score was regressed on these two subgroup comparisons, with terms also included for the potentially confounding effects of age at death, sex, education, and race.

In these analyses, both MCI and dementia were associated with higher levels of each symptom cluster compared to those without cognitive impairment (Table 5). As shown in Figure 1, which is based on these analyses, all four behavioral and psychological clusters were slightly elevated in MCI and markedly elevated in dementia.

To determine whether the behavioral and psychological symptom clusters in cognitively impaired individuals varied by race, we repeated each regression model with terms added for the interaction of race (White vs Black, White vs mixed) with each subgroup comparison. Of the resulting 16 interaction terms, only one was significant: the association of dementia with psychotic symptoms was marginally weaker in persons of mixed race compared to White persons (estimate = -0.373, standard error [SE] = 0.169, $P = .027$).

4 | DISCUSSION

As part of a community-based study of aging and dementia, knowledgeable informants of more than 2300 older Brazilian decedents underwent a structured interview designed to support clinical classification of MCI and dementia and assessment of four clusters of behavioral and psychological symptoms. Symptoms in each cluster were elevated in those with MCI and dementia compared to those without cognitive impairment. The results support the idea that these clusters of behavioral and psychological symptoms are core manifestations of dementia and its precursor, MCI, in older persons of Latin descent.

Knowledge about behavioral and psychological symptoms in MCI and dementia is mainly based on research in Caucasians of non-Latin descent. This research has reported higher levels of behavioral and psychological symptoms in dementia[30,31] and usually in its precursor, MCI.[30,32–35] One previous study examined these associations in older Brazilian decedents.[12] The researchers reported that behavioral and psychological symptoms were elevated in those with dementia compared to those without cognitive impairment, but symptoms in the MCI subgroup did not differ from the no cognitive impairment subgroup. In the present study, we found a robust elevation of all four clusters of behavioral and psychological symptoms in MCI relative to no cognitive impairment, which is consistent with prior research in non-Latin Caucasians, possibly because using symptom domains as outcomes rather than individual Neuropsychiatric Inventory items reduced measurement error. The present results are also consistent with a previous finding of comparable overall levels of behavioral and psychological symptoms in Mexican Americans and non-Latin Caucasians with MCI.[11]

Prior research on racial differences in behavioral and psychological symptoms associated with MCI and dementia has been conducted mainly on Black and White persons of non-Latin descent. Results have been mixed. In dementia, Black persons have had more behavioral and psychological symptoms than White persons in some studies,[8,10] and fewer symptoms in other studies;[7,10] in MCI, behavioral and psychological symptoms are reportedly less common in Black than in White persons.[10] In contrast to prior research, the present analyses are based on Black and White persons of Latin descent. We found no racial differences in the behavioral and psychological symptoms in MCI. The only racial difference in those with dementia or MCI was marginally significant and involved only one clinical group (dementia), one factor score (psychosis), and one racial subgroup (mixed). Overall, therefore, there was little evidence of racial differences in the neuropsychiatric symptoms of MCI and dementia.

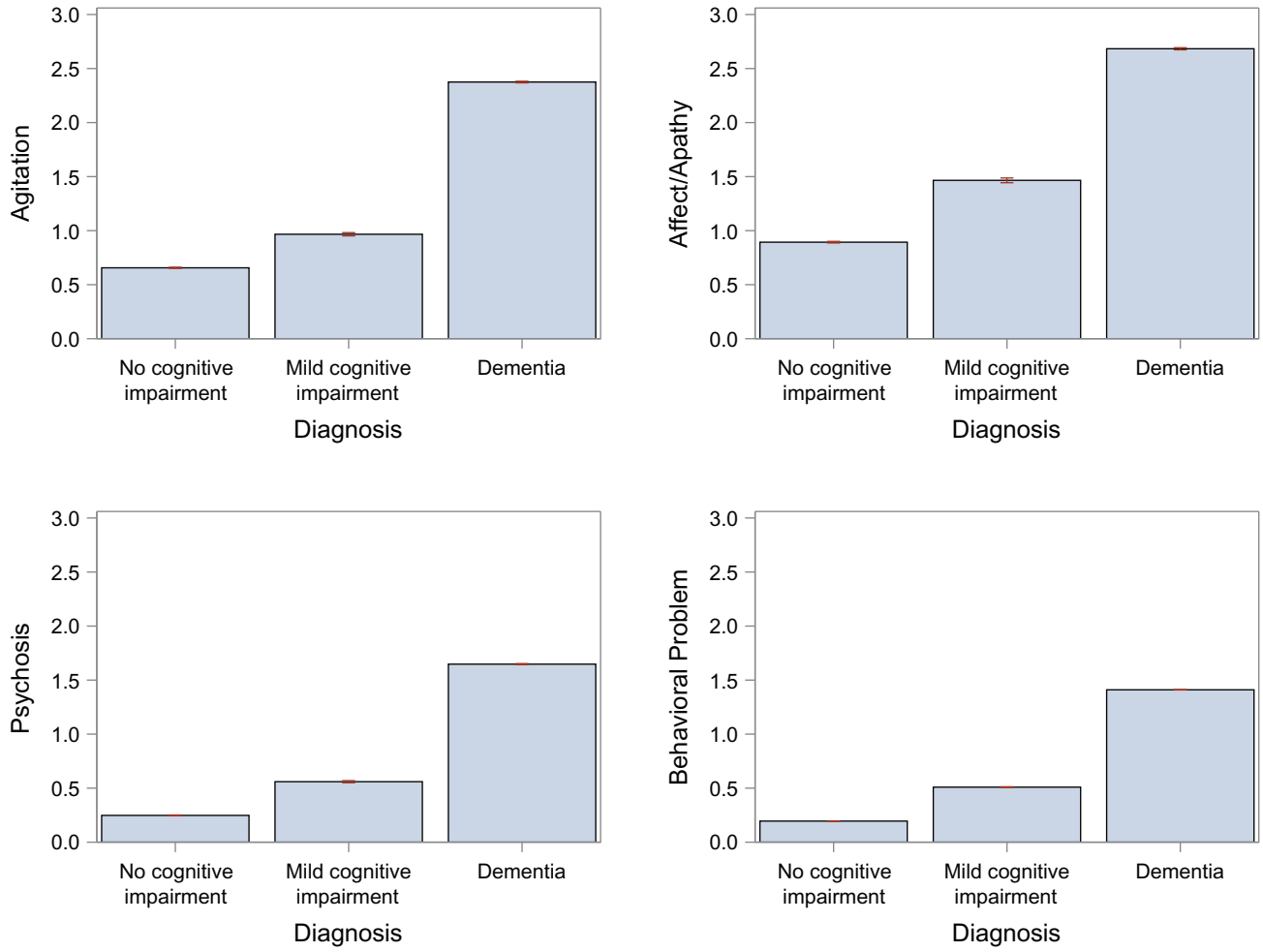

FIGURE 1 Severity of four clusters of behavioral/psychological symptoms in persons with no cognitive impairment, mild cognitive impairment, or dementia, adjusted for age at death, sex, education, and race

We found that the profile of behavioral and psychological symptoms in older persons of Latin descent with MCI and dementia was similar to the profile described in non-Latin groups. In addition, the association of MCI and dementia with behavioral and psychological symptoms was similar in Black and White persons of Latin descent. The similarity in these symptoms across racial and ethnic lines underscores that they are core components of dementia and that they are probably driven more by dementia-related changes in brain structure, chemistry, and function and less by sociodemographic factors.

Strengths and limitations of these data should be noted. Findings are based on a large racially diverse group of participants. Behavioral and psychological symptoms were assessed with a widely used inventory from which composite measures of four symptom clusters were derived, likely minimizing measurement error. Clinical classification of MCI and dementia was based on a uniform previously validated evaluation, but basing the evaluation solely on informant report may have contributed to diagnostic error. Another limitation is that participants were selected, so the generalizability of the findings remains to be determined.

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AUTHOR CONTRIBUTIONS

Study concept and design: RSW, JMF, DAB. Acquisition of data: CS, JMF. Statistical analysis: AWC, SEL. Analysis and interpretation of data: RSW, AWC, CS, SEL, LLB, JMF, DAB. Drafting of the article: RSW. Critical revision of the article for important intellectual content: AWC, CS, SEL, LLB, JMF, DAB. Obtaining funding: JMF, DAB.

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