

Prediction of amyloid- β , tau PET pathology, and dementia conversion in adults with Down syndrome using intraindividual cognitive variability

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Background

- Nearly all individuals with DS develop AD-neuropathology by age 40.¹
- Despite stereotypical progression of the AD pathology, onset of dementia and preclinical symptoms is variable.²
- Intra-individual cognitive variability (IICV) is a sensitive marker for pre-clinical changes in AD³ not yet tested in individuals with DS.

We aimed to characterize the relationship between baseline IICV, AD-biomarkers (including brain amyloid- β and tau by positron emission tomography, PET), cognitive decline and subsequent dementia in adults with DS from the ABC-DS (Alzheimer's Biomarker Consortium-DS) study⁴.

Participants and Methods

460 adults with DS (ages 25-81, mean 43.2, 45.7% female) assessed at baseline and followed approximately 40 months later, standard deviation of 7.8 months). Participants completed neuropsychological assessments, consensus dementia diagnosis, and brain PET amyloid- β and tau imaging. Intellectual disability: 50% mild, 41.5% moderate and 8.5% severe. APOE e4carriers: 23.3%. At baseline: 8% had dementia, 12.4% MCI. At follow up: 20.5% dementia, 9.8% MCI.

Table 1. Tests and subtests included in the intraindividual cognitive variability (IICV) measures

Cognitive domain	Test	Measures included	Type of IICV
Memory	Cued Recall	• Total learning free and cued recall	Across-test Within-domain
	Rivermead Picture Recognition Delay	• Total correct	
	Down syndrome Mental Status Examination (DSMSE)	• Memory score (location)	
Executive function*	Cats & Dogs	• Naming time (multiplied to minus 1)	Across-test Within-domain
	Rivermead Picture Recognition Delay	• Switching time (multiplied to minus 1)	
	Cued Recall	• Total false positive (multiplied to minus 1)	
Memory/ Executive	All tests included in IICV Memory and IICV Executive Function	• Total intrusions (multiplied to minus 1)	Across-test Across domain

IICV measures: within-person standard deviation of z-scores³ (table 1). Higher IICV scores = greater variability across cognitive measures.

Table 2. Cognitive and imaging characteristics of the participants at baseline and follow-up of approximately three years apart.

	Baseline (N = 460)	Follow-up (N = 275)
Cognitive variability measures		
Intraindividual cognitive variability, mean (SD)/ range		
Memory (n=346)	0.83 (0.72) / 0.04 – 3.21	
Executive function (n=320)	0.83 (0.71) / 0.03 – 5.11	
Memory/ executive (n=320)	0.87 (0.61) / 0.08 – 3.09	
Neuroimaging findings		
Amyloid- β measured in centiloids, mean (SD)/ range (Baseline n = 239, Follow-up n=87)	30.91 (38.39)/ -19.19- 180.11	19.14 (26.77)/ -7.60 – 109.21
Amyloid age*, years	-2.42 (10.04)/ -37.50 – 13.72	-4.16 (10.21)/ -33.50 – 10.29
Amyloid age $\geq 2.5^*$, n (%)	78 (32.0)	20 (23.0)
PET-tau Neurofibrillary Braak tangle stage		
(Baseline n = 141, Follow-up n = 80)		
Assessed using standardized uptake value ratio (SUVR)		
I-II	1.18 (0.19)	1.20 (0.18)
III-IV	1.14 (0.18)	1.15 (0.20)
V-VI	1.08 (0.21)	1.09 (0.19)
*Amyloid age derived using Sampled Iterative Local Approximation (SILA) ⁵ , ^a Amyloid age corresponding to the expected tau rise ⁶		

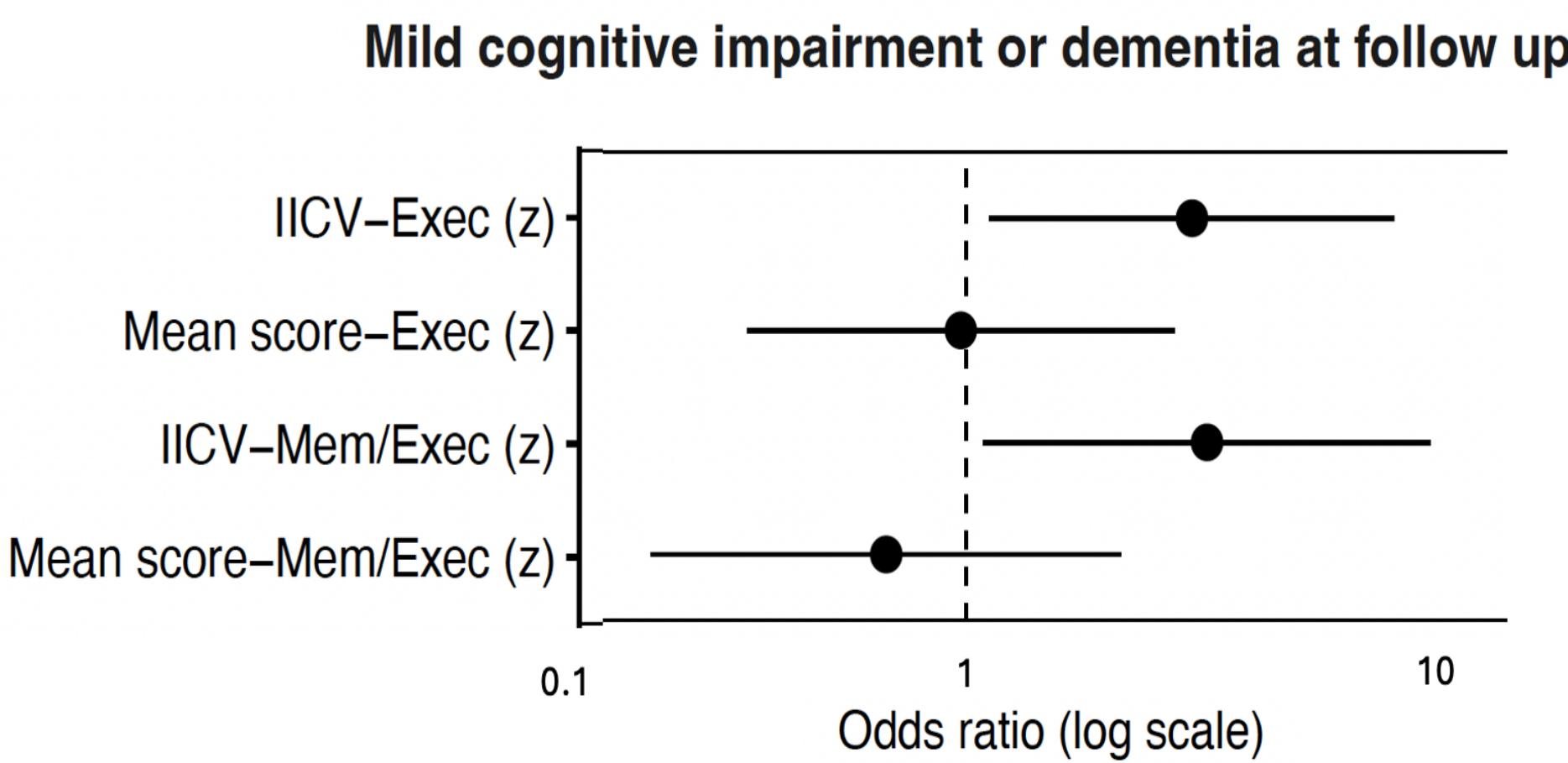
Analyses

Generalized linear models assessed associations between IICV and outcomes, adjusting for age, sex, intellectual disability, APOE ϵ 4, site, follow up interval (when applicable), mean cognitive scores and Bonferroni correction. Analyses predicting incident MCI/dementia or cognitive decline were conducted in participants who were cognitively stable at baseline. Exploratory sex-by-IICV interactions were tested.

Results

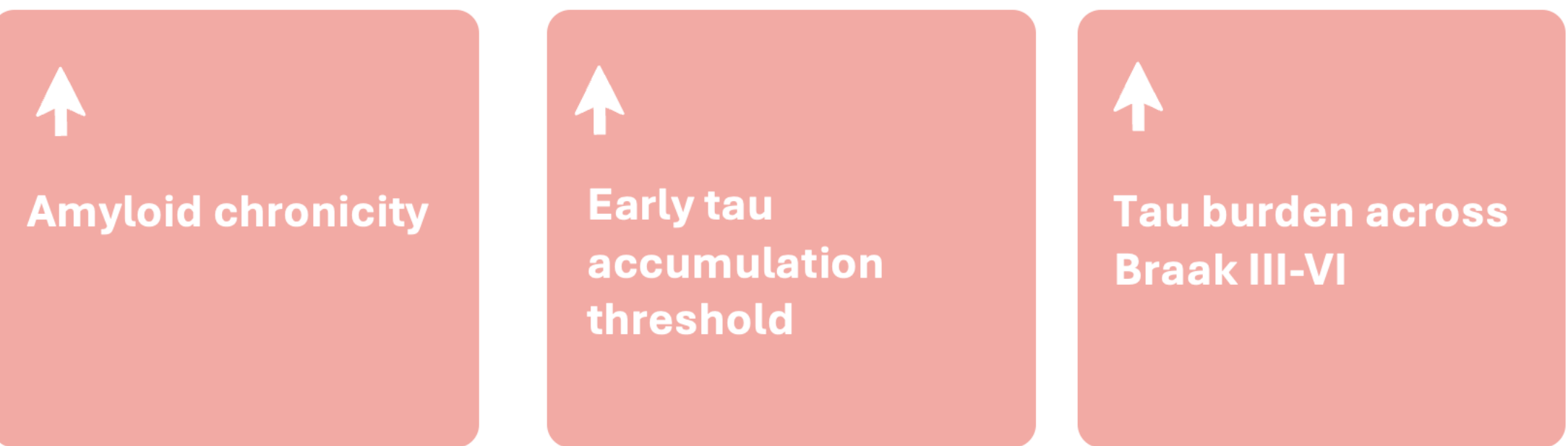
Greater baseline IICV-Exec and IICV-Memory/Exec significantly predicted incident MCI/dementia, baseline amyloid chronicity, early tau accumulation and tau burden across Braak stages III–VI. Exploratory analyses further suggested sex-specific interactions between IICV and tau-related outcomes: memory-based IICV interactions were stronger on males, whereas executive-based interactions were stronger in females

Clinical Finding



Biomarker Findings

IICV tracks AD biomarkers (EF variability showed strongest associations)



Data presented are from:
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Conclusion

IICV captures clinically and biologically meaningful heterogeneity in AD risk among individuals with DS. Elevated IICV was associated with clinical conversion and tau-related pathology independent of mean cognitive performance, underscoring its unique contribution beyond traditional cognitive metrics. Further research is needed to elucidate the neurobiological mechanisms underlying cognitive variability and to evaluate its utility for secondary prevention trials, and as a sensitive outcome measure in interventions targeting amyloid, tau, and clinical progression.

Ref: ¹Fortea et al. 2021. Lancet Neurol. Doi:10.1016/S1474-4422(21)00245-3; ²Lott & Head. 2019. Nat Rev Neurol doi:10.1038/s41582-018-0132-6; ³Holtzer et al 2008. JAMA doi:10.1001/jama.300.7.823; ⁴Handen et al 2025. Alzheimers Dement doi:10.1002/alz.70294; ⁵Schworer et al. 2024. Lancet Neurol doi:10.1016/S1474(24)00426-5; ⁶Zammit et al. Alzheimers Dement doi:10.1002/alz.13444

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