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NEUROIMAGING

Brain Volumetric Trajectories in Down Syndrome and Autosomal Dominant Alzheimer Disease

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Abstract

Background: Alzheimer disease (AD) related cognitive decline occurs at relatively young ages in individuals with Down syndrome (DS, early-mid 50s) and in those with autosomal dominant mutations (ADAD, 40-50s). Both groups show similar patterns of amyloid accumulation. We examined if brain volumes are similarly affected by AD pathology in individuals with DS and ADAD.

Method: Data for cognitively stable and declining participants was obtained from the Alzheimer Biomarker Consortium-Down Syndrome (ABC-DS) and the Dominantly Inherited Alzheimer Network (DIAN). Stability/decline was identified based on cognitive testing and interview of individuals and caregivers by trained assessors. Cognitively stable family members without DS/ADAD mutations were recruited as controls from both studies. Participants underwent MRI and amyloid positron emission tomography (PET) scans from which brain volumes and amyloid (centiloids) were derived, respectively. Participants from DIAN had Pittsburgh Compound-B (PIB) scans, ABC-DS had PIB or florbetapir. Nonlinear cross-sectional associations between regional brain volumes and estimated years to onset of cognitive decline (EYO, negative values before onset, positive after) and centiloid were evaluated using generalized additive models while controlling for sex and random effects of family. EYO was set to 52 for all participants with DS and based on parental decline/mutation type for participants with ADAD. EYO for controls was based on the EYO of their family member.

Result: Data from 239 participants with DS (47 declining), and 340 participants with ADAD (122 declining), and 263 familial controls were included. Higher EYO and centiloid values were associated with lower brain volumes in almost all regions. At earlier EYOs, individuals with DS typically had smaller regional volumes than ADAD or sibling controls, with volume declining linearly across the EYO range. By contrast, ADAD mutation carriers had similar volumes to non-carriers at early EYOs, with

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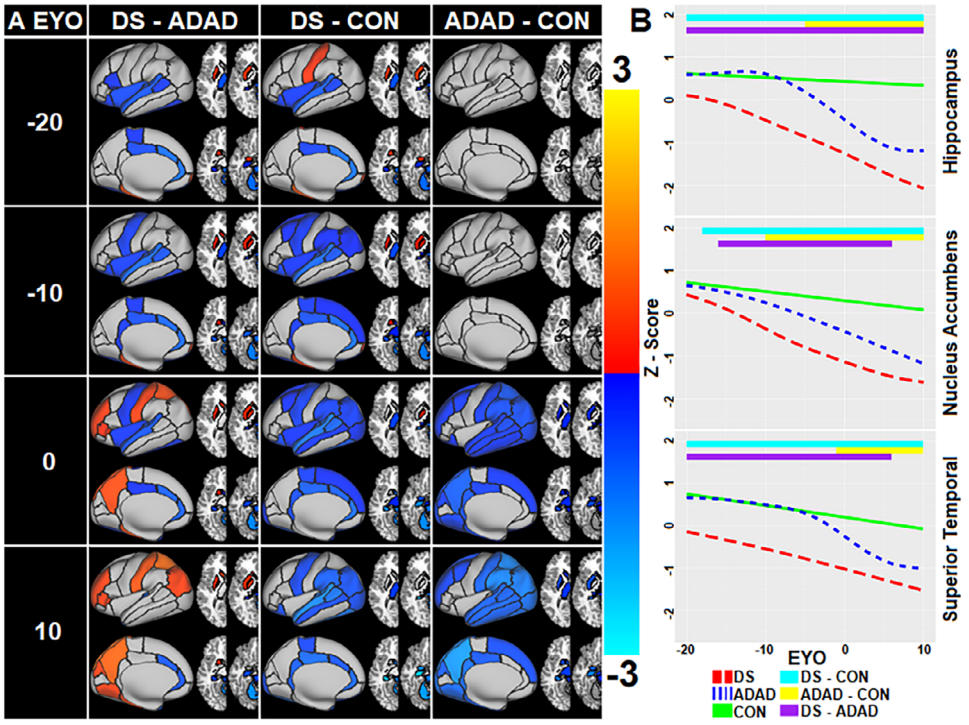
volumes diverging as early as 10 years before decline. Brain volumes and centiloid values were inversely related in ADAD and DSAD. Volume in key cortical regions were similar by the expected year of onset in both groups.

Conclusion: ADAD and DSAD demonstrated different temporal patterns of regional neurodegeneration prior to cognitive change despite being similarly affected by early onset amyloid.

	All			Stable			Declining		
	Control	DS	ADAD	Control	DS	ADAD	Control	DS	ADAD
N (Male)	263 (101)	239 (131)	340 (149)	263 (101)	183 (96)	212 (96)	-	47 (32)	128 (50)
N Amyloid Scans	244	184	306	244	157	196	-	36	110
N APP/PSEN1/PSEN2	0/0/0	0/0/0	60/238/25	0/0/0	0/0/0	35/142/24	-	0/0/0	25/96/1
APOE E4 Prevalence	0.294	0.212	0.285	0.294	0.189	0.278	-	0.34	0.297
Age (SD)	40.2 (11.5)	42.5 (9.5)	39.6 (10.6)	40.2 (11.5)	41.1 (8.9)	35.5 (9.3)	-	52.2 (5.5)	46.4 (9.1)
EYO (SD)	-8.4 (11.7)	-8.5 (9.5)	-6.9 (10.9)	-8.4 (11.7)	-10.9 (8.9)	-13.3 (8.6)	-	0.1 (3.9)	3.6 (3.9)
Centiloid (SD)	-0.9 (3.4)	25.5 (35.9)	46 (51.1)	-0.9 (3.4)	15.7 (27.3)	24.5 (30.9)	-	74.9 (57.3)	84.3 (37.5)



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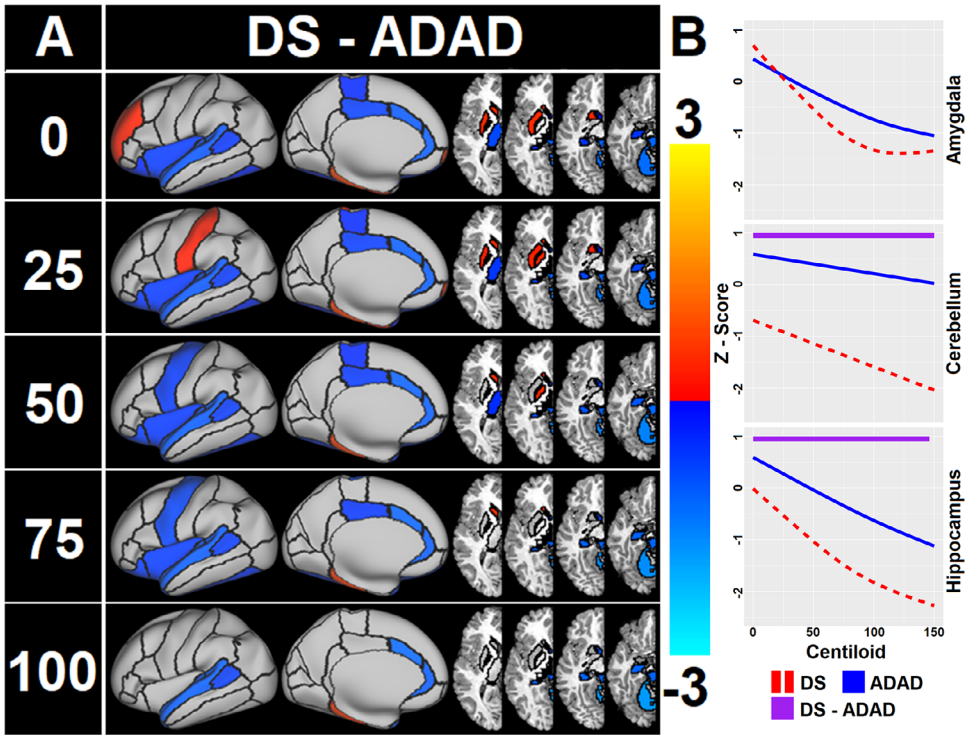

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