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RESEARCH ARTICLE

Neuropsychiatric symptoms and emerging dementia in people with Down syndrome and older adults

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Abstract

INTRODUCTION: Neuropsychiatric symptoms (NPS) are common as Alzheimer's disease (AD) dementia emerges, both in older adults (OA) and in individuals with Down syndrome (DS).

METHODS: We compared neuropsychiatric inventory (NPI) scores and NPI score trajectories in large cohorts of individuals with DS and OA. Participants were stratified as cognitively normal/stable, mild cognitive impairment, or dementia.

RESULTS: The pattern of NPI domain scores in cohorts with DS (n = 396) or OA (n = 35,217) were qualitatively similar across the cognitive groups. The relationships between cognitive group and both the NPI total score and the rate of NPI score change over time were similar in the two cohorts (multivariate Wald test, $p = 0.28$ and $p = 0.52$, respectively).

DISCUSSION: These findings support a conjecture that the shared pathophysiology among individuals with DS and OA may be reflected in the similar clinical profiles and clinical trajectories. NPS are important considerations in the early diagnosis and clinical management.

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KEYWORDS
Alzheimer's disease, cognition, down syndrome, neuropsychiatric inventory, neuropsychiatric symptoms, older adults

Highlights

- Neuropsychiatric symptoms (NPS) often precede cognitive decline in late-onset AD.
- People with Down syndrome (DS) are a vulnerable population for AD.
- Psychiatric symptoms in people with DS and emergent dementia are poorly understood.
- Symptoms in people with DS and older adults (OA) were similar across cognitive groups.
- Similar symptoms in the two groups may reflect shared amyloid or related pathology.

1 | INTRODUCTION

Alzheimer's disease (AD) is a prevalent public health issue with 6.9 million affected in the United states in 2024.[1] The estimated U.S. population over the age of 65 is projected to increase from 58 million in 2022 to 82 million by 2050, leading to a marked increase in the number of individuals with AD and other related dementias.[1] AD is characterized by the accumulation of amyloid plaques and neurofibrillary tangles, which are hypothesized to inhibit neuron communication, damage brain tissue, and initiate neuronal degeneration.[2] Individuals with Down syndrome (DS) are an especially vulnerable population to developing AD due to the overexpression of amyloid precursor protein (APP) through the triplication of chromosome 21, where the APP gene is located.[3,4] Almost all individuals with DS develop AD neuropathology by age 40 and > 50% of individuals over the age of 60 exhibit cognitive decline.[4–6]

In late-onset sporadic Alzheimer's disease (LOAD), neuropsychiatric symptoms (NPS), such as depression, anxiety, and apathy, may precede or develop in parallel with cognitive impairment.[7,8] Several studies have shown a positive association between the development of late-life NPS and the progression of cognitive and functional decline in those who are cognitively unimpaired or those with mild cognitive impairment (MCI).[8–13] The mild behavioral impairment (MBI) construct considers these late-life, new onset, persistent psychiatric symptoms as risk factors for subsequent cognitive decline, either as early clinical expressions of underlying neurodegeneration or as conditions that accelerate the pathophysiologic process.[14,15] Recent research suggests that amyloid pathology is linked to psychiatric symptoms or MBI in cognitively unimpaired older adults (OA) or those with MCI or AD dementia.[16–19] For example, results from the Mayo Clinic Study of Aging showed that cortical amyloid burden measured using PET, was associated with depression and anxiety symptoms in cognitively unimpaired OA or those with MCI.[16] Amyloid deposition may also contribute to the link between NPS and subsequent cognitive decline.[20–22]

NPS are also observed in some individuals with DS prior to, or coincident with a decline in cognition as dementia develops.[23–25] Fonseca et al. reported differences in delusions, agitation, apathy, aberrant motor behavior, and nighttime behavioral disturbances among participants with DS across cognitive groups. They also noted that higher NPI total scores were associated with a greater odds of an AD dementia diagnosis compared to those with stable cognition.[24] Similarly, Jenkins et al. found higher levels of NPS among people with DS with MCI or dementia compared to those who were cognitively stable, and that higher baseline brain amyloid and neurofibrillary tangles seen on PET imaging were associated with greater increase in some NPS over time.[25] Other longitudinal studies also indicate that NPS represent early evidence of emerging dementia in people with DS, perhaps prior to memory decline.[26,27] The shared amyloid pathology of LOAD and individuals with DS suggests the potential for consistent manifestations of NPS in these two groups. In particular, we hypothesize that, as individuals with DS and LOAD share cortical amyloid deposition and its downstream consequences, if such pathologies were causally related to NPS then the symptom patterns and progression over time may align. In addition, understanding the specific NPS that occur in cohorts with DS or LOAD may promote awareness of their clinical symptom profiles, help distinguish NPS related to neurodegenerative processes from traditional psychiatric disorders, and potentially reveal treatment targets or other opportunities for early intervention. Lastly, there is a pressing need to compare data on individuals with DS and LOAD in order to understand disease progression and develop effective treatments. Studies comparing the two populations can contribute to understanding of disease pathogenesis and the timing of interventions. This study is one of the first bridging the gap between these two cohorts. In particular, in this study we compared the prevalence and severity of NPS in OA and people with DS across three cognitive groups, to identify comparative clinical features and consider their relationships with AD pathophysiology.

2 | METHODS

2.1 | Overall study design

We utilized longitudinal data from the Alzheimer Biomarker Consortium–Down Syndrome (ABC-DS)[28] study and the National Alzheimer's Coordinating Center (NACC) Uniform Dataset (UDS)[29] to compare NPS in people with DS and OA, respectively. In each cohort, participants from three cognitive groups were included based on clinical criteria: cognitively normal (OA) or cognitively stable (individuals with DS), MCI, or clinical dementia. The Neuropsychiatric Inventory (NPI) scores for each participant were used to compare the NPS profiles in people with DS and OA, across these three cognitive statuses. We assessed whether the association of NPS and cognitive status was modified by either the presence of DS or OA status, cross-sectionally and longitudinally. Individuals with DS and OA share some AD pathologies (such as amyloid and inflammation), and if these pathologies similarly contribute to symptom expression in individuals with DS and OA, we postulated this would result in similar patterns of NPS by cognitive status in the two cohorts. Further, we assessed the relationship between baseline NPS and the trajectory of NPS within individuals with DS specifically, as previous research has found a predictive relationship between baseline NPS and the trajectory of NPS in the OA population.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature on neuropsychiatric symptoms (NPS) in late-onset sporadic Alzheimer's disease (LOAD) and Down syndrome-associated AD (DSAD). In each group, NPS may emerge prior to or coincident with the development of AD dementia, although NPS in individuals with DS have been understudied.
2. **Interpretation**: This study is among the first to compare NPS in large cohorts of older adults (OA) and individuals with DS, across cognitive impairment status. Results indicate that total NPS, individual symptoms, and the trajectory of NPS over time are similar across groups at each cognitive status.
3. **Future directions**: This work sets precedence for investigating the hypothesis that the shared cortical patterns of amyloid neuropathology or its downstream consequences contributes to similar NPS profiles. The results also highlight the importance of NPS in early diagnosis, clinical management, and caregiver concerns. Further research can validate these findings and explore links to specific neuropathologies.

2.2 | Study populations

2.2.1 | Data source and assessments: participants with DS in ABC-DS

The ABC-DS study is a longitudinal, multi-center study whose goal is to identify biomarkers of AD progression within the DS population, and is funded by the National Institute on Aging, the National Institute of Child and Human Development, and the INCLUDE Project.[28] We utilized data extracted from the database on June 26, 2024. Participants' cognitive status was categorized as cognitively stable (CN/CS), MCI, or clinical dementia (DEM) at each visit using clinical information and structured assessments through consensus conference. Visits were ≈ 16 months apart. Cognitive stability (CS) in the participants with DS represents no recent decline in cognitive skills and allows alignment with the cognitively normal (CN) group in the OA cohort who similarly have no evidence of emerging cognitive decline. Thus, we refer to this cognitive group in the participants with DS and OA as CN/CS. Individuals with a missing cognitive status at baseline but a later status of "cognitively stable" ($n = 2$) were imputed as cognitively stable at prior missing visits, and individuals with missing cognitive status after a status of DEM were imputed as DEM ($n = 1$). Due to limited sample sizes, we grouped individuals into mutually exclusive race and ethnicity groups based on self-reported race and ethnicity (Hispanic or Latino regardless of race, Not Hispanic or Latino [NH] Asian, NH Black, NH White, and other). The ABC-DS study did not initially require all sites to gather NPI information on individuals and some sites added this assessment at a later point. In this study, we used the first observed NPI assessment to represent the "baseline" assessment in the participants with DS.

2.2.2 | Data source and assessments: OA participants in the UDS

The UDS is a large database containing standardized assessment data collected annually across the National Institute on Aging funded Alzheimer's Disease Research Centers and archived at the National Alzheimer's Coordinating Center.[29] For the purposes of the current study, we excluded participants under the age of 55 and those diagnosed with DS. At each annual visit, clinical information and assessments were used to assign a cognitive diagnosis by either an expert clinician or a consensus conference. We aligned cognitive status with the DS cohort classifications of CN/CS, MCI, and DEM. An additional diagnostic category, Impaired-not-MCI is utilized in the UDS. We omitted individuals with this diagnosis from our analyses as the category definition is not likely applied similarly across sites and does not align with available cognitive diagnoses in the cohort of individuals with DS. We adjusted demographic categories in the OA cohort to harmonize this coding with that used in the individuals with DS dataset for the residence variable (family, group home, independent, and other) and the mutually exclusive race and ethnicity variable (Hispanic or Latino, NH Asian, NH Black, NH White, and other). For baseline diagnosis, indi-

viduals were subset to their first visit. At baseline, participants with missing values for symptoms ($n = 10$), an indication of the NPI not being administered ($n = 888$), or a stated symptom presence with missing severity ($n = 96$) were omitted from analyses. This approach was also taken longitudinally.

2.3 | Clinical assessments

2.3.1 | The neuropsychiatric inventory

The NPI[30] is a validated informant-based interview that assesses 12 NPS and behavioral disturbances: delusions, hallucinations, depression, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, nighttime behavioral disturbances, and appetite/eating changes. A study partner, that is, informant, is asked to describe the presence, frequency, and severity of each symptom over the previous month. The NPI-Questionnaire (NPI-Q) is an abridged version of the NPI that includes only ratings of symptom severity based on one or two probe queries regarding each symptom, with possible scores of 0 (symptom not present), 1 (mild), 2 (moderate), or 3 (severe).[31] NPI-Q scores were used in this study to quantify NPS in both the participants with DS and OA. For our analysis, we computed a composite score of the severity of symptoms, NPI sum of severity, with a total score ranging from 0 (no observed NPS) to 36 (severe for all 12 symptoms). To ensure that the responses given by informants for the OA were optimally aligned with the participants with DS, we included NPI-Q data only from OA whose study partner was a spouse, partner, companion, child, or sibling (excluding participants with informant types such as friend, neighbor, and paid caregiver).

2.4 | Statistical analysis

We characterized the sample, stratified by cognitive status within the groups of participants with DS and OA, using means and standard deviations for continuous covariates and frequency and proportions for categorical covariates. We quantified the cross-sectional difference in mean NPI total score between participants with DS and OA within each cognitive group (CN/CS, MCI, DEM) using linear regression. Specifically, NPI sum of severity score was regressed on cognitive group, an indicator of the presence of DS versus OA, and the interaction between the two. This model allowed for the estimation of mean NPI sum of severity score in each cognitive group and individuals with DS/OA cohort, as well as the difference in mean NPI score between participants with DS and OA within each cognitive group. We adjusted for potential confounding factors identified a priori, including sex, mutually exclusive race and ethnicity groups, living situation, AD medication use, antidepressant medication use, sleep apnea, and thyroid conditions. When contrasting NPI scores in participants with DS and OA, we did not adjust for age given the lack of overlap in age distributions between the two groups. For analyses stratified by cohort, however, we did adjust for age as a continuous covariate. Individuals with a missing cognitive status at their first NPI assessment were excluded from the analysis ($n = 12$). We computed 95% Wald-based confidence intervals for mean NPI score within groups and for the difference in NPI score across groups. We further computed p-values corresponding to the Wald test of no difference in population mean NPI score between individuals with DS and OA for each cognitive group. We tested whether the difference in mean NPI score between DS and OA varied by cognitive status using a multivariate Wald test of all interaction terms between individuals with DS/OA and cognitive status. For all inference, we used Huber White robust variance estimator to guard against a potential violation of homoscedasticity.[32]

We conducted a longitudinal analysis to assess whether the association of trajectory of NPI score over time and cognitive status was modified by cohort (i.e., participants with DS or OA). To account for within subject correlation, we utilized a generalized estimating equations (GEE) framework with an identity link function and autoregressive (AR-1) working correlation structure. For the GEE mean model, we regressed NPI score on time since first visit, the indicator of presence of DS versus OA, cognitive status, and the two-way and three-way interactions between each covariate. We further adjusted for the same confounding factors as in our previous cross-sectional model. As the focus of this analysis was estimation of mean NPI scores over time, we omitted individuals with fewer than 3 observed NPI total scores. Further, to fairly compare mean NPI trajectories over time, we limited the observation time for individuals from the OA population to 6.5 years, as that was the maximum observation time in the participants with DS. Wald-based inference for the mean trajectory of NPI scores over time within and between individuals with DS and OA utilized robust variances estimates to guard against potential misspecification of the assumed working correlation structure. Finally, to address the persistence of NPS over time in the participants with DS, we also conducted a longitudinal analysis using a similar GEE framework to assess the relationship between baseline NPI total score and the rate of change of NPI score in this cohort. We adjusted for cognitive status and age in addition to the same confounding factors as in the previous models. The predictor of interest, baseline NPI sum of severity score, was treated continuously as well as categorically by quantiles.

For all models, we performed influential diagnostics. These analyses did not reveal strong evidence of implausible covariate values leading to undo influence, so all data were maintained in our presented analyses. We utilized R statistical software (version 4.3.1) for all analyses.[33]

3 | RESULTS

3.1 | Descriptive statistics

Summary statistics of key demographics and characteristics at the time of baseline NPI assessment, stratified by cohort and cognitive group are provided in Table 1. The average age at first NPI was 42.1 and 71.1 years for individuals assessed as CN/CS within the participants with DS and OA, respectively. The participants with DS included more males

TABLE 1 Demographics and characteristics at first NPI assessment, stratified by clinical cohort.

	DS			OA		
	Stable cognition	MCI	Dementia	Normal cognition	MCI	Dementia
Covariate	*N* = 295	*N* = 54	*N* = 47	*N* = 12,954	*N* = 8419	*N* = 13,844
Age at first NPI	42.1 (8.6)	53.4 (7.3)	54.9 (6.0)	71.1 (8.2)	73.1 (8.1)	73.2 (9.1)
Race and ethnicity						
NH White	264 (0.89)	50 (0.93)	43 (0.91)	9599 (0.74)	6263 (0.74)	10,855 (0.78)
Hispanic	18 (0.06)	1 (0.02)	1 (0.02)	951 (0.07)	737 (0.09)	1103 (0.08)
NH Black	3 (0.01)	2 (0.04)	2 (0.04)	1821 (0.14)	1044 (0.12)	1383 (0.10)
NH Asian	5 (0.02)	1 (0.02)	0 (0.00)	415 (0.03)	287 (0.03)	312 (0.02)
Other	5 (0.02)	0 (0.00)	1 (0.02)	168 (0.01)	88 (0.01)	191 (0.01)
Male						
(Yes vs. No)	163 (0.60)	34 (0.60)	23 (0.50)	4996 (0.40)	4555 (0.50)	6866 (0.50)
Sleep apnea						
(Yes vs. No	121 (0.40)	20 (0.40)	10 (0.20)	884 (0.07)	743 (0.09)	680 (0.05)
AD medication						
(Yes vs. No)	3 (0.01)	1 (0.02)	1 (0.02)	181 (0.01)	2137 (0.25)	8717 (0.63)
Antidepressant medication						
(Yes vs. No)	32 (0.11)	5 (0.09)	2 (0.04)	2536 (0.20)	2563 (0.30)	5680 (0.40)
Residence						
Family	173 (0.59)	21 (0.39)	12 (0.26)	9949 (0.768)	6851 (0.814)	11,191 (0.808)
Group home	77 (0.26)	29 (0.54)	31 (0.66)	343 (0.026)	197 (0.023)	656 (0.047)
Independent	45 (0.15)	4 (0.07)	4 (0.09)	2593 (0.200)	1307 (0.155)	1511 (0.109)
Other	0 (0.00)	0 (0.00)	0 (0.00)	69 (0.005)	64 (0.008)	486 (0.035)
Thyroid condition						
(Yes vs. No)	114 (0.40)	12 (0.20)	5 (0.10)	2478 (0.20)	1480 (0.20)	2237 (0.20)

Note: Categorical variables are described by counts (proportion) and continuous variables are described by mean (standard deviation), stratified by participants with DS or OA and cognitive status.

Abbreviations: AD, Alzheimer's disease; DS, Down syndrome; MCI, mild cognitive impairment; NH, non-Hispanic individuals; NPI, Neuropsychiatric Inventory; OA, older adults.

while the OA cohort included more females, although the proportions overall were generally similar. Sleep apnea and thyroid conditions were more common in the participants with DS, as expected.[34] Figure 1 shows the frequency of individual NPI items in the two cohorts, stratified by cognitive status. NPI-rated symptoms were more common across increasing levels of cognitive impairment in both cohorts. In the participants with DS, we observed that the individual symptoms of agitation, depression, anxiety, apathy, and irritability were at least twice as prevalent in the MCI cognitive status group as compared to the stable cognition group. Overall, the prevalence of individual NPI symptoms was similar between the two cohorts, with agitation and hallucinations slightly overrepresented in the participants with DS and depression and anxiety slightly overrepresented in the OA cohort at all cognitive statuses. Figure 2 illustrates the marginal distribution of total NPI scores in participants with DS and OA, across cognitive groups. Total NPI scores were similar in the two cohorts at each cognitive status, with larger variation in the OA cohort across all cognitive statuses.

3.2 | Cross-sectional comparisons of mean NPI total score between individuals with DS and OA

Table 2 describes the analysis results that tested for a differential association between baseline NPI and cognitive group by individuals with DS and OA. Compared to the referent cognitive group, CN/CS, individuals classified with MCI had a higher estimated average baseline NPI total score of 1.443 (95% confidence interval [CI]: [0.391, 2.494]) and 1.617 (95% CI: [1.53, 1.704]) for the participants with DS and OA, respectively. Similarly, compared to the referent cognitive status, CN/CS, individuals classified with DEM had a higher estimated average baseline NPI total score of 3.711 (95% CI: [2.555, 4.868]) and 4.651 (95% CI: ([4.522, 4.779]) for participants with DS and OA, respectively. The estimated mean difference in NPI total scores between OA and participants with DS stratified by cognitive group was: −0.208 (95% CI: [−0.535, 0.119]; $p = 0.212$) for CN/CS; −0.034 (95% CI: [−1.049, 0.982]; $p = 0.948$) for MCI; and 0.731 (95% CI: [−0.395, 1.857];

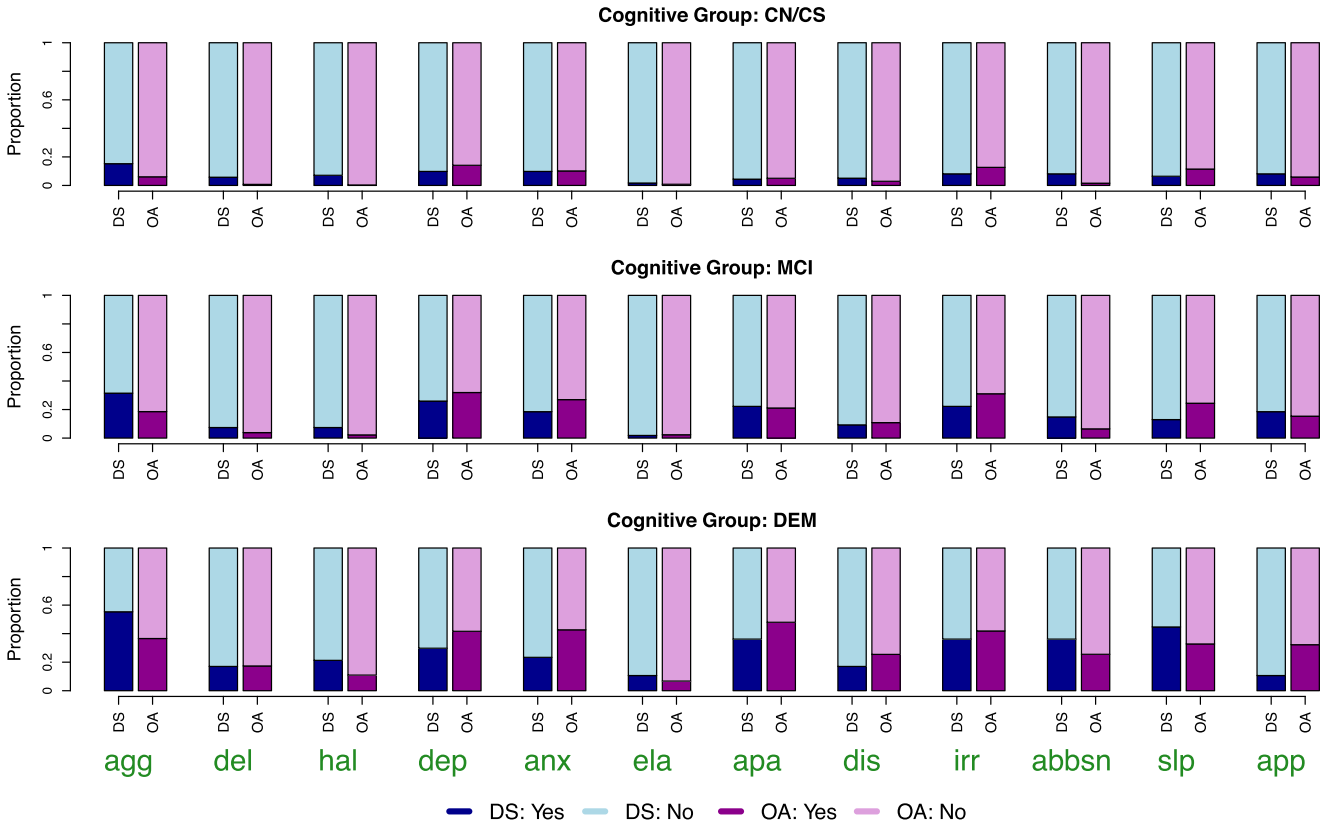

FIGURE 1 Paired bar plots for Neuropsychiatric Inventory (NPI) item presence by participant group (those with Down syndrome [DS] vs. older adults [OA]) and cognitive status at baseline assessment. NPI items were abbreviated as the following: agitation/aggression (agg), delusions (del), hallucinations (hal), depression (dep), anxiety (anx), euphoria (ela), disinhibition (dis), irritability/lability (irr), aberrant motor activity (abbsn), night-time behavioral disturbances (slp), and appetite and eating abnormalities (app).

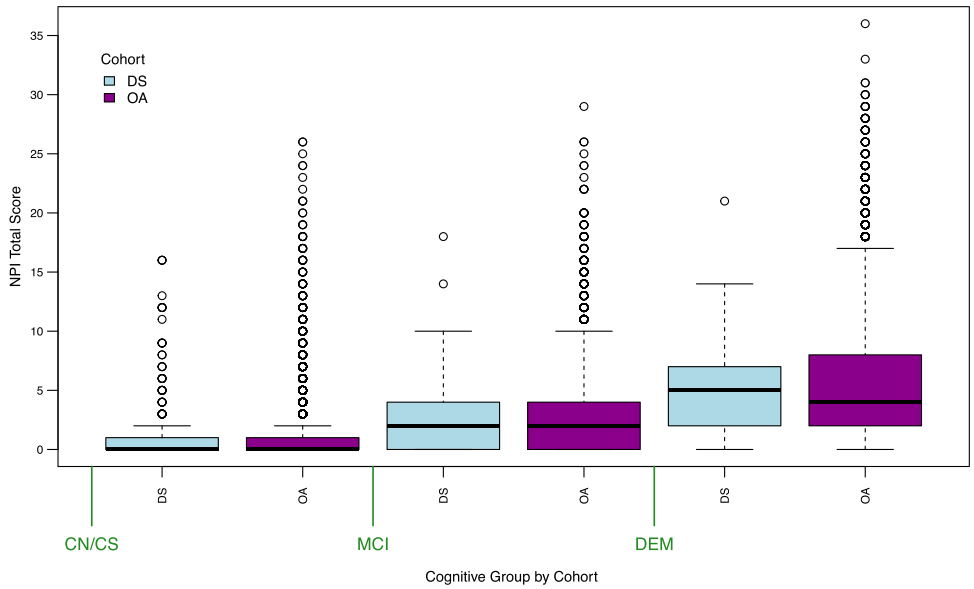

FIGURE 2 Boxplots of total Neuropsychiatric Inventory (NPI) scores, stratified by individuals with Down syndrome (DS) or older adults (OA) and cognitive status. The horizontal black line represents the median NPI total score for each group. The sides of box parallel to the horizontal black line represent the 25th and 75th percentile, and the whiskers represent the minimum and maximum non-outlier values. Outliers are plotted as points. CN/CS, cognitively normal/cognitively stable; DEM, clinical dementia; MCI, mild cognitive impairment.

TABLE 2 Regression estimates, corresponding 95% CI, and *p*-values for the cross-sectional analysis regarding a differential association of cognitive status and NPI score by cohort of participants with DS or OA).

	DS			OA		
Covariate	Estimate	95% CI	*p*-value	Estimate	95% CI	*p*-value
CN/CS		Referent			Referent	
MCI	1.443	(0.391, 2.494)	0.007	1.617	(1.53, 1.704)	< 0.001
DEM	3.711	(2.555, 4.868)	< 0.001	4.651	(4.522, 4.779)	< 0.001

Abbreviations: CI, confidence interval; CN/CS, cognitively stable/cognitively normal; DEM, clinical dementia; DS, Down syndrome; MCI, mild cognitive impairment; NPI, Neuropsychiatric Inventory; OA, older adults.

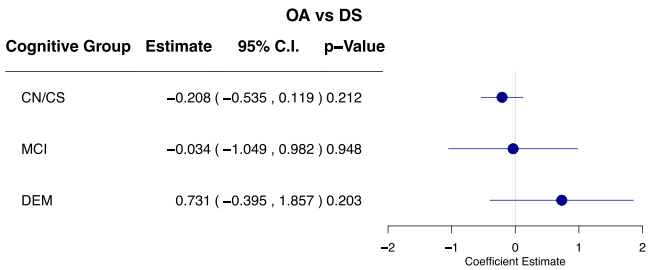

FIGURE 3 Regression estimates, corresponding 95% confidence intervals, and *p*-values for the analysis regarding a differential association of cognitive status and Neuropsychiatric Inventory (NPI) total score by participant group (those with Down syndrome [DS] or older adults [OA]). The point estimate is represented by the solid dot and the horizontal line represents the confidence interval. *Note*: a point estimate to the left of the midline indicates higher NPI total score in the participants with DS compared to the OA. CN/CS, cognitively normal/cognitively stable; DEM, clinical dementia; MCI, mild cognitive impairment.

$p = 0.203$) for DEM (Figure 3). There was not statistical evidence to suggest that the association between baseline NPI total score and cognitive group was modified by clinical cohort (individuals with DS vs. OA) ($p = 0.282$).

3.3 | Comparison of NPI score changes over time between individuals with DS and OA

Table 3 quantifies the association between cognitive status and the rate of change of NPI score over time by cohort. In the CN/CS and MCI cognitive groups, there were slight downward trends in NPI total score over time, with greater downward trends among participants with DS compared to OA. Among participants with DEM, there were similar upward trends in NPI total score over time in the participants with DS and OA. Stratifying by cognitive group, the estimated mean difference in NPI score rate of change between OA and participants with DS was: 0.286 (95% CI: [0.120, 0.453]; $p = 0.001$) for CN/CS; 0.352 (95% CI: [0.021, 0.682]; $p = 0.037$) for MCI; and −0.019 (95% CI: [−0.507, 0.469]; $p = 0.939$) for DEM. There was no statistically significant difference in the association between cognitive status and change of NPI over time by cohort ($p = 0.516$).

3.4 | Association between baseline NPI score and change over time NPI score in the individuals with DS

Within the participants with DS, we estimated that the mean difference in the rate of change of NPI score over time, comparing individuals with a 1-point difference in baseline NPI total score was 0.082 points per year (95% CI: [−0.001, 0.164]; $p = 0.052$). Figure 4 depicts the positive association between baseline NPI score and rate of change of NPI score, relative to the estimated rate among individuals with a baseline NPI score of 0. When assessing the association categorically, we observed a nonlinear trend between baseline NPI percentiles. Specifically, the mean change in NPI per year was estimated as −0.168 (95% CI: [−0.528, 0.192]; $p = 0.361$), −0.448 (95% CI: [−0.992, 0.097]; $p = 0.107$), 0.054 (95% CI: [−0.502, 0.610]; $p = 0.849$), 0.453 (95% CI: [−0.258, 1.165]; $p = 0.212$) for baseline NPI score categorized as ≤ 25th percentile, > 25th and ≤ 50th percentile, > 50th and ≤ 75th percentile, and > 75th percentile, respectively (Table 4).

4 | DISCUSSION

This study assessed the prevalence and progression of NPS in people with DS who were cognitively stable and those with MCI, or had dementia, and compared these features to those in neurotypical older adults. Overall, we found that total NPI scores and the pattern of individual NPI symptoms were similar across the two cohorts at each level of cognitive status. Similarly, the progression of total NPI scores over time was comparable in the two cohorts. Finally, in the participants with DS, the change in NPI score trajectory was greater among those with a higher initial NPI score, although this trend did not reach statistical significance.

In the cohort of participants with DS, our analysis demonstrated that the severity of total NPS became more pronounced across the CS, MCI, and DEM cognitive status. We observed that several individual symptoms were substantially more common in participants with DS MCI compared to those with stable cognition: agitation, depression, anxiety, apathy, and irritability—were at least twice as prevalent in the MCI group (Figure 1), suggesting a potential association of these symptoms with early AD-related processes. Among individuals with a dementia diagnosis, agitation was the most common symptom,

TABLE 3 Regression estimates, corresponding 95% CI, and *p*-values for the longitudinal analysis regarding a differential association of cognitive group and rate of change of NPI total score by cohort of participants with DS or OA.

	DS			OA			OA versus DS		
Covariate	**Estimate**	**95% CI**	***p*-value**	**Estimate**	**95% CI**	***p*-value**	**Estimate**	**95% CI**	***p*-value**
Mean NPI score at baseline									
CN/CS*		Referent			Referent		−1.1	(−1.817, −0.383)	0.003
MCI*	0.675	(−0.589, 1.94)	0.295	1.385	(1.293, 1.478)	< 0.001	−0.39	(−1.525, 0.745)	0.5
DEM*	1.106	(−0.369, 2.581)	0.142	3.07	(2.94, 3.201)	< 0.001	0.864	(−0.402, 2.131)	0.181
Mean change in NPI score per year									
CN/CS	−0.282	(−0.448, −0.116)	0.001	0.004	(−0.005, 0.014)	0.385	0.286	(0.120, 0.453)	0.001
MCI	−0.393	(−0.722, −0.064)	0.019	−0.041	(−0.067, −0.015)	0.002	0.352	(0.021, 0.682)	0.037
DEM	0.233	(−0.253, 0.72)	0.347	0.214	(0.182, 0.247)	< 0.001	−0.019	(−0.507, 0.469)	0.939

Abbreviations: CI, confidence interval; CN/CS, cognitively stable/cognitively normal; DEM, clinical dementia; DS, Down syndrome; MCI, mild cognitive impairment; NPI, Neuropsychiatric Inventory; OA, older adults.
*The difference in estimated mean NPI scores at baseline between the cross-sectional and longitudinal analyses is due to differences in the samples used; the longitudinal analysis was conducted on a subset of the cohort used in the cross-sectional analysis, specifically those with sufficient follow-up data to estimate the slope.

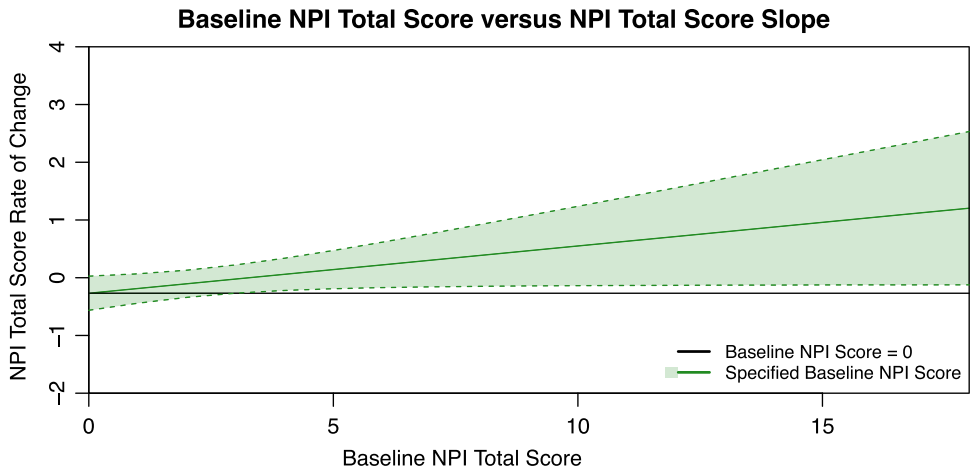

FIGURE 4 Estimated Neuropsychiatric Inventory (NPI) total score rate of change as a function of baseline NPI total score among participants with Down syndrome (DS). For each estimated rate of a change a corresponding confidence interval was plotted. The horizontal black line represents the estimated NPI total score rate of change given a baseline NPI score of 0 (no symptoms).

occurring in ≈ 40% of individuals with DS. Several previous studies have evaluated the prevalence of NPS across cognitive groups in people with DS, although samples have generally been small and heterogeneous, and assessment tools, cognitive diagnostic criteria, and findings have been variable.[24,26,35–37] Most found that the prevalence of NPS increased across the continuum from CS to AD dementia. Interestingly, the studies by Urv et al.[36] and Fonseca et al.[24] suggested that apathy, anxiety, and agitation were substantially more common in participants with DS with prodromal/questionable dementia compared to those who were cognitively stable, similar to our findings in the participants with DS MCI. Moreover, Holland et al.[35] found that apathy was the most frequent symptom observed by carers of those with DS exhibiting early clinical decline, exceeding the frequency of memory difficulty. Thus, the overall evidence indicates that several distinct NPS, particularly apathy and agitation, may be early expressions of DSAD, and these findings align with observations in OA in the clinical transition to sporadic AD dementia.[15,38,39]

We also found that, within the cohort of participants with DS, baseline NPI total score was associated with change in NPI score over time; however, this finding was not statistically significant. We further estimated that participants with DS in the highest quartile of NPI scores at baseline had the largest positive change of NPI score over time. These findings indicate a correlation of high levels of NPS and higher levels of NPS over time, highlighting the general persistence or worsening of these symptoms over time. One implication of this result is the ability to further inform clinical care for the individual with DS and strategies for support and education of family and other caregivers.

TABLE 4 Among participants with DS, regression estimates and corresponding 95% CI, and *p*-values of the longitudinal analysis testing an association between baseline NPI score and the rate of change of NPI score per year.

Covariate	Est.	95% CI	*p*-value
Mean change in NPI per year by baseline NPI			
0–25 percentile	−0.168	(−0.528, 0.192)	0.361
25–50 percentile	−0.448	(−0.992, 0.097)	0.107
50–75 percentile	0.054	(−0.502, 0.610)	0.849
75–1 percentile	0.453	(−0.258, 1.165)	0.212

Abbreviations: CI, confidence interval; DS, Down syndrome; NPI, Neuropsychiatric Inventory.

The principal goal of this study was to compare NPS in participants with DS and OA across three levels of cognitive status: CN/CS, MCI, and DEM. Results revealed similar severity of total NPS in the two cohorts at each AD stage and a similar monotonic rise in NPS severity associated with progression across cognitive strata. The frequency of individual NPS as measured by NPI items was strikingly similar in the two cohorts (Figure 1), with agitation, depression, anxiety, apathy, and irritability most common in both cohorts across all cognitive stages. Agitation, delusions, hallucinations, and abnormal motor activity appeared to be modestly more common in the participants with DS, whereas depression, anxiety, irritability, and sleep disturbance were slightly more common among OA. These subtle qualitative between-cohort differences were most apparent at the MCI and DEM cognitive statuses, although they were not tested statistically.

Similar to the cross-sectional finding of similar NPI total scores in the OA and participants with DS, our longitudinal analysis also found that the change in total NPI score over time within cognitive groups was similar in the two cohorts. NPI total scores lowered (improved) annually by a small amount in the OA cohort with MCI and in the individuals with DS who were CN/CS or had MCI. While the rationale for these NPS improvements in the CN/CS and MCI groups is not clear, the modest changes may reflect mild adaptation and accommodation by collateral informants in their perception and ratings of an individual's NPS over time, leading to lower behavioral scores. In contrast to the findings in the CN/CS and MCI groups, participants with clinical dementia showed higher NPI scores over time in both cohorts, as expected. The magnitude of annual changes was similar in the two cohorts, reflecting similar clinical consequences of the advancing neurodegenerative process in the dementia phase.

Overall, the total NPS at each cognitive status, the progression of NPS across the cognitive continuum, and the profile of individual symptoms in the OA and individuals with DS were notably similar, a phenomenon not examined in prior studies. The shared NPS features in the two cohorts suggest the possibility of shared etiologic factors. AD-related neuropathologies such as β-amyloid, neurofibrillary tangles, α-synuclein and TAR DNA-binding protein 43 (TDP-43) pathology, neuroinflammation, cerebral amyloid angiopathy (CAA), and cholinergic neurotransmitter dysregulation are present in both OA and DS with AD and progress similarly over time[3,5,40,41] and may be important factors in the similar clinical profiles. Prior studies[16,18,22] have suggested that amyloid-related pathologies contribute to distinct NPS in the early stages of AD clinical expression. Therefore, while AD biomarkers were not assessed in this study, the presence of brain amyloid plaque in the participants with DS would be presumed, based on the known natural history of amyloid deposition in individuals with DS, and amyloid pathology would likely be highly prevalent in the OA cohort with dementia in the NACC sample. The similarity in NPS profiles across OA and DS may plausibly reflect shared etiological mechanisms, with amyloid and related downstream neuropathologies contributing to these clinical features. Such overlap, however, may also extend beyond amyloid, implicating additional pathophysiological processes. Furthermore, individuals with DS have more amyloid plaque in the basal ganglia, more extensive CAA and microhemorrhages, greater locus coeruleus pathology, more prominent obstructive sleep apnea, and less extensive cerebral atherosclerosis and arteriolosclerosis than do OA with AD,[3,42–44] suggesting that these features may be less consequential to the expression of specific NPS. The shared NPS profiles and their longitudinal course in participants with DS and OA, along with their potentially similar pathophysiologies, suggest that optimal behavioral assessment strategies, predictions for clinical progression, treatment targets, and intervention approaches may also be similar in the two diagnostic groups and that clinical lessons learned in one group may also be applicable to the other. In addition, these findings indicate that the development of NPS in individuals with DS is likely an expression of the AD process, rather than exclusively a consequence of situational factors, underlying disability, or traditional psychiatric disorders.

This study is one of the first to compare NPS in DS and OA at risk for AD and took advantage of large samples of participants in the ABC-DS and ADRC programs. This study, however, is not without limitations. The data was obtained from two independent longitudinal observational programs that had different clinical sites and overall assessment strategies. The NPI, however, was used in each cohort, using standardized rating instructions. NPI ratings were informant-based and we attempted to minimize differential effects of informant type by including data from participants with DS only when the informant type aligned with usual OA informants. Second, diagnostic information and criteria for cognitive status were similar in the two cohorts but may not have been applied identically. The sensitivity of the cognitive tests may have differed due to participants' premorbid intellectual ability, especially among participants with DS, and ongoing and variable intellectual disability severity among participants with DS may have led to some misalignment between cohorts. Third, we were unable to adjust for the effect of age in the cohort comparisons, as there was little overlap in age distribution. Fourth, hypotheses linking NPS to brain amyloid specifically are tenuous, as AD biomarker status was not known. Finally, hypotheses regarding links between regional neuropathology and NPS must acknowledge that other factors, including environmental circumstances, caregiver interactions, cultural aspects, and personal background, certainly contribute to NPS in the evolution of clinical AD.

5 | CONCLUSION

In summary, our findings demonstrate that the magnitude of total NPS and prevalence of individual symptoms is similar in participants with DS and OA, across cognitive statuses. The rate of change in NPS symptoms is also similar in the two cohorts. These findings suggest that the shared AD-related neuropathologies and downstream consequences may contribute to the expression of distinct NPS in both clinical cohorts. These findings also contribute to a better understanding of NPS in individuals with DS specifically and can improve clinical awareness and care. Future studies can further explore clinical phenomenology, specific biomarker links to brain amyloid and other neuropathologies, other factors contributing to NPS risk or resilience, and treatment opportunities to improve NPS and maintain cognitive and functional skills for both individuals with DS and OA.

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CONSENT STATEMENT

All human subjects provided informed consent to participate in the UDS and ABC-DS study, according to institutional review board (IRB)-approved procedures.

CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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