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Neuropsychiatric Symptoms of Alzheimer's Disease in Down Syndrome and Its Impact on Caregiver Distress

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Abstract.
Background: Neuropsychiatric symptoms (NPS) are non-cognitive manifestations common to dementia and other medical conditions, with important consequences for the patient, caregivers, and society. Studies investigating NPS in individuals with Down syndrome (DS) and dementia are scarce.
Objective: Characterize NPS and caregiver distress among adults with DS using the Neuropsychiatric Inventory (NPI).
Methods: We evaluated 92 individuals with DS (≥30 years of age), divided by clinical diagnosis: stable cognition, prodromal dementia, and AD. Diagnosis was determined by a psychiatrist using the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS). NPS and caregiver distress were evaluated by an independent psychiatrist using the NPI, and participants underwent a neuropsychological assessment with Cambridge Cognitive Examination (CAMCOG-DS).
Results: Symptom severity differed between-groups for delusion, agitation, apathy, aberrant motor behavior, nighttime behavior disturbance, and total NPI scores, with NPS total score being found to be a predictor of AD in comparison to stable cognition (OR for one-point increase in the NPI = 1.342, $p = 0.012$). Agitation, apathy, nighttime behavior disturbances,

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and total NPI were associated with CAMCOG-DS, and 62% of caregivers of individuals with AD reported severe distress related to NPS. Caregiver distress was most impacted by symptoms of apathy followed by nighttime behavior, appetite/eating abnormalities, anxiety, irritability, disinhibition, and depression ($R^2 = 0.627$, $F(15,76) = 8.510$, $p < 0.001$).
Conclusion: NPS are frequent and severe in individuals with DS and AD, contributing to caregiver distress. NPS in DS must be considered of critical relevance demanding management and treatment. Further studies are warranted to understand the biological underpinnings of such symptoms.

Keywords: Alzheimer's disease, dementia, Down syndrome, intellectual disability, Neuropsychiatric Inventory, neuropsychiatric symptoms

INTRODUCTION

Neuropsychiatric symptoms (NPS) are behavioral and psychiatric symptoms related to an underlying neurocognitive disorder [1]. NPS represent non-cognitive manifestations present in many cases of dementia [2] and often precede the emergence of significant cognitive decline [3]. NPS have deleterious effects on patient quality of life and care. They are regarded as the major reason for long-term care in patients with dementia and are estimated to be the source of one third of the total cost of dementia care in the United States [3, 4]. NPS in dementia are highly correlated with higher rates of caregiver burden [5] and caregiver mental health disorders [6], compared to the burden on caregivers related to other kinds of impairments. Although it is believed that NPS have the same underlying pathology as dementia, the etiological foundations of NPS are not completely clear [7]. Indeed, some psychological factors and the presence of pre-existing psychiatric illnesses can interfere with the prevalence and intensity of NPS during dementia [8, 9]. Moreover, different types of dementia appear to lead to different NPS subsyndromes [10].

Despite the established link between Down syndrome (DS) and Alzheimer's disease (AD), studies on NPS in individuals with DS and dementia are scarce [11]. In individuals with DS, there is a premature appearance of neuropathological aspects related to AD, such as the presence of neural plaques and neurofibrillary tangles [12, 13]. In these individuals, early striatal deposition of amyloid-β visible by positron emission tomography with Pittsburgh compound B [14] from the age of 40 [15, 16] has been described. It has been argued that DS-specific brain and behavior phenotypes may cause differences in dementia presentation [17–19]. Although cognitive and behavioral symptoms of dementia in people with DS have been described, studies presented differing results. Currently, it is inconclusive how much of the initial cognitive and neuropsychological symptomatology of AD in DS would be typical of the most common symptomatology found in the general population, such as decline in episodic memory [20, 21]. Some studies suggested the initial presentation to be more atypical with early impairment related to the frontal circuitry of the brain such as executive dysfunction, deficits in working memory and behavior changes [22–25]; or a combination of all of the above and amnestic symptoms [26–29]. A longitudinal study on maladaptive behaviors in adults with intellectual disabilities showed that in such individuals some of these behaviors started before the appearance of adaptive and functional decline [30]. A later study of the same group investigating psychiatric symptoms during dementia in adults with DS and AD indicated a clinical presentation similar to that observed in AD in the general population and suggested that some psychiatric symptoms were early indicators of dementia, appearing before any evidence of functional changes [31]. The recognition of behavioral symptoms of dementia in DS can be important for identifying neurobiological pathogenesis, as well as early diagnosis and referral for pharmacological and non-pharmacological interventions.

The Neuropsychiatric Inventory (NPI) [2] was developed to identify behavioral disturbances common in different dementia syndromes. Although the NPI is a widely used tool for the assessment of dementia in the general population, we have found no studies using the NPI to document the presence of NPS in individuals with DS. In a study aimed to validate an instrument to assess NPS in individuals with DS and dementia, the authors report items that change in relation to dementia status, but do not report the prevalence or severity found for different symptoms [32]. The only two studies we found using the NPI in caregivers of individuals with DS used the instrument for measuring secondary outcomes and they did not report on specific NPI results [33, 34]. The first was a study that investigated the efficacy of using donepezil in the treatment of adults with DS with moderate AD, in which the NPI was used together with other instruments to measure the medication's secondary

efficacy [33]. The second was conducted by our group to determine whether bereavement and behavioral changes correlated with cognitive decline, in which the NPI was used to measure behavioral changes [34]. The main objective of this study was to characterize NPS using the NPI in a sample of individuals with DS divided into three diagnostic groups: those with stable cognition, those with prodromal dementia, and those meeting criteria for AD. We hypothesized that NPS in DS and AD would be similar to those found for the general population with AD. Our secondary aim was to describe the impact of the NPS on caregiver burden. Regarding the secondary aim, we hypothesized that the presence of NPS would be associated with caregiver burden.

MATERIALS AND METHODS

Study design and ethics

This is a cross sectional study conducted in the Institute of Psychiatry of the University of São Paulo School of Medicine *Hospital das Clinicas* in partnership with the Institute Jo Clemente (former Association of Parents and Friends of Individuals with Intellectual Disability of São Paulo, APAESP) and the Association for the Holistic Development of Individuals with Down syndrome (ADID), Brazil. Ethical approval for the study was obtained from the Research Ethics Committee of the University of São Paulo School of Medicine and registered with the *Plataforma Brasil* (CAAE no. 37381414.8.0000. 0065). For all participants, the study was explained in an objective and simplified manner and all questions were addressed. Written consent was obtained from the participants or an appointed consultee for participants lacking the capacity to consent to participation.

Study sample

The sample comprised 92 individuals that met the ICD-10 criteria for a diagnosis of DS (code, Q90) and who were ≥ 30 years of age, as well as their caregivers (Table 1). All participants were recruited from the Institute Jo Clemente and ADID or were individuals who became aware of the study and demonstrated interest in participating. Assessments were performed in sound-proof rooms either at the Institute of Psychiatry of the University of São Paulo School of Medicine *Hospital das Clinicas* or at one of the associations involved. All participants were native Portuguese speakers. The informants were formal or informal caregivers who had daily contact with the participant. The data was collected between 2015 and 2016.

Dementia diagnostic assessment

All participants with DS underwent dementia assessment with the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS) [35] adapted and validated for Brazil [36], which includes an informant detailed interview investigating cognitive decline and direct cognitive assessment with the participant. The CAMDEX-DS was administered by a trained psychiatrist. Three diagnostic categories were established: stable cognition, prodromal dementia, and AD. AD criteria was based on the International Classification of Disease, 10th edition, (ICD–10) [37] and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) [38]. Prodromal dementia was defined as an intermediate state in which there was evidence of informant-reported cognitive or functional decline that did not meet the full criteria for AD or other non-dementia causes of functional decline. It is important to note that in this study, none of the participants met criteria for decline due to causes other than dementia. The CAMDEX-DS questionnaire was administered to the primary caregiver of each participant by a psychiatrist blinded to all other assessments.

Other medical conditions

The study protocol involved collecting data related to the presence of the following comorbidities: hypothyroidism, cardiopathy, hypertension, diabetes, hypercholesterolemia, and epilepsy. All cases with comorbidities were effectively treated.

Neuropsychiatric symptoms

The NPI [2] was administered to the caregiver to evaluate the frequency and severity of NPS that are commonly present in AD in each participant with DS. The NPI evaluates twelve NPS domains (delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite and eating abnormalities). It was translated to Portuguese and validated in Brazil for the general population, showing good psychometric qualities [39]. In the present study, the NPI was administered

Table 1
Characteristics of the participants and differences among the diagnostic groups

		Diagnostic group by CAMDEX-DS			
	Total ($N = 92$)	Stable cognition ($n = 62$)	Prodromal dementia ($n = 17$)	AD ($n = 13$)	*p*
Age (y), mean (SD)/range	42.43 (8.48)/ 30–64	39.69 (7.37)[a]/ 30–60	46.35 (5.06)[b]/ 39–59	50.46 (10.30)[b]/ 32–64	<0.001[c]
Female gender, *n* (%)	34 (36.9)	23 (37.0)	8 (47.0)	3 (23.0)	0.465[d]
Degree of intellectual disability, *n* (%)					
Mild	34 (37.0)	28 (45.2)[a]	4 (23.5)[a,b]	2 (15.4)[b]	
Moderate	34 (37.0)	24 (38.7)[a]	9 (52.9)[a]	1 (7.7)[b]	<0.001[e]
Severe	22 (23.9)	10 (16.1)[a]	4 (23.5)[a]	8 (61.5)[b]	
Unspecified	2 (2.2)	0[a]	0[a]	2 (15.4)[b]	
Other medical conditions					
Hypothyroidism, *n* (%)	48 (52.2)	29 (46.8)	13 (76.5)	6 (46.2)	0.092[e]
Cardiopathy, *n* (%)	14 (15.2)	11 (17.7)	3 (17.6)	0 (0.0)	0.330[d]
Hypertension, *n* (%)	2 (2.2)	2 (3.2)	0 (0.0)	0 (0.0)	0.999[d]
Diabetes, *n* (%)	5 (5.4)	4 (6.5)	1 (5.9)	0 (0.0)	0.999[d]
Hypercholesterolemia, *n* (%)	9 (9.8)	5 (8.1)	3 (17.6)	1 (7.7)	0.434[d]
Epilepsy, *n* (%)	13 (14.1)	7 (11.3)	2 (11.8)	4 (30.8)	0.225[d]
Caregiver, *n* (%)					
Parent	52 (56.5)	41 (66.1)[a]	8 (47.1)[a,b]	3 (23.1)[b]	
Sibling or other relative	38 (41.3)	21 (33.9)[a]	9 (52.9)[a]	8 (61.5)[a]	0.004[d]
Formal caregiver or other	2 (2.2)	0[a]	4 (16.7)[a,b]	2 (15.4)[b]	
Caregiver female gender, *n* (%)	77 (83.7)	54 (87.1)	12 (70.6)	11 (84.6)	0.263[d]
CAMCOG-DS total score[f], mean (SD)/range (range 0–109)	60.7 (23.9)/ 7–98	67.1 (21.1)[a]/ 17–98	59.8 (17.4)[a]/ 16–91	24.1 (14.3)[b] 7–49	<0.001[g]
Orientation, mean (SD)/range CAMCOG-DS (range 0–12)	8.6 (3.5)/ 1–12	9.3 (3.1)[a]/ 2–12	9.3 (3.0)[a]/ 1–12	3.5 (2.1)[b]/ 1–7	<0.001[g]
Language[f], mean (SD)/range (range 0–27)	16.3 (6.0) 0–26	17.7 (5.2)[a]/ 6–26	16.7 (4.8)[a]/ 3–24	7.2 (4.4)[b]/ 0–15	<0.001[g]
Memory[f], mean (SD)/range (range 0–29)	13.1 (7.1)/ 1–26	15.1 (6.7)[a]/ 1–26	11.2 (5.7)[a]/ 1–22	4.6 (3.8)[b]/ 1–13	<0.001[g]
Praxis[f], mean (SD)/range (range 0–18)	10.8 (3.9)/ 1–17	11.8 (3.5)[a]/ 1–17	11.1 (2.3)[a]/ 5–15	4.8 (3.3)[b]/ 1–10	<0.001[g]
Perception[f], mean (SD)/ range (range 0–8)	4.7 (1.9)/ 0–8	5.2 (1.8)[a]/ 1–8	4.3 (1.4)[a]/ 2–7	2.7 (2.3)[b]/ 0–8	<0.001[g]
CAMCOG-DS EF and attention[f], mean (SD)/range (range 0–22)	9.93 (5.31)/ 0–19	11.15 (4.92)[a]/ 1–19	10.00 (4.38)[a]/ 2–17	2.5 (2.22)[b]/ 0–7	<0.001[g]

AD, Alzheimer's disease; CNS, central nervous system; CAMCOG-DS, The Cambridge Cognitive Examination adapted for individuals with Down syndrome; EF, executive function; CAMDEX-DS, Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities; SD, standard deviation. [a,b]Same subscript letter denotes a subset of variables whose column proportion/means do not differ significantly from each other at the 0.05 level; [c]Kruskal-Wallis test, [d]Fisher's exact test, [e]Pearson's chi-square test, [f]N = 86 (no data for six individuals), [g]one-way ANOVA.

by a second psychiatrist blinded to the CAMDEX-DS dementia diagnosis. For the analysis we used frequency and severity measures of NPI.

For the administration of the NPI, within each of the 12 NPI domains, there is a screening question in which the informant is asked about the individual's behaviors that have changed and that are present in the last month. Behaviors that have always been present throughout the patient's life and that have not changed are not considered. Initial responses to each domain question are "yes" (present) or "no" (absent). If the response to the domain question is "no", the informant goes to the next question. If "yes", the informant then rates the frequency of the symptoms (1 = occasionally, less than once a week; 2 = often, about once a week; 3 = often, several times a week but less than every day; 4 = very frequently, once or more a day or continuously) as well as their severity (1 = mild, little discomfort in the patient; 2 = moderate, more disturbing for the patient but can be handled by the caregiver, and 3 = severe, very disturbing and difficult to handle) within the last month. The total of each domain score is the product of frequency x severity of that domain (range, 0–12).

Scores from each domain are added together to produce a total NPI score (range, 0–144).

Caregiver burden

The measures of caregiver distress that are included in the NPI were also evaluated. For all NPI domains when the initial response to that domain was "yes" and the presence of any NPS was reported, caregivers were asked to indicate how distressing he/she finds the symptom on a six-point Likert scale ranging from zero to five, with zero denoting no distress and five denoting extreme or severe distress (0 = no distress or symptom absent; 1 = minimum distress; 2 = mild distress; 3 = moderate distress; 4 = moderately intense distress; and 5 = very intense or extreme distress).

Neuropsychological assessment

Individuals with DS completed The Cambridge Cognitive Examination adapted for individuals with DS (CAMCOG-DS), which is part of the CAMDEX-DS. The CAMCOG-DS assessment has been well described in previous publications [36, 40]. CAMCOG-DS performance, particularly related to executive function (EF) and attention, was analyzed by combining scores for verbal fluency, attention, calculation, clock drawing, and abstract thinking, similar to previous studies with DS and AD using the same instrument [24, 41]. The CAMCOG-DS was administered by a neuropsychologist blinded to all other assessment and was not considered for clinical diagnosis.

Intellectual disability

The level of intellectual disability (ID) of participants with DS was classified by a psychiatrist who was blind to the results of CAMDEX-DS diagnosis of dementia. The degree of ID refers to the pre-morbid ability determined by the maximum level of adaptive behavior achieved throughout life and was measured using information gathered by detailed medical history and according to the American Association on Intellectual and Developmental Disabilities framework [42], in addition to the results of neuropsychological assessment performed before any sign of cognitive decline and using the Wechsler Abbreviated Scale of Intelligence or Wechsler Adult Intelligence Scale when available in medical history [43, 44]. The level of intellectual disability was classified by ICD-10 codes F70 (mild intellectual disability), F71 (moderate intellectual disability), F72 (severe intellectual disability), F73 (profound intellectual disability), and F79 (unspecified intellectual disability), with the latter being used for cases without a consensus on the degree of disability due to the presence of cognitive decline and unsatisfactory information about the individual's previous adaptive behavior history.

Statistical analysis

Descriptive statistics were calculated and presented as absolute and relative frequencies or as means and standard deviations for the sample as a whole and for each diagnostic group (stable cognition, prodromal dementia, and AD). The Kolmogorov-Smirnov test was used to test for data normality. For characteristics of the sample, differences between diagnostic groups for continuous outcome variables were assessed by the Kruskal-Wallis test for non-parametric data and the one-way ANOVA was used for data with a normal distribution. The Tukey's HSD for one-way ANOVA and Mann-Whitney for Kruskal-Wallis *post-hoc* tests were used to identify specific differences between pairs of means that were statistically significant. Group differences for categorical variables were evaluated using the Pearson's chi-square test or Fisher's exact test, with the latter being used when the number of cases was less than 5 for one or more variables. For analyses comparing the presence of symptoms (yes/no) in the three groups, *post-hoc* test testing proportions was used. The Bonferroni correction was used for conducting between-group comparisons. For differences between diagnostic groups for mean NPS score and mean caregiver distress score, we conducted one-way ANCOVA with the covariates age, sex, and intellectual disability.

Logistic regression was carried out for the total NPI score to predict diagnostic groups. The predictor variable was total NPI score and the outcome variable was diagnoses (considered in pairs: AD x stable cognition; AD x prodromal dementia; prodromal dementia x stable cognition). All models were adjusted for age, sex, and level of intellectual disability. Separate linear regression analysis was conducted with CAMCOG-DS total score as the dependent variable and each NPI domain score as an independent variable adjusting for age, sex, and level of intellectual disability to determine the association between cognitive performance and neuropsychiatric symptoms. Multiple

linear regression analysis was conducted with total NPI caregiver distress score as the dependent variable and all NPI domain scores as independent variables adjusting for age, sex, and level of intellectual disability to determine the degree to which caregiver distress was predicted by specific NPS. Spearman's rho coefficient was used to establish the correlation between NPI scores and cognitive performance of the individual.

The level of statistical significance was set at 5%. All selected data were tabulated with the Research Electronic Data Capture Program (RedCap) [45], and statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS), version 26 for Windows.

RESULTS

Demographic comparisons

Table 1 shows participant characteristics and group differences. Thirteen participants (14.1%) were diagnosed with AD, 17 (18.4%) with prodromal dementia, and 62 (67.5%) with stable cognition. There were significant differences between groups in age, level of intellectual disability, and type of relationship with the caregiver, in addition to the results of the cognitive tests. Those in the AD and prodromal dementia groups were older than those in the stable cognition group. Moreover, when compared with individuals with stable cognition and prodromal dementia, those in the AD group were more likely to have a sibling or professional caregiver, rather than parents, as informants. With regard to intellectual disability severity, those with AD were more often classified as having severe pre-morbid intellectual deficits and less often having moderate pre-morbid deficits compared to the other two groups, with those in the stable cognition group more often classified as having a mild pre-morbid intellectual disability. As expected, those with AD also exhibited poorer performance on the cognitive test battery (CAMCOG-DS) compared to the other two groups.

Prevalence and severity of neuropsychiatric symptoms

Table 2 presents the results for the total NPI and the specific symptoms evaluated by the scale across diagnostic groups, either as mean scores or frequencies of the participants with symptoms. The *p*-values presented in the table refer to the comparisons between mean total domain scores (frequency x severity) by diagnostic group adjusted by intellectual disability, age, and sex. Based on these results, almost 80% of the total sample presented with one or more NPS with no significant between-group differences. The symptoms showing the highest frequencies were anxiety and irritability. Nearly 50% of the caregivers reported the presence of these symptoms, with non-significant differences among the three diagnostic groups for these variables. In terms of prevalence (frequency), hallucination, agitation, apathy, and nighttime behavior disturbance were more common in those with AD compared to those with prodromal dementia and stable cognition, while aberrant motor behavior was more common in both prodromal and AD groups compared to stable cognition. Euphoria was not reported by any caregiver.

In terms of NPS total domain (frequency x severity) scores, delusion, agitation, apathy, aberrant motor behavior, nighttime behavior disturbances, and total NPI mean scores showed significant differences among the three diagnostic groups, with the AD group showing higher mean scores when compared to the prodromal dementia and stable cognition groups for almost all of the symptoms (Table 2).

Impact of NPS among different diagnostic groups

Logistic regression analysis was carried out to assess whether NPS total score was predictive of diagnostic group. The data in Table 3 shows the degree to which a one-point increase in total NPI score increases the chance of each diagnosis over the previous one (less severe) when adjusting for age, gender, and level of intellectual disability. Higher NPI score increased the odds of AD diagnosis compared to both stable cognition and prodromal dementia.

Relationship between cognitive performance and NPS

Six participants did not perform the cognitive assessment: three from AD group because of their advanced stage of dementia; one from prodromal dementia group because of his inability to communicate through expressive language (no speech); and two from stable cognition group: one because the individual refused to complete the cognitive assessment even though consent was maintained for all other evaluations, and the other because of his inability to communicate through expressive language (no speech). Table 4 presents the associations

Table 2
Mean NPI scores, frequency of participants with symptoms and differences among the groups adjusting for age, sex, and intellectual disability

NPI items	Diagnostic group by CAMDEX-DS				*p* for severity
	Total ($N = 92$)	Stable cognition ($n = 62$)	Prodromal dementia ($n = 17$)	AD ($n = 13$)	
	Frequency x severity, range 0–12- Mean (SD)/ N (%) of participants with symptoms (any severity)				
Delusions	0.10 (0.56)/ 4 (4.3)	0.06 (0.39)^{a}/ 2 (2.3)	0.00 (0.00)^{a}/ 0 (0.0)	0.46 (1.19)^{b}/ 2 (15.4)	0.032
Hallucinations	0.18 (0.70)/ 8 (8.7)	0.12 (0.63)/ 3 (4.8)^{A}	0.05 (0.24)/ 1 (5.9)^{A,B}	0.61 (1.29)/ 4 (30.8)^{B}	0.051
Agitation	0.18 (0.70)/ 7 (7.6)	0.09 (0.56)^{a}/ 2 (3.2)^{A}	0.05 (0.24)^{a}/ 1 (5.9)^{A,B}	0.74 (1.34)^{b}/ 4 (30.8)^{B}	0.032
Depression	0.59 (1.85)/ 15 (16.3)	0.62 (2.00)/ 9 (14.5)	0.64 (1.96)/ 3 (17.6)	0.38 (0.76)/ 3 (23.1)	0.912
Anxiety	1.00 (1.63)/ 43 (46.7)	1.08 (1.84)/ 28 (45.2)	1.05 (1.24)/ 10 (58.8)	0.53 (0.77)/ 5 (38.5)	0.902
Euphoria	0.00 (0.00) 0 (0.00)	0.00 (0.00) 0 (0.00)	0.00 (0.00) 0 (0.00)	0.00 (0.00) 0 (0.00)	N/A
Apathy	0.82 (2.77)/ 11 (12.0)	0.11 (0.67)^{a}/ 2 (3.2)^{A}	0.82 (2.89)^{a}/ 3 (17.6)^{A,B}	4.23 (5.38)^{b}/ 6 (46.2)^{B}	<0.001
Disinhibition	0.23 (1.44) 3 (3.3)	0.09 (0.76)/ 1 (1.1)	0.23 (0.97)/ 1 (5.9)	0.92 (3.32)/ 1 (7.7)	0.667
Irritability	1.01 (1.59)/ 45 (48.9)	0.96 (1.70)/ 29 (46.8)	0.64 (0.70)/ 9 (52.9)	1.69 (1.75)/ 7 (53.8)	0.281
Aberrant motor behavior	0.51 (1.88)/ 8 (8.7)	0.00 (0.00)^{a}/ 0 (0.0)^{A}	0.58 (1.69)^{a}/ 2 (11.8)^{B}	2.84 (3.99)^{b}/ 6 (46.2)^{B}	<0.001
Nighttime behavior disturbances	0.26 (0.81)/ 12 (13.0)	0.16 (0.63)^{a}/ 5 (8.1)^{A}	0.05 (0.24)^{a}/ 1 (5.9)^{A}	1.00 (1.47)^{b}/ 6 (42.6)^{B}	0.035
Appetite and eating abnormalities	0.50 (1.47)/ 15 (16.3)	0.41 (1.40)/ 8 (12.9)	0.11 (0.33)/ 2 (11.8)	1.38 (2.25)/ 5 (38.5)	0.149
Total NPI (range 0–144)/ Any symptom (NPI $\geq$ 1)	5.42 (6.32)/ 73 (79.3)	3.75 (4.50)^{a}/ 44 (71.0)	4.29 (5.54)^{a}/ 16 (94.1)	14.84 (6.84)^{b}/ 13 (100.0)	<0.001

AD, Alzheimer's disease; NPI, The Neuropsychiatric Inventory; CAMDEX-DS, Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities; SD, standard deviation. ^{a,b}Same subscript letter denotes a subset of variables whose column proportion/means do not differ significantly from each other at the 0.05 level for total domain score (frequency x severity) and ^{A,B}for frequency (% of participants with symptom).

Table 3
Associations between NPI score and the odds of a clinical diagnosis, adjusted for age, sex, and intellectual disability

Comparison group	Odds ratio	95% CI	*p*
AD versus stable cognition ($N = 75$)	1.342	1.066–1.689	0.012
Prodromal dementia versus stable cognition ($N = 79$)	1.087	0.954–1.238	0.211

NPI, The Neuropsychiatric Inventory; AD, Alzheimer's disease.

between CAMCOG-DS total score and NPS total domain scores (N = 86). Agitation, apathy, nighttime behavior disturbances, and total NPI were negatively associated with total CAMCOG-DS such that the more severe the symptom, the worse the cognitive performance.

Caregiver distress

More than 60% of the caregivers of individuals with AD reported very severe or extreme distress associated with the presence of NPS in individuals with DS (four or five points on the Likert scale). They described having difficulty dealing with or even feeling unable to cope with their family member/patient significantly more often than the stable cognition group (22.6%) and comparable to the prodromal dementia group (29.4%). Table 5 shows the results of total caregiver distress (mean and standard deviation) related to each NPS and group diagnosis, adjusted by intellectual disability, age, and sex. Apathy, aberrant motor behavior, nighttime behavior disturbances, and total caregiver distress were significantly more distressing for the AD group, when compared to the stable cognition or prodromal dementia groups.

Association between neuropsychiatric symptoms and caregiver distress

Table 6 shows the results of a multiple linear regression calculated to predict caregiver distress based on all twelve neuropsychiatric symptoms adjusting for participant age, sex, and intellectual disability. A significant regression equation was found ($F(15, 76) = 8.510$, $p < 0.001$), with an R^2 of 0.627. In order of importance, apathy, nighttime behavior disturbances, appetite and eating abnormalities, anxiety, irritability, disinhibition, and depression predicted caregiver distress.

DISCUSSION

In our investigation on NPS using NPI in a sample of adults with DS with stable cognition, prodromal dementia, and AD, we found the presence of NPS to be common in individuals with DS with and without dementia and to have important consequences in caregiver distress. Some of these symptoms have significant between-group differences and may be useful to assist in the clinical diagnosis. Moreover, total NPI proved to be effective in distinguishing diagnostic pairs. Our study is the first to report the prevalence and severity of NPS in individuals with DS using the NPI.

The high prevalence of NPS in all three groups of our sample is noteworthy (more than 80% of the total sample). Furthermore, all participants from the AD group presented with some NPS. Since the NPI was particularly designed to identify symptoms related to

Table 4
Associations between cognitive performance and neuropsychiatric symptoms. Separate linear regressions with the dependent variable CAMCOG-DS Total score and NPI score as independent variable, adjusted by age, sex and level of intellectual disability (N = 86)

	Unstandardized B	Std. Error	Standardized Coefficients Beta	Lower bound	Upper bound	*p*
NPI items						
Delusions	–2.894	2.729	–0.070	–8.325	2.536	0.292
Hallucinations	–2.300	2.236	–0.070	–6.749	2.149	0.307
Agitation	–6.029	2.164	–0.185	–10.334	–1.723	0.007
Depression	0.009	0.854	0.001	–1.690	1.708	0.991
Anxiety	0.093	0.978	0.006	–1.853	2.039	0.924
Euphoria	N/A	N/A	N/A	N/A	N/A	N/A
Apathy	–2.911	0.627	–0.278	–4.148	–1.665	<0.001
Disinhibition	0.456	2.096	0.015	–3.714	4.626	0.828
Irritability	–2.205	1.150	–0.128	–4.494	0.084	0.059
Aberrant motor behavior	1.502	0.934	0.114	–0.356	3.361	0.112
Nighttime behavior disturbances	–4.747	1.985	–0.166	–8.697	–0.798	0.019
Appetite and eating abnormalities	–3.383	1.025	–0.213	–5.422	–1.344	0.001
Total NPI	–0.928	0.264	–0.226	–1.453	–0.402	0.001

NPS, Neuropsychiatric Inventory; CAMCOG-DS, Cambridge Cognitive Examination for Older Adults with Down Syndrome.

Table 5
Caregiver distress mean scores by neuropsychiatric symptom and differences among the groups adjusting for age, sex, and intellectual disability

Caregiver distress by NPS	Total ($N=92$)	Diagnostic group by CAMDEX-DS			p
		Stable cognition ($n=62$) *Range 0–4,*	Prodromal dementia ($n=17$) *Mean (SD)*	AD ($n=13$)	
Delusions	0.05 (0.34)	0.06 (0.40)	0.08 (0.27)	0.46 (1.19)	0.663
Hallucinations	0.18 (0.79)	0.12 (0.63)	0.05 (0.24)	0.61 (1.29)	0.240
Agitation	0.16 (0.69)	0.13 (0.71)	0.06 (0.24)	0.46 (0.87)	0.509
Depression	0.40 (1.05)	0.39 (1.07)	0.59 (1.32)	0.23 (0.43)	0.677
Anxiety	0.84 (1.30)	0.94 (1.40)	0.76 (1.03)	0.46 (1.12)	0.896
Euphoria	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	N/A
Apathy	0.41 (1.28)	0.13 (0.71)[a]	0.53 (1.51)[a]	1.62 (2.21)[b]	0.002
Disinhibition	0.15 (0.83)	0.06 (0.50)	0.29 (1.21)	0.38 (1.38)	0.445
Irritability	0.90 (1.30)	0.94 (1.37)	1.00 (1.32)	0.62 (0.87)	0.862
Aberrant motor behavior	0.17 (0.67)	0.00 (0.00)[a]	0.18 (0.52)[a]	1.23 (1.87)[b]	<0.001
Nighttime behavior disturbances	0.35 (1.05)	0.24 (0.86)[a]	0.06 (0.24)[a]	0.69 (1.43)[b]	0.018
Appetite and eating abnormalities	0.28 (0.91)	0.23 (0.85)	0.18 (0.52)	0.69 (1.43)	0.309
Total NPI (range 0–48)	3.91 (4.17)	3.25 (3.82)[a]	3.88 (4.02)[a]	7.07 (4.80)[b]	0.018

Key: AD, Alzheimer's disease; NPS, Neuropsychiatric symptom; CAMDEX-DS, Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities; SD, Standard Deviation. [a,b] Same subscript letter denotes a subset of variables whose column means do not differ significantly from each other at the 0.05 level.

Table 6
Associations between neuropsychiatric symptoms and caregiver distress by order of importance

	Unstandardized B	Std. Error	Standardized Coefficients Beta	95% CI for B		p
				Lower bound	Upper bound	
Multiple linear regression with the dependent variable NPI caregiver total distress.						
Constant	2.420	1.932		–1.427	6.267	0.214
Apathy	0.550	0.128	0.365	0.295	0.805	<0.001
Nighttime behavior	1.581	0.481	0.307	0.624	2.538	0.002
Appetite and eating abnormalities	0.804	0.237	0.283	0.332	1.277	0.001
Anxiety	0.669	0.189	0.261	0.292	1.046	0.001
Irritability	0.644	0.215	0.246	0.215	1.073	0.004
Disinhibition	0.704	0.217	0.244	0.273	1.135	0.002
Depression	0.365	0.167	0.163	0.034	0.697	0.031
Hallucinations	1.452	0.247	0.247	–0.092	2.995	0.065
Aberrant motor behavior	0.034	0.178	0.015	–0.322	0.389	0.851
Delusion	–1.331	0.890	–0.180	–3.103	0.441	0.139
Agitation	–0.694	0.569	–0.118	–1.828	0.439	0.226
Sex	0.782	0.625	0.090	–0.468	2.026	0.214
Participant age	–0.061	0.039	–0.124	0.123	–0.138	0.017
Intellectual disability	0.010	0.389	0.002	–0.765	0.785	0.963

NPI, The Neuropsychiatric Inventory.

dementia, it is expected that a high number of individuals, if not all participants, with AD present some NPS. An NPS prevalence of 100% was also found in other studies in the general population with AD [10, 46], and in a study including participants with AD and vascular dementia, more than 90% of the participants presented with at least one NPS [47]. However, surprisingly, more than 70% of the individuals considered to be in the stable cognition group in our study also presented with at least one NPS and more than 90% of the individuals in the prodromal dementia group. There was no difference between the groups in the frequency of at least one NPS. This highly contrasts with studies of healthy individuals from the general population that demonstrate much lower rates of NPS (15% to 27% [48–50]). Further, those considered to have mild cognitive impairment (MCI) in the general population [51], the equivalent

of prodromal dementia in those with DS, have NPS prevalence rates from 36% to 51% [1, 49, 50]. In a study investigating NPI trajectories over six years in individuals with MCI from the general population, mean NPI scores were significantly higher in those who converted compared to those who did not convert to dementia [52]. We found no studies in individuals with DS that showed NPS prevalence or severity using a standardized instrument. Our findings suggest that NPS are common in individuals with DS. It is unclear, however, if these symptoms may be characteristic of DS independent of cognitive decline, or whether these symptoms may appear years before the development of cognitive decline and dementia. Given evidence of a long pre-clinical phase of AD in DS, when there is evidence of neuropathology without cognitive symptoms [15, 53], it is possible that NPS reported in the stable cognition group may be due to early AD pathology, rather than a long-standing feature of DS. Future studies that explore NPS in younger individuals with DS may help to differentiate symptoms that are premorbid from those related to neurodegeneration and longitudinal studies that include investigations with neuroimaging and NPS may clarify how much the presence of NPS in adults with DS may be due to early neurodegeneration. Additionally, in our study, the high number of caregivers from the total sample who reported the presence of anxiety and irritability in the participant with DS is quite high (almost 50%). Moreover, for these two symptoms, there were no significant differences among the diagnostic groups, indicating that these symptoms may be characteristics related to DS and not necessarily related to cognitive decline. This is consistent with a previous study on NPS and DS in which a substantial proportion of non-demented individuals also displayed increased irritability [11]. However, longitudinal studies would be needed to confirm this hypothesis.

We found that the prevalence of hallucination, agitation, apathy, aberrant motor behavior, and nighttime behavior disturbances significantly differed among the diagnostic groups. When considering the total domain scores (frequency x severity), delusion, agitation, apathy, aberrant motor behavior, nighttime behavior disturbances, and total NPI showed significant differences among the groups when adjusting for age, sex, and intellectual disability. The AD group presented with increased total domain scores when compared to the prodromal dementia and stable cognition groups in all of these symptoms. When the frequency of the symptom was considered, independent of severity, differences were generally found between the AD and stable cognition groups, with the prodromal dementia group appearing as an intermediate group. With most of those symptoms (hallucination, agitation, and apathy) the prodromal dementia group did not differ significantly from either AD or stable cognition groups, although aberrant motor behavior was more common in the prodromal dementia group compared to the stable cognition group (and similar to AD group). The only symptom in which was more common in the AD group than in the other two groups was nighttime behavior disturbances. Moreover, the odds of being diagnosed with AD or prodromal dementia was shown to increase in parallel with increases in the NPI total score.

In agreement with the study of Dekker and collaborators [32], our study found increased frequencies and severities of nighttime behavior disturbances, agitation, aberrant motor behavior, and apathy in individuals with DS and AD. Regarding hallucinations, in our study, only the frequency, but not the severity, was associated with the AD group when compared to the stable cognition group, but not when compared to the prodromal dementia group. NPI total delusion was found to be higher in individuals with DS and AD compared with both the stable cognition and prodromal groups, but not its frequency. In a previous study of 281 participants with DS divided into three diagnostic groups (AD, questionable dementia, and no dementia) focused on NPS instrument validation specific for DS, frequencies changes in hallucinations and delusions did not differ among the groups and the authors suggested it might be of limited relevance [11]. In a study using the NPI in 1,969 non-demented participants without DS, presence of psychotic symptoms did not distinguish healthy groups from those with MCI [49], and baseline psychotic symptoms in healthy individuals did not increase the risk of MCI five years later [54]. In contrast with our current finding that disinhibition scores did not differ across groups, we previously reported that disinhibition scores were significantly higher in those with prodromal dementia compared to stable cognition using a different measure of disinhibition in the same sample [24]. In this previous analysis, disinhibition was measured using the Frontal System Behavior Scale [55], which includes 15 questions, while the NPI only include two questions. Thus, it is possible that the NPI disinhibition score does not take into account behaviors that may be more sensitive to disinhibition in individuals with DS, making this item on the NPI inappropriate for use in DS. In another

study with DS and AD, disinhibition was measured by eight different items, with only one of them ("loss of decorum") being significantly different among the diagnostic groups [32].

Unlike some studies of dementia in individuals without DS [46, 56], our investigation did not find a high incidence of depression in individuals with AD and DS. Furthermore, we did not find significant differences in the frequency or severity of depressive symptoms across diagnostic groups, which has previously been reported in DS and AD [32]. Assessment of mood in individuals with intellectual disability is a challenge [57] and the difference in the study of Dekker and collaborators [32] and ours raises the question of whether depression is being appropriately evaluated for this population.

In our study euphoria was not reported by any caregiver, suggesting that this symptom is rare in people with DS with or without dementia. Unfortunately, the only study we found specifically investigating NPS in DS and AD did not investigate euphoria [32], so a comparison could not be made. However, euphoria is also a rare symptom in individuals with MCI without DS [49], and was the least frequently reported symptom in individuals with AD without DS [46, 58]. Euphoria is considered to have a greater incidence in frontotemporal dementias compared to other types of dementia [59, 60]. Although the results of our study suggest that this item could be excluded, it would be important to investigate euphoria in larger samples of individuals with DS to confirm this recommendation.

The most important neuronal foundations of neuropsychiatric manifestations in AD are frontal-subcortical circuits, cortical-cortical networks, and monoaminergic system [7, 61–63]. Individuals with DS are known to have frontal lobe hypoplasia and other dysfunction in neuronal circuits that involve the prefrontal cortex [18, 64, 65], in addition to suggestion of other specific neurochemical dysregulation, such as altered levels of GABAergic and monoaminergic neurotransmitters [66–69]. In our study, we found a high prevalence of some of the NPS in all three diagnostic groups. The NPS pattern in the AD group involves a higher prevalence of delusion, agitation, apathy, aberrant motor behavior, and nighttime behavior disturbances. Some studies have indicated that the frontal lobe processes relevant to episodic memory have been correlated with delusional memories in the elderly [70, 71]. Additionally, the prefrontal cortex circuit is believed to be related to agitation [61], and neuroimaging studies have found a correlation between agitation and deposits of neurofibrillary tangles in the frontal regions of the brain [72]. Moreover, apathy is known to be associated with the anterior cingulate circuit [62, 73]. In individuals with AD, executive dysfunction can cause deficits in the ability to perform tasks, leading to inappropriate or purposeless activities, which includes aberrant motor behavior [74]. In addition, dysfunction in frontal-subcortical circuits can result in changes in behavior [73]. Future studies, including neuroimaging and measures of neurochemical dysfunction, will be able to indicate whether the NPS pattern in AD and DS is related to frontal lobe dysfunction and/or neurotransmitter dysregulation.

In our study, non-cognitive (NPS) and cognitive symptoms were associated. Agitation, apathy, nighttime behavior disturbances, appetite/eating abnormalities, and total NPI were associated with impairments in the total CAMCOG-DS score. These findings are in agreement with previous studies conducted with the general population that have found that NPS measured by the NPI were correlated with impairments in global cognition in individuals with MCI [75, 76] and in individuals with AD [77]. The presence of NPS was shown to significantly increase the risk of cognitive decline and dementia in the general population [78], and it is expected that NPS increase during the course of dementia [10] alongside with declining cognition. Further longitudinal studies with this population are needed to explore the extent to which NPS may be associated with cognitive decline over time. Other studies have reported significant correlations between different neuropsychiatric symptoms and cognition in the general population. In patients at the clinical stage of dementia but with no DS, agitation is associated with more rapid cognitive and functional decline [79, 80]. Other studies in individuals with DS indicate a higher prevalence of agitation in subjects with dementia than in those without [31, 32, 81]. Agitation is often reported to increase as the severity of dementia increases [80, 82]. Agitation may be related to the degeneration of brain circuits that control and inhibit behavior, or to difficulties in expression and understanding [83, 84]; the latter abilities may be impaired premorbidly in individuals with DS due to intellectual disability and this may, therefore, lower the threshold for emergence of agitation in association with cognitive decline. Apathy has been associated with dysfunction of important brain structures related to cognitive deficits [62, 85]. Previous investigations have reported significant correlations of apathy with cognitive decline during the course of dementia [86], including studies in adults

with DS [24, 87]. Some studies with the general population indicated the correlation of sleep disturbances and cognitive deficits [88, 89], and nighttime behavior disturbance is considered one of the most important symptoms for institutionalization [90, 91]. Obstructive sleep apnea and other nighttime behavior disturbances are also reported as frequent in individuals with DS, and they are often correlated with the severity of cognitive deficits [92–94]. Additional studies are needed to identify the type of the interaction between sleep and cognition in individuals with DS and dementia. A healthy dietary behavior has been consistently related to better cognitive outcomes in older adults [95], being associated with less cognitive decline and a lower risk of dementia [96]. Although eating abnormalities are more frequently reported in subjects with frontotemporal dementia [97], AD-related neurodegeneration also affects regions of the brain involved in regulating appetite [98]. Eating abnormalities are common in individuals with DS throughout life [99] and the aging process is likely to cause dysphagic problems and other impairments that affect eating behavior in those individuals [100]. Therefore, further research investigating associations between eating abnormalities and cognitive decline in individuals with DS are warranted. The identification of specific associations between cognitive and non-cognitive symptoms of dementia in the population with DS may add knowledge about the brain dysfunction involved with behavioral expression. Moreover, the detection of specific symptoms that can predict cognitive decline may assist in the choice of preventive measures and diagnosis.

In this study we identified some demographic variables that were significantly different between the diagnostic groups. First, participants in the prodromal and AD groups were older than those in the stable cognition group, an expected finding since age is considered a risk factor for dementia in people with DS [17, 101, 102]. This association of age with diagnosis may have also influenced group differences found for other demographic variables, such as the type of caregiver relationship. The number of primary caregivers other than parents (siblings or professionals) tended to increase in parallel with an increase in the degree of dementia. Since in Brazil, parents are the most common primary caregivers of individuals with DS, it is possible that with age, their parents are less likely to be living or capable of assisting them, thereby increasing the number of siblings or professional caregivers, a hypothesis that would need to be demonstrated with further studies.

While we found that there was an association between the degree of intellectual disability and diagnostic groups, it is important to note that this determination was estimated based on data on premorbid functioning and cognitive performance before the appearance of any cognitive decline. In addition, our results show that there were group differences in NPI scores even when adjusting for the severity of intellectual disability. Nevertheless, the fact that in our findings, surprisingly, participants with a higher degree of pre-morbid intellectual impairment were more frequently classified in the prodromal and dementia groups, raises hypotheses about the influence of cognitive reserve on the subsequent development of dementia in this population, an association already noted for the general population [103, 104]. However, our cross-sectional study design does not allow us to refine the nature of these associations. Considering the challenges of diagnosing dementia in this population and the fact that the determination of degree of intellectual disabilities used retrospective data found in medical records, another hypothesis for these findings is that the retrospective data used for determining degree of intellectual disability were already biased due to cognitive decline prior to any diagnosis. Also, information on the highest level of functionality acquired throughout life was collected through the caregiver. Caregivers of people with dementia or decline may have been influenced by the current state of their family members when answering questions. Prospective cohort studies are needed to determine if severity of intellectual disability alters risk for subsequent AD. Regarding the association of diagnosis with current cognitive test performance, individuals with dementia were expected to have cognitive decline and therefore lower scores on cognitive performance tests. Nevertheless, this data may also be due to greater premorbid intellectual disability in the prodromal and AD groups. For a better appreciation of the association between current cognitive performance and diagnostic groups, it would be necessary to also consider the severity of dementia, which was not included in our study.

Caregiver distress

The majority of the caregivers in our sample were females (more than 80% of the total sample), with no differences in caregiver gender across diagnostic groups. This finding is similar to other studies of caregivers of those with dementia or other disabilities from the general population [105, 106]. We

also found that severe caregiver distress related to NPS in the individuals with DS and AD was common (more than 60%), a rate significantly higher than that observed in caregivers of individuals in the stable cognition group (22.6%). This rate is comparable to another study that investigated burden in caregivers of people with AD in the general population (63%) [105], however, suggesting that DS does not increase the already high caregiver distress associated with AD. The NPS that contributed to group differences in caregiver distress were agitation, apathy, aberrant motor behavior, nighttime behavior and the total NPI score. When accounting for all the NPS together, the level of caregiver distress was significantly greater for those caring for individuals with DS with dementia compared to the other two groups. The only study we found investigating NPS in DS did not include any data on either the frequency or severity of distress in the caregiver by NPS or the impact of different NPS on total caregiver distress [32], making our study particularly unique in this area.

We found that total caregiver distress considering the total sample was impacted largely by symptoms of apathy, followed by nighttime behavior, appetite/eating abnormalities, anxiety, irritability, disinhibition, and depression. Some studies in the general population have also identified apathy as having the greatest impact on caregiver burden [107–109]. However, other studies have shown differences in the order of importance of NPS in relation to caregiver burden [108], with some pointing out higher impacts of irritability [110, 111], while others cite delusion [112, 113] or agitation [46] as the most significant causes of burden. In a recent systematic review of caregiver burden and dementia using the NPI in the general population considering almost 30 years of publications, the authors indicated that apathy, irritability, agitation, sleep disturbance, anxiety, and delusion seems to have the most impact on caregiver burden [106]. However, the authors added that heterogeneity in measures makes it difficult to make conclusive interpretations.

Limitations

Although this is one of the first studies to document NPS in individuals with DS and the first one to document it using the NPI, our study has some limitations that need to be considered. First, we are limited by the small size of the prodromal dementia and AD groups, which may hinder some analyses and make it difficult to draw strong conclusions about some specific results, in particular, the effect of individual NPS on diagnosis should be considered exploratory. A larger sample would allow, for example, to analyze caregivers distress by diagnostic group. In addition, even though we have adjusted our analyzes for the level of intellectual disability, sex, and age, we acknowledge that this adjustment may be limited for some analyzes due to the small sample size. Another limitation is that we did not consider the severity of dementia in our analyses. Dementia severity may have influenced the association of current cognitive performance with diagnostic groups. We were also unable to determine whether NPS are early or late symptoms of AD in DS. Additionally, we measured the degree of intellectual disability through the analysis of data found in medical records, when available. A more rigorous approach would have been to measure intellectual disability prospectively using the same instruments before any risk of cognitive and functional decline. Also, our study had a cross-sectional design that does not allow us to understand the direction of the associations found. Finally, NPS were identified through caregiver reports, which can be biased when compared with the direct observation of the participants' behavior. However, at the moment, no NPS instrument has been validated for direct assessment of individuals with DS.

Clinical implications

This is the first study to consider the evaluation of NPS in people with DS using a gold standard instrument used in the general population and known to psychiatrists, geriatricians, and neurologists, who make the diagnosis of dementia. Therefore, the NPI has the advantage of being familiar to dementia providers in the general population. It can be particularly useful when used in conjunction with other instruments by primary care providers who regularly perform preventative care for individuals with DS and make subsequent referrals to specialized care. NPS are expected during the course of dementia and increased NPS has been shown to be a good predictor of conversion from MCI to AD in the general population [52]. Furthermore, longitudinal increases in NPS rates and symptom fluctuations have been associated with the greater hazards of prodromal dementia and AD conversion over four years [114]. Thus, the identification of these symptoms in individuals with DS is critical for proper referral for non-pharmacological and pharmacological management, which

considerably reduces the suffering of patients and families, as well as societal costs.

Future studies

Our findings have implications for future studies on the intersection of dementia and DS. In individuals with DS, the identification of non-cognitive and cognitive symptoms can be particularly challenging due to the pre-existence of intellectual deficits and other psychiatric comorbidities. However, studies including younger participants with DS prior to the onset of cognitive decline could provide useful information about the typical characterization of NPS in this population throughout life and regardless of cognitive decline, as well as the contribution of intellectual disability severity in the ultimate development of AD. Furthermore, longitudinal studies could indicate the progression of NPS in adults with DS. In addition, studies investigating NPS in the context of neuroimaging may add important knowledge about underlying mechanisms involved with NPS in these individuals. Such future studies may also confirm whether our findings can be generalized to other samples of individuals with DS.

CONCLUSION

The findings of this study indicate that NPS are common in adults with DS and tend to worsen significantly with AD. NPS are important to assess and monitor during adulthood and, particularly, during the progression of prodromal dementia and AD in individuals with DS. Here, adults with DS and AD exhibited increased greater delusion, apathy, agitation, aberrant motor behavior, and nighttime behavior disturbances, when compared to individuals with DS and prodromal dementia and/or stable cognition. Hallucination, agitation, apathy, irritability, aberrant motor behavior, nighttime behavior disturbances, and total NPI were also correlated with cognitive performance, with total NPI being found to be a predictor of AD when adjusting for demographic variables. These symptoms have important impacts on patient quality of life and significantly increase the stress on caregivers, contributing to caregiver burden. Caregiver distress was greatest for the symptoms of apathy, followed by nighttime behaviors, appetite/eating abnormalities, anxiety, irritability, disinhibition, and depression in the participant with DS. Overall, NPS represent important behavior features in aging adults with DS and should be considered for effective management and treatment of patients with DS and to alleviate long-term caregiver burden.

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