Neuropsychiatric Symptoms Across Levels of Cognition in Alzheimer's Disease in Down Syndrome Alzheimer's Disease and Late-Life Sporadic Alzheimer's Disease

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Background

- Alzheimer's disease (AD) can be characterized by abnormal amyloid plaques, formed when amyloid precursor protein (APP) is processed incorrectly, disrupting brain function and causing cognitive decline.
- People with Down Syndrome (DS) are at high risk of developing abnormal amyloid protein plaques due to the APP overexpression associated with chromosome 21 triplication.
- An estimated 50% of DS individuals develop dementia with age. By age 40, nearly all show pathological brain changes consistent with AD, though not all develop symptoms.

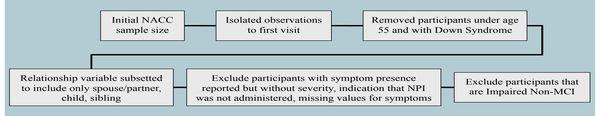
Objectives

- Identify and compare the pattern of NPS (neuropsychiatric symptoms) in two cohorts of participants: DSAD (AD due to Down Syndrome) and LOAD (late-life onset AD), at three levels of cognitive impairment – cognitively stable/unimpaired, mild cognitive impairment, and mild AD dementia.
- Measure the longitudinal change in NPS over a 6.5-year period in those with DSAD. Assess the relationship between baseline NPS and the change in NPS over time and the change in cognitive skills over a similar period.

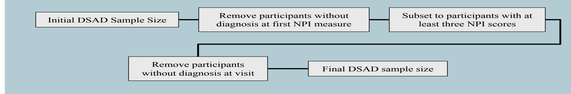
Methods

- Data sources: Alzheimer Biomarkers Consortium-Down Syndrome (ABC-DS) and the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set. ABC-DS and NACC pertain to the DSAD and LOAD populations, respectively.
- NPS was measured using the Neuropsychiatric Inventory (NPI), with the sum of severity score being used for the analyses.
- Adjusted for confounding factors: age, race, sex, AD medication antidepressants, living situation, sleep apnea, and thyroid issues.

Exclusion criteria for NACC pertaining to LOAD group



For both NACC and ABC-DS, patients needed at least three visits, with observations limited to a 6.5-year period since first visit



Cross-sectional analysis

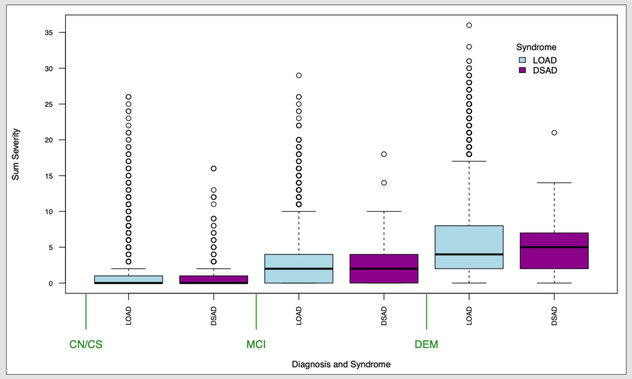
- Model estimated mean NPI score in each cognitive and DSAD/LOAD group, as well as the difference in mean NPI score between DSAD/LOAD within each cognitive group.

Longitudinal analysis

- Model assessed whether the association of trajectory of NPI score over time and cognitive status was modified by syndrome DSAD/ LOAD.
- Regressed NPI score on time since first visit, baseline NPI score, and the two-way of the covariates to assess the relationship of baseline NPI and the rate of change of NPI with the DSAD syndrome.

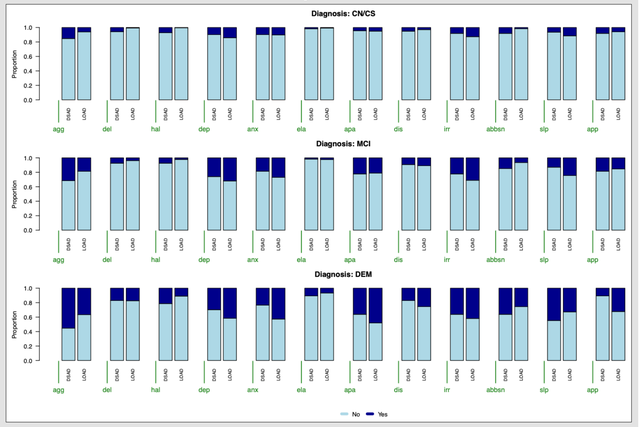
Data and Statistical Analysis

Figure 1: Distribution of Sum Severity at First NPI stratified by diagnosis and syndrome



Participants' baseline sum of severity scores across cognitive status and syndrome (DSAD or LOAD).

Figure 2: Paired bar plots for NPI item presence by DSAD and LOAD syndrome



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), appetite /eating abnormalities (app) at baseline.

Table 1: Demographics and Characteristics at First NPI stratified by LOAD and DSAD populations

	LOAD			DSAD		
Covariate	Normal Cognition N = 12954	MCI N = 8419	Dementia N = 13844	Normal Cognition N = 295	MCI N = 54	Dementia N = 47
Age at First NPI	71.13 (8.15)	73.11 (8.07)	73.23 (9.10)	42.06 (8.59)	53.35 (7.33)	54.91 (6.01)
Race and Ethnicity						
NH White	9599 (0.74)	6263 (0.74)	10855 (0.78)	264 (0.89)	50 (0.93)	43 (0.91)
Hispanic	951 (0.07)	737 (0.09)	1103 (0.08)	18 (0.06)	1 (0.02)	1 (0.02)
NH Black	1821 (0.14)	1044 (0.12)	1383 (0.10)	3 (0.01)	2 (0.04)	2 (0.04)
NH Asian	415 (0.03)	287 (0.03)	312 (0.02)	5 (0.02)	1 (0.02)	0 (0.00)
Other	168 (0.01)	88 (0.01)	191 (0.01)	5 (0.02)	0 (0.00)	1 (0.02)
Male						
Yes (vs No)	4996 (0.4)	4555 (0.5)	6866 (0.5)	163 (0.6)	34 (0.6)	23 (0.5)
Sleep Apnea						
Yes (vs No)	884 (0.07)	743 (0.09)	680 (0.05)	121 (0.4)	20 (0.4)	10 (0.2)
AD Medication						
Yes (vs No)	181 (0.01)	2137 (0.25)	8717 (0.63)	3 (0.01)	1 (0.02)	1 (0.02)
Antidepressants						
Yes (vs No)	2536 (0.2)	2563 (0.3)	5680 (0.4)	32 (0.11)	5 (0.09)	2 (0.04)
Residence						
Family	9949 (0.768)	6851 (0.814)	11191 (0.808)	173 (0.59)	21 (0.39)	12 (0.26)
Group Home	343 (0.026)	197 (0.023)	656 (0.047)	77 (0.26)	29 (0.54)	31 (0.66)
Independent	2593 (0.200)	1307 (0.155)	1511 (0.109)	45 (0.15)	4 (0.07)	4 (0.09)
Other	69 (0.005)	64 (0.008)	486 (0.035)	0 (0.00)	0 (0.00)	0 (0.00)
Thyroid						
Yes (vs No)	2478 (0.2)	1480 (0.2)	2237 (0.2)	114 (0.4)	12 (0.2)	5 (0.1)

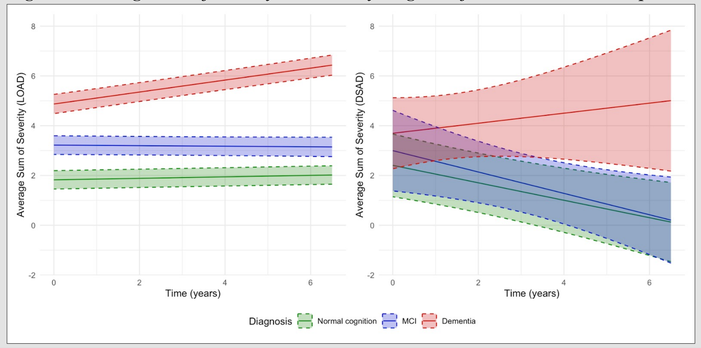
Table 2: Regression estimates and corresponding 95% CIs, and p-values of cross-sectional analysis regarding a differential association of cognitive status and rate of change of NPI by LOAD or DSAD

	LOAD			DSAD			LOAD vs DSAD		
Covariate	Est	95 C.I.		Covariate	Est	95 C.I.	Covariate	Est	95 C.I.	P-Value
Cognitive Status										
CN/CS		Referent		CN/CS		Referent	CN/CS	-0.208	(-0.535 , 0.119)	0.212
MCI	1.617	(1.53 , 1.704)		MCI	1.443	(0.391 , 2.494)	MCI	-0.034	(-1.049 , 0.982)	0.948
DEM	4.651	(4.522 , 4.779)		DEM	3.711	(2.555 , 4.868)	DEM	0.731	(-0.395 , 1.857)	0.203

Table 3: Regression estimates and corresponding 95% CIs, and p-values of longitudinal analysis regarding a differential association of cognitive status and first NPI by LOAD or DSAD

	LOAD			DSAD			LOAD vs DSAD		
Covariate	Est	95 C.I.	P-Value	Est	95 C.I.	P-Value	Est	95 C.I.	P-Value
Mean NPI at Baseline									
CN/CS		Referent			Referent		-1.100	(-1.817 , -0.383)	0.003
MCI	1.385	(1.293 , 1.478)	<0.001	0.675	(-0.589 , 1.94)	0.295	-0.390	(-1.525 , 0.745)	0.50
DEM	3.07	(2.94 , 3.201)	<0.001	1.106	(-0.369 , 2.581)	0.142	0.864	(-0.402 , 2.131)	0.181
Mean Change in NPI Per Year									
CN/CS	0.004	(-0.005 , 0.014)	0.385	-0.282	(-0.448 , -0.116)	0.001	0.286	(0.12 , 0.453)	0.001
MCI	-0.041	(-0.067 , -0.015)	0.002	-0.393	(-0.722 , -0.064)	0.019	0.352	(0.021 , 0.682)	0.037
DEM	0.214	(0.182 , 0.247)	<0.001	0.233	(-0.253 , 0.72)	0.347	-0.019	(-0.507 , 0.469)	0.939

Figure 3: Average sum of severity over time by diagnosis for LOAD and DSAD patients



Results

Cross-sectional analysis

- We found that compared to the referent cognitive status, CN/CS, individuals classified with MCI had a higher estimated average baseline NPI total score.
- Compared to the referent cognitive status, CN/CS, individuals classified with DEM had a higher estimated average baseline NPI total score.
- Through a multivariate Wald test at (P = 0.282), we were not able to claim that the association of baseline NPI total score and cognitive status was modified by syndrome.

Longitudinal data analysis

- Based on the results of a multivariate Wald test (P = 0.516), we were not able to conclude syndrome significantly modifies the relationship between cognitive status and the rate of change of NPI significantly.
- We observed some heterogeneity in the rate of change of NPI score of CN/CS and MCI cognitive status across syndrome.
- We estimated no association within the CN/CS LOAD group and a negative association, i.e. a more positive outcome of NPS with time, among the CN/CS DSAD subgroup.
- DSAD exhibits greater variability and faster symptom progression in the dementia group compared to LOAD.

Discussion

- Prior to getting other tests for diagnosis, symptoms of cognitive impairment is how AD is identified early.
- DSAD group has a "purer" form of AD with fewer mixed pathologies; therefore, similarities in NPS between LOAD and DSAD would suggest a relation to shared amyloid pathology.
- People with early DSAD and LOAD share the presence of amyloid plaques in the brain, in generally the same locations and with similar progression over time.
- Negative rate of change for MCI LOAD may be due to bias in memory recall or early stages of AD symptoms being indistinguishable, compared to when individuals progress to dementia symptoms.

Applications

- Similarity of trends implicates the importance of early diagnosis and treatment.
- Useful for caregivers of the individuals to be aware of possible symptom development and severity over time, beyond just memory decline.
- Understanding the specific NPS in DSAD and LOAD can bring awareness to distinguish these symptoms from traditional psychiatric disorders, improve differential diagnosis, and reveal opportunities for better targeted treatments early in the illness course.

References and Acknowledgment

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Supported in part by the NIA P30 AG066519 (UCI ADRC) and NIA U19 AG068054 (ABC-DS)