# RESEARCH

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# Brain volumes, cognitive, and adaptive skills in school-age children with Down syndrome

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## Abstract

**Background** Down syndrome (DS) is the most common congenital neurodevelopmental disorder, present in about 1 in every 700 live births. Despite its prevalence, literature exploring the neurobiology underlying DS and how this neurobiology is related to behavior is limited. This study fills this gap by examining cortical volumes and behavioral correlates in school-age children with DS.

**Methods** School-age children (mean = 9.7 years  $\pm$  1.1) underwent comprehensive assessments, including cognitive and adaptive assessments, as well as an MRI scan without the use of sedation. Children with DS (n=35) were compared to available samples of typically developing (TD; n=80) and ASD children (n=29). ANOVAs were conducted to compare groups on cognitive and adaptive assessments. ANCOVAs (covarying for age, sex, and total cerebral volume; TCV) compared cortical brain volumes between groups. Correlations between behavioral metrics and cortical and cerebellar volumes (separately for gray (GM) and white matter (WM)) were conducted separately by group.

**Results** As expected, children with DS had significantly lower cognitive skills compared to ASD and TD children. Daily Living adaptive skills were comparable between ASD children and children with DS, and both groups scored lower than TD children. Children with DS exhibited a smaller TCV compared to ASD and TD children. Additionally, when controlling for TCV, age, and sex, children with DS had significantly smaller total GM and tissue volumes. Cerebellum volumes were significantly correlated with Daily Living adaptive behaviors in the DS group only.

**Conclusions** Despite children with DS exhibiting lower cognitive skills and smaller brain volume overall than children with ASD, their deficits in Socialization and Daily Living adaptive skills are comparable. Differences in lobar volumes (e.g., Right Frontal GM/WM, Left Frontal WM, and Left and Right Temporal WM) were observed above and beyond overall differences in total volume. The correlation between cerebellum volumes and Daily Living adaptive behaviors in the DS group provides a novel area to explore in future research.

**Keywords** Down syndrome, Autism spectrum disorder, Neurodevelopmental disorder, Intellectual disability, Neuroimaging, Neurobehavioral/behavioral profiles, School-age children, Brain volumes, MRI, Cognitive, Adaptive, Cortical volumes

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Down Syndrome (DS) is the most common congenital neurodevelopmental disorder (NDDs) with a prevalence rate of 1 in 700 live births [1, 2]. DS is diagnosed when genetic testing reveals an additional copy of the 21st chromosome, referred to as Trisomy 21. Characteristics of DS include differences in facial features (e.g., flattened nasal bridge, almond-shaped eyes), body characteristics (e.g., small hands and feet, low muscle tone) and intellectual differences (mild to moderate intellectual disability) [1, 3, 4]. While DS has a known congenital cause, ongoing research is still working to understand its impact on brain development.

Existing research suggests that individuals with DS exhibit distinct neuroanatomical differences compared to typically developing children. Magnetic resonance imaging (MRI) studies have shown reductions in brain weight, cerebellum size, and atypical cortical surface features in individuals with DS, albeit with small sample sizes [1]. Studies have also shown differences such as decreased total brain volume [5-7], total gray matter (GM) and white matter (WM) volumes [8], reductions in frontal WM volume [9], increased parietal GM and WM [7, 9], increased temporal GM and WM [7, 9], as well as increased occipital GM [9]. Studies including both children and adults with DS have reported reduced WM integrity in various brain tracts, such as frontal tracts [10, 11], corpus callosum [11], and cortico-spinal tracts [10, 12]. Voxel-based morphometry MRI on 21 children and adolescents with DS (mean age = 10.5 years, SD = 3.3; age range: 7-16 years) identified GM volume reductions in the cerebellum, hippocampus, parahippocampal gyri, and the frontal lobe. Additionally, Carducci et al. (2013) found preservation of parietal and temporal GM volumes in children with DS when compared to TD children. [13] Menghini et al. [14] and Pinter, Eliez, et al. (2001a) found decreases in total GM and WM in DS studies focusing on school age children through adolescence [8, 14]. Notably, studies in this area have mainly included adult samples, with limited inclusion of children, such as Gunbey et al. (2017), which included a small group of DS toddlers (N=10, ages 2-4 years old), [10] and two other studies that included N = 12 and N = 23 school age children with DS (Mean age = 5.94 and Mean age = 6.7) [5, 6]. This suggests that individuals with DS have unique patterns of brain development that may contribute to cognitive and functional differences observed in the population. However, the small sample sizes and broad age ranges emphasize the need for more comprehensive research to better understand these patterns in DS.

DS mouse models, such as Ts65Dn, found an overexpression of GIRK, a potassium channel that can alter excitatory input in different brain regions, such as the hippocampus and prefrontal cortex [15-17]. Other studies have reported altered DYRK1A gene expression in the cerebellum, which is necessary for brain growth in mice and humans [18, 19]. Cognition and memory research in children with DS have also revealed distinct patterns. Pennington et al. [20] investigated prefrontal (holding information or working memory) and hippocampal (episodic information in long term memory [LTM]) functions in DS. The study found that children with DS (Mean age=14.7 years, SD=2.7) performed worse on all hippocampal measures, including a virtual Morris water maze (p < 0.05), compared to typically developing children who were mental age-matched (Mean age = 4.9 years, SD = 0.75), but not on prefrontal measures (Ecological Memory Index) [20]. All hippocampal, or LTM dependent measures, were converted to z-scores, or composites, for comparison, indicating that the DS group performed significantly worse on the NEPSY List (p < 0.05) and Paired Associates (p < 0.001) than their typically developing mental age-matched counterparts. The prefrontal composites were better in DS children, but no significant group differences were found. Further research is needed to dissect the relationship between cognition and brain morphology.

This study was motivated by the limited research on the brain and behavior development in children with DS. To address this gap, a sample of school-aged children with DS completed neuroimaging and behavioral assessments, and were compared to same-aged typically developing (TD) and autism spectrum disorder (ASD) comparison groups. The overlapping behavioral characteristics between DS and ASD makes ASD a particularly important contrast group. Research estimates that approximately 10% of individuals with DS also have diagnoses of autism, rates  $5-10 \times$  higher than the general population [21, 22]. Intellectual disability is characteristic of DS and present in approximately 30-50% of ASD individuals [23, 24]. Additionally, individuals with DS share challenges with ASD individuals in verbal and socialcommunicative abilities [23, 25, 26], and atypical patterns of sensory reactivity [27-30], though the presentation of these behaviors is highly heterogeneous across both diagnoses. One recent study compared DS individuals with co-occurring autism (DS+ASD) to ASD individuals with intellectual disability ID (ASD+ID), and individuals with ID that did not meet criteria for ASD (ID; [26]). Results indicated that the DS+ASD and ASD+ID groups had similar ASD symptoms as well as similar cognitive scores (that were higher than those with ID alone). However, those with DS+ASD had elevated disruptive behaviors and lower adaptive functioning compared to the other groups, highlighting the unique behavioral profiles that may exist in certain co-occurring groups [26]. While the diagnoses of DS and ASD are distinct, research has

identified overlaps in behavior. Comparing DS with ASD allows us to evaluate whether neurobiological patterns are specific to DS or if they overlap with those observed in ASD.

No study, to our knowledge, has 1) evaluated brain volumes in school-age children with DS, 2) directly compared the neurobiology of those with DS to those with ASD [1, 4] or 3) examined the relationship between brain morphology and behavioral presentations (such as cognitive and adaptive skills). This groundbreaking work would be the first to address these gaps in literature.

## Methods

## Participants

The sample consisted of children with DS (n=35), ASD (n=29), and TD (n=80) children. Children included in the analyses were comparable in chronological age. See Table 2 for mean age and age ranges by group.

Children with DS were enrolled based on parent report of trisomy 21 diagnosis and associated phenotypic profiles. The sample with DS was acquired simultaneously with same-aged ASD and typically developing children through the Infant Brain Imaging Study (IBIS), which provided comparison samples in this work. In accordance with the IBIS study design, all ASD children were at high likelihood for autism due to having an older ASD sibling at the time of enrollment (as young as 6 months of age). All children in the ASD group received an ASD diagnosis at their school-age visit associated with this longitudinal study. Children in the TD group were at low likelihood for developing ASD as they did not have an older ASD sibling. Children with an older sibling diagnosed with a known genetic or psychiatric condition were excluded from the TD group, and all TD children had an older TD sibling.

Exclusion criteria across groups included: a diagnosis of a genetic condition or syndrome reported to be associated with autism (with the exception of Down syndrome in the Down syndrome group), a medical or neurological condition known to impact growth and development, significant uncorrected vision or hearing loss (blindness; deafness), low birth weight (<2000 g) or prematurity (<36-weeks' gestation), exposure to in-utero exogenous compounds known to affect the brain adversely (alcohol, certain prescription medications, etc.), non-English speaking families, contraindication for MRI, a family history of intellectual disability, psychosis, schizophrenia, or bipolar disorder in a first degree relative, and adopted subjects.

The IBIS network includes four data collection sites (The University of North Carolina at Chapel Hill, University of Washington, Children's Hospital of Philadelphia, and Washington University in St. Louis). Parents provided informed consent and children provided assent when appropriate, and the institutional review board at sites approved the research protocol. Note that the children included in this study constitute a subsample from the larger study cohort, chosen based on the availability of processed and usable data at the time this manuscript was written.

#### **Behavioral assessments**

Participants were evaluated with a battery of behavioral and developmental tests. The battery included measures of cognitive ability, social communication, adaptive behaviors, and autism symptoms. Developmental level and adaptive functioning were assessed using the Differential Ability Scales (DAS) [31] and the Vineland Adaptive Behavior Scale (VABS) [32], respectively. The Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) [33] was used to collect autism symptoms. Refer to Table 2 for participant demographics alongside cognitive, adaptive, and autism measures.

## DAS

The School-Age version of the Differential Ability Scales, Second Edition (DAS-II) [31] was utilized to assess cognitive abilities in children and gleans information about a child across multiple subscales. The DAS-II provides standard scores (mean=100; SD=15) for the General Conceptual Ability (GCA) score, and additional domains including, Verbal Ability, Nonverbal Reasoning Ability, and Spatial Ability. The DAS was administered by trained research personnel and was designed for children between the ages of 30 months and 17 years, 11 months and was administered by trained research personnel.

## Vineland

The Vineland Adaptive Behavior Scales, Third Edition (VABS-3) [32] is a parent interview that gleans information about adaptive functioning in school-aged children across 3 subdomains: Socialization, Daily Living Skills and Communication. The VABS provides standard scores (mean=100; SD=15) for each of these domains, as well as the and the Adaptive Behavior Composite (ABC) score. The ABC score offers an overall impression of a child's general level of adaptive functioning (integrating subdomain standard scores), while highlighting specific strengths and weaknesses in a skill profile is assessed within subdomains. The Motor Skills domain was excluded from analyses because the participant's age was beyond the age range for which the VABS-3 motor domain is standardly administered. Additionally, this domain is not required or included in the ABC score. All assessors underwent formal training in the

administration of the VABS, ensuring consistent and accurate assessment across all participants.

## ADOS

The Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) [33] is a direct observation measure of autism symptoms. The ADOS-2 is only considered valid when conducted without personal protective equipment (PPE). For this reason, only ADOS administrations conducted without PPE, before the onset of the COVID pandemic, were included.

The ADOS-2 is composed of 5 different modules, of which one is selected based on an individual's age and language level. For this study, module 1 (no to minimal use of words) was conducted with 5 children (2 ASD, 3 DS), module 2 (phrase speech) was conducted with 16 children (1 ASD, 15 DS), and module 3 (fluent speech) was administered for 84 children (50 TD, 19 ASD, and 15 DS). The ADOS-2 has strict reliability and validity standards; research reliability was obtained by all IBIS staff who conducted the ADOS-2. Reliability was maintained through quarterly cross-site reliability calls. The ADOS-2 yields calibrated severity scores (CSSs), ranging from 1 (least impairment) to 10 (most impairment) across social affect (SA), restricted and repetitive behaviors (RRBs), and overall (CSS); these scores allow for cross module comparisons of autism symptoms. In our group with DS, 11 (31%) met cut-offs for autism spectrum disorder (ASD) on the ADOS-2. However, none of the children with DS were formally diagnosed with ASD based on clinician impressions.

## **MRI** methods

#### MRI acquisition

MRI scans were performed at each site on identical 3 T Siemens Prisma scanners using a 32-channel head coil. A board-certified behavior analyst (BCBA, author AS) trained site personnel at the beginning of the study and provided ongoing consultation to clinical sites. The BCBA developed an MRI-specific protocol of behavioral training methods based on applied behavior analysis, which demonstrated high success in acquiring scans from school-age ASD children, including those with co-morbid intellectual disability [34] without the need for sedation. This training protocol included an assent-based desensitization strategy, including methods to train participants to lie still in the scanner. In addition to this, the protocol included a desensitization stage where the participants prepared for the scan in a "Mock" MRI scanner (nonfunctional), introducing the child to the sounds and stimuli associated with the MRI while practicing remaining still. The structural imaging protocol included two scans of 3D T1 weighted MPR: TR=2500 ms, TE=2.03 ms,

176 sagittal slices, FOV 240 mm, voxel size = 1.0 mm<sup>3</sup>, and *a* 3D T2 weighted SPC: TR = 3200 ms, TE = 564 ms, 176 sagittal slices, FOV 240 mm, voxel size 1.00 mm<sup>3</sup>.

## Structural MRI Quality Control (QC)

Structural MRI data was assessed quantitatively and visually to detect MRI artifacts (e.g., excessive motion, insufficient coverage, or ghosting). Two raters, one for volumetric measurements and one for cortical surface measurements, respectively, visually assessed image quality for the entire study, assigning a QC score and determining usability. This single rater was trained and reliable with other raters in the Neuro Image Research and Analysis Laboratories (NIRAL).

Of the sample that passed initial QC and were used for processing, none failed total cerebral volume (TCV; excluding the brainstem and cerebellum), total tissue, or total GM and WM, but there were some failures in lobar volumes (16 failed for frontal and parietal and 1 for occipital) and 6 for total surface area. Additionally, some volume measurements could not be calculated. Specifically, in the group with DS, 4 children did not have measurements for the left or right frontal and parietal WM and GM volumes. One child in this group did not have measurements for the left and right occipital GM and WM volumes, and surface area measurements. In the ASD group, 3 children did not have left or right frontal and parietal WM volumes.

The total tissue measurement includes GM and WM from the cerebrum, subcortical regions, cerebellum, and the brainstem, which includes the inferior extent of the cerebellum. More details on the procedures for IBIS and scanner QC can be found elsewhere (see [35]).

### Image processing

Global and lobar brain tissue volumes were derived from each scan that passed QC. All processing was conducted blind to group, sex, and diagnostic information. The T1-weighted (T1w) and T2-weighted (T2w) brain images underwent a correction process for intensity non-uniformity employing the N4 bias field correction algorithm [36] as well as rigid transformation to stereotactic space [37, 38]. To mask the brain, a majority voting approach was employed, which included the joint warping and registration of T1w and T2w images with the best outcome and six predefined atlases, either single or averaged. Additional manual adjustments to the brain masks were made with the itkSNAP software [36] to ensure maximum accuracy.

For the segmentation process, tissues were segmented into whole brain WM and GM followed by a multi-atlas based regional parcellation. The definition of the regions was based on a single-atlas label based ROI template, as well as 18 selected and edited tissue templates from the pilot study (without participants with DS). A multi-modality (T1w and T2w) multi-atlas segmentation workflow was employed, utilizing the in-house, open-source MultiSegPipeline software [39]. This software facilitated the label fusion techniques derived from the Advanced Normalization Tools (ANTs) toolset [40]. An extensive visual assessment was conducted to ascertain the segmentation quality of all images in terms of anatomical accuracy, leading to the conclusion that no processed data warranted exclusion based on the segmentation quality.

The cortical surface area (SA) was derived using a modified CIVET workflow ([41, 42]), which involved the application of tessellate and deformable surface evolution to WM, followed by the expansion of the WM surface to the boundary between GM and CSF. After mapping to spherical domain and co-registration using cortical features such as the sulcal depth [42], the regional SA was then calculated using a simple one-ring neighborhood extraction method. Measurements were taken at the mid-cortical surface, averaging surfaces from the computed white and pial surfaces. Both surfaces underwent visual quality control (QC) with surface cuts overlaid on the magnetic resonance (MR) images for verification.

Table 1 provides a comprehensive list of the brain regions examined in this manuscript, along with a comparison to existing neuroimaging studies on DS (to TD) that report findings related to these regions, if available.

**Table 1** Comparison of brain regions studied with existing DS neuroimaging literature

Neuroimaging	Existing DS Ne Literature	Existing DS Neuroimaging Literature					
Total volumes:	Larger	Smaller					
Cerebrum		5, 6, 7, 8, 9, 13					
White matter (W)		8, 9, 13					
Gray matter (G)		8					
Tissue*							
Cerebral Surface Area							
Lobar brain tissues (left ar	nd right):						
Cerebrum <sup>G,W</sup>							
Frontal <sup>G,W</sup>		9 <sup>W</sup>					
Parietal <sup>G,W</sup>	8, 9 <sup>G</sup> ; 9 <sup>W</sup>						
Occipital <sup>G,W</sup>	9 <sup>G</sup>						
Temporal <sup>G,W</sup>	9 <sup>G</sup> ; 8, 9 <sup>W</sup>						
Cerebellum <sup>G,W</sup>							

\* This measurement includes total G and W volume from the whole cerebrum, which includes subcortical regions, the cerebellum, and the brainstem

## Analyses

Analyses of variance (ANOVAs) were used to compare descriptive, cognitive, and adaptive behaviors across DS, ASD, and TD groups. Analyses of Covariance (ANCO-VAs) were conducted to evaluate group differences on brain volume metrics while controlling for total cerebral volume (TCV), age and sex. Age-squared was explored as a confounding variable, but no significant relationships were found; therefore, it was eliminated from analyses. Separate correlations by group were conducted to evaluate the relationship between select brain volumes and cognition (DAS), adaptive behaviors (VABS) and autism symptoms (ADOS). See Table 1 for an overview of which variables were selected. For all analyses, an alpha level of 0.001 was used to account for multiple comparisons [43, 44]. Data analyses and visualization were conducted via SPSS and Matlab [45].

## Results

Children with DS were compared to TD and ASD children to provide a comprehensive understanding of cognitive abilities, adaptive behaviors, global brain volumes and surface area measurements. These analyses explored potential relationships between brain volumes and behavioral outcomes. The following results detail the findings from the ANOVAs, ANCOVAs, and correlations which offer insight into behavioral profiles and differences in brain volumes and surface area across groups.

## Cognitive

Analyses revealed statistically significant differences (TD > ASD > DS) across groups on the DAS GCA, (p < 0.001), Verbal (p < 0.001), and Spatial (p < 0.001) domains, such that TD children scored higher than children with ASD who, in turn, scored higher than children with DS. Additionally, children with DS scored significantly lower (p < 0.001) than ASD children in Non-Verbal Reasoning (DS < ASD, TD). See Table 2 for range of scores.

## Adaptive

Analyses of overall Vineland ABC scores revealed the DS and ASD groups were significantly lower than the TD group (p < 0.001, TD > ASD = DS). This relationship was also present in the Communication (p < 0.001), Daily Living (p < 0.001) and Socialization (p < 0.001) domains. See Table 2 for details.

## Autistic symptoms

Analyses of CSS, CSS-SA, and CSS-RRB revealed statistically significant differences (p < 0.001) between all groups

Demographics:	TD (n	= 80)	ASD (1	n = 29)	DS (n = 35)		
	mean (SD)	Range	mean (SD)	Range	mean (SD)	Range	
Age	9.52 (1.06)	5.88-13.06	10.27 (1.02)	7.55-11.83	9.72 (1.21)	7.26-11.93	
	n(%)		n(e	%)	n(%)		
Sex (Male)	45 (	[56)	23 (	79)	18 (51)		
Ethnicity							
Non-Hispanic	76 (95)		28 (	97)	28 (80)		
Hispanic	2 (2.5)		0 (	0)	4 (11)		
Race							
White	66 (	66 (83)		83)	25 (71)		
Black	3 (4)		1 (	3)	3 (9)		
Asian	1 (1)		1 (	3)	1 (3)		
1+ Race	8 (	10)	3 (1	10)	3 (9)		

 Table 2
 Participant demographics and cognitive, adaptive, autism measures

I + Raee	1)0	0)	5 (1	0)	5 (.	/)					
							DS	8 – ASD	A	SD – TD	
	mean (SD)	Range	mean (SD)	Range	mean (SD)	Range	p-value	95% CI Difference	p-value	95% CI Difference	Post-Hoc
DAS											
GCA	114 (14)	85-147	91 (23)	43-129	52 (8)	37-69	< 0.001	-48.65, -29.20	< 0.001	-31.56, -14.79	DS < ASD < TD
Verbal	112 (11)	80-143	88 (30)	27-126	49 (11)	29-70	< 0.001	-49.64, -28.12	< 0.001	-33.71, -14.95	DS < ASD < TD
Non-Verbal	111 (17)	76-150	96 (18)	57-129	61 (10)	42-84	< 0.001	-46.04, -24.52	< 0.01	-23.75, -5.82	DS < ASD, TD
Spatial	112 (15)	82-146	96 (19)	53-124	55 (13)	25-77	< 0.001	-51.05, -31.31	< 0.001	-24.93, -7.91	DS < ASD < TD
Vineland											
ABC	101 (11)	79-126	71 (16)	31-98	69 (10)	52-97	n.s.	n.s.	< 0.001	-36.45, -23.50	DS, ASD < TD
Communication	102 (9)	81-120	71 (21)	20-94	61 (14)	36-81	0.01	n.s.	< 0.001	-38.37, -23.60	DS, ASD < TD
Daily Living	101 (11)	79-126	76 (14)	41-102	73 (12)	56-108	n.s.	n.s.	< 0.001	-31.78, -18.90	DS, ASD < TD
Socialization	102 (10)	79-120	71 (21)	30-108	76 (12)	46-108	n.s.	n.s.	< 0.001	-37.70, -23.16	DS, ASD < TD
ADOS	(n=5	50)	(n=2	2)	(n=3	33)					
CSS	1.40 (1.07)	1-6	7.77 (1.77)	3-10	3.06 (1.80)	1-6	< 0.001	-5.52, -3.90	< 0.001	5.62, 7.13	TD < DS < ASD
SA- CSS	1.84 (1.42)	1-7	7.41 (2.13)	3-9	3.33 (2.71)	1-7	< 0.001	-4.99, -3.16	< 0.001	4.72, 6.42	TD < DS < ASD
RRB-CSS	1.64 (1.48)	1-5	8.05 (1.59)	5-10	4.36 (2.83)	1-7	< 0.001	-4.78, -2.58	< 0.001	5.38, 7.43	TD < DS < ASD

such that TD group had lower (fewer autism symptoms) scores than the DS group which had lower scores than those with ASD (TD < DS < ASD).

## Global brain volumes and surface area

Age and sex were found to significantly interact with several brain volume metrics, as shown in Table 3. ANCOVA analyses indicated that TCV and total tissue volume had significant associations between all groups. TCV in children with DS was significantly smaller than both the TD and ASD groups (p < 0.001 vs. TD, p < 0.001 vs. ASD). The same relationship was found in total tissue volume (p < 0.001, p < 0.001). The total surface area and total GM was significantly smaller in DS compared to TD (p < 0.001, p < 0.001 respectively), but not significantly different from ASD (p = 0.002, p = 0.003 respectively). No significant differences were found across groups in total WM volume (p = 0.03) in the primary ANCOVA; therefore pairwise analyses were not run. Of note, analyses of

specific WM regions indicated significant regional differences across frontal, temporal, and cerebellar WM (see *Lobar and Cerebellar White Matter* section below). See Table 3 and Fig. 1.

### Lobar and cerebellar Gray Matter (GM)

Age and sex had a significant relationship with total GM volume (p < 0.001). ANCOVA analyses indicated that GM volumes of the left and right frontal lobe and left and right cerebellum were significantly different across groups. Pairwise tests revealed the DS group had significantly smaller volumes than the ASD group in the left frontal lobe (p = 0.001) but not the TD group (p = 0.002). However, the DS group had significantly smaller volumes than both ASD and TD groups in the left (p < 0.001), p < 0.001) and right cerebellum (p < 0.001, p < 0.001). See Table 3 and Supplementary Fig. 1.

## Table 3 ANCOVAs for brain volumes

Neuroimaging	p-value	Т	D - DS	AS	SD - DS	Post-Hoc	
	(ANCOVA)	p-value	95% CI Difference	p-value	95% CI Difference		
Total Volumes:							
Cerebral Volume <sup>†</sup>	< 0.001	0.000	0.939, 1.713	0.000	0.678, 1.668	ASD, TD > DS	
White Matter <sup>††</sup>	0.032					n.s.	
Gray Matter <sup>†,††</sup>	< 0.001	< 0.001	0.100, 0.319	0.003	0.049, 0.295	TD > DS	
Tissue Volume	< 0.001	< 0.001	0.152, 0.247	< 0.001	0.115, 0.221	ASD, TD > DS	
Surface Area	0.001	0.001	0.087, 0.395	0.002	0.077, 0.420	TD > DS	

		Gray Matter (G) White Matter (W)										
		т	D - DS	AS	SD - DS			1	FD - DS	А	SD - DS	
Tissues	p-value	p-value	95% CI Difference	p-value	95% CI Difference	Post-Hoc	p-value	p-value	95% CI Difference	p-value	95% CI Difference	Post-Hoc
Left cerebral $^{\dagger \dagger G,W}$	0.570					n.s.	0.845					n.s.
Right cerebral $^{\dagger \dagger G,W}$	0.968					n.s.	0.756					n.s.
Left frontal <sup>††W</sup>	< 0.001	0.002	0.098, 0.540	0.001	0.140, 0.638	ASD > DS	< 0.001	< 0.001	0.198, 0.565	< 0.001	0.272, 0.684	ASD, TD > DS
Right frontal	< 0.001	0.001	0.110, 0.547	0.000	0.184, 0.675	ASD, TD > DS	< 0.001	< 0.001	0.162, 0.533	< 0.001	0.257, 0.676	ASD, TD > DS
Left parietal <sup>++W</sup>	0.209					n.s.	0.112					n.s.
Right parietal <sup>++G</sup>	0.228					n.s.	0.103					n.s.
Left occipital <sup>++G</sup>	0.018					n.s.	0.157					n.s.
Right occipital	0.228					n.s.	0.759					n.s.
Left temporal	0.003					n.s.	< 0.001	< 0.001	-0.876, -0.267	0.001	-0.870, -0.187	ASD, TD > DS
Right temporal	0.009					n.s.	< 0.001	0.001	-0.775, -0.167	0.001	-0.876, -0.193	ASD, TD > DS
Left cerebellum <sup>††</sup>	< 0.001	< 0.001	0.931, 1.607	< 0.001	0.689, 1.449	ASD, TD > DS	< 0.001	< 0.001	1.058, 1.658	< 0.001	0.77, 1.451	ASD, TD > DS
Right cerebellum <sup>†G,††W</sup>	< 0.001	< 0.001	0.947, 1.626	< 0.001	0.713, 1.476	ASD, TD > DS	< 0.001	< 0.001	1.061, 1.670	< 0.001	0.802, 1.486	ASD, TD > DS

<sup>†</sup>Indicates sex as a significant interaction term.

<sup>††</sup>Indicates age as a significant interaction term.



**Fig. 1** Total volumes and surface area: violin plots by group. \*Comparison between DS and other groups: Stars indicate significant differences between the DS group and both ASD and TD groups (p < 0.001) except for total surface area (TD > DS) and gray matter (TD > DS)



Fig. 2 Total cerebral volume and DAS domains

#### Lobar and cerebellar White Matter (WM)

ANCOVA results revealed that WM volumes of the left and right frontal lobes, temporal lobes, and cerebellum were different across groups. The DS group had significantly smaller volumes than both the TD and ASD groups in left (p < 0.001 vs. TD, p < 0.001 vs. ASD) and right frontal lobes (p < 0.001, p < 0.001), left (p < 0.001, p < 0.001) and right cerebellum (p < 0.001, p < 0.001), and left (p < 0.001, p = 0.001) and right (p = 0.001, p = 0.001) temporal lobes. Other comparisons were not statistically significant, as detailed in Table 3. See Supplementary Fig. 2.

## **Brain-behavior associations**

Vineland Daily Living scores were significantly positively associated with left and right GM and WM cerebellum volumes in the DS group only, such that larger GM and WM cerebellum volumes associated with higher or better adaptive skills. No significant correlations were observed with ABC, Socialization, and Communication scores.

In the ASD group, TCV was significantly negatively associated with DAS GCA (p < 0.001), meaning that larger TCV was associated with lower or worse global cognitive ability. Similarly, DAS GCA was negatively associated with total GM (p < 0.001) and total tissue (p < 0.001) volumes in the ASD group. The total surface

area was also negatively associated with DAS GCA in the ASD group, indicating that higher GCA scores (better cognitive ability) was associated with smaller surface area volumes (p < 0.001).

No significant correlations between ADOS CSS, CSS-SA, and CSS-RRB and regional brain volumes was observed. Some of these correlations, such as the relationship between CSS-RRB and left cerebellum volumes in the DS group (p=0.02), did not meet our alpha level to deem significant, though trends indicate these relationships should continue to be explored in larger samples. See Figs. 2 and 3 and Supplementary Table 1.

## Discussion

This study characterized selected brain volumes in school-aged children with DS in contrast to children with ASD and those with typical development. We found converging findings with the literature demonstrating that children with DS have lower cognitive and adaptive scores compared to TD children. However, despite having significantly lower cognitive skills, children with DS showed comparable adaptive scores to those with ASD. Contrasting the commonly reported observation of a discrepancy between ability and "performance" in ASD, children with DS demonstrated adaptive skills consistent





Fig. 3 Cerebellar GM and WM z-scores across Vineland ABC scores

with their cognitive skills [46–48]. About one-third of children with DS met cutoffs for autism on the ADOS, consistent with published findings [49]. Although none of the children with DS received clinical a diagnosis of autism, these ADOS findings demonstrate that a large proportion of school age children with DS exhibited elevated autistic characteristics. However, these results may overlap with characteristics associated with DS, rather than indicating a clear diagnosis of ASD. This highlights the need for careful interpretation when using the ADOS in DS, as it can affect the specificity of this measure for diagnosing ASD.

To date, neuroimaging studies of DS are limited by small samples and broad age ranges [1, 6, 8, 50–52]. To our knowledge, this study is the first to examine brain volumes in school age children with DS and the first to contrast that to school age children with idiopathic ASD. Consistent with prior reports of other DS groups, we observed that children with DS have significantly smaller brains than TD and the ASD comparison groups [53–55]. A trend towards similar differences was observed in total GM volume, total tissue volume, and total cortical surface area, right frontal GM and WM, left frontal WM, and bilateral cerebellar GM and WM volumes. However, while children with DS were observed to have smaller total brain volume, the differences across brain regions varied by structure. For example, when controlling for differences in TCV, age, and sex, parietal, temporal, or occipital lobe volumes (left and right; GM and WM) did not significantly differ. In contrast, right frontal and cerebellar lobe volumes (left and right; GM and WM) were smaller than comparison groups when controlling for the aforementioned TCV, age, and sex. This is consistent with previously published findings in children with DS that show preserved parietal and temporal lobe GM volume despite smaller overall brain volume than TD counterparts [13, 55]. Further exploration of the structural neuroanatomy of DS is necessary, as studies have been inconsistent with some showing volume reductions of WM in temporal and parietal lobes [13, 56]. The underlying functional implications of disproportionally larger region-specific volumetric decreases is unknown, though could reflect particularly impaired higher order deficits (e.g., frontal-mediated) versus relatively intact somatosensory abilities (e.g., parietal-mediated), though both functions are impaired compared to typical development [57–59]. This hypothesis is consistent with previous research that has shown volume reduction in the frontal lobes of the DS brain [13] and may be related to decreased cognitive and executive functioning in individuals with DS [23].

This study is the first to include an ASD comparison sample and link behavioral and brain volume findings. The reduced brain volumes seen in children with DS has motivated researchers to delve into genetic and neuronal factors contributing to this abnormality. Transcriptomic and induced pluripotent stem cell (iPSC) studies have consistently reported altered gene expression on chromosome 21, albeit to varying degrees [60– 64]. Martinez et al. (2024) utilized in vitro DS models with iPSCs and identified consistent genes altered during neural induction, including TIAM1, CHODL, PSCP4, and TTC3 [60]. These genes play roles in neurite growth, neuron differentiation and maturation [60], likely associated with downstream volume differences in DS. Postmortem studies of DS have found decreased synaptic density and length, and fewer dendritic spines which are critical for neuronal communication [65–68]. Collectively, these observations are associated with an overexpression of DYRK1A, APP, and S1OOB genes located on chromosome 21 [69-71]. The overexpression in DYRK1A and APP genes has been reported to be associated with brain development [69], and disrupting mitochondrial redox states in DS nervous system stem cells, or neural progenitor cells thereby increasing cell death [71]. S1OO $\beta$  is involved in growth and function of neurons, specifically playing a role in neuroblasts and glia function [72]. Overexpression of S1OO $\beta$  has been linked to dendritic abnormalities, neuroinflammation and neuronal damage [70].

We found no significant difference in occipital lobe tissue volume between DS and comparison groups under the control variables. Most (60-80%) children with DS often have atypical visual function and poorer visual acuity [73], including conditions such as nystagmus (3–33%), strabismus (36%) and others [74]. In addition, impairment in adaptive behavior is associated with larger visual impairment in children with DS [75]. The lack of difference in occipital volumes may indicate that atypical visual function in the DS group is most prominent in lower-order structures (e.g., optic nerve, retina, etc.), but may not fundamentally alter factors that regulate volume (e.g., neurogenesis, dendritic branching, and synapse formation, or pruning mechanisms) in cortical areas that process visual information. While we did not specifically address this relationship due to sample size, future work should continue to explore the relationship between adaptive behaviors, neurobiology, and visual impairment in DS samples.

Other studies have identified a relationship between IQ and global brain volumes such that larger brains are correlated with greater cognitive skills in typical development [76–78]. This has also been reported in individuals with psychiatric conditions, including schizophrenia and

Bipolar I Disorder [76, 77]. In this study, there was not an association between cognitive abilities and brain volumes in the TD and DS groups. However, there was a trend that did not reach statistical significance in the DS group that larger brains (TCV) were associated *verbal* cognitive skills. It is possible that a larger sample of children with DS would have revealed a statistically significant relationship. One study of DS has shown an association between cognitive abilities and brain regions, such as positive correlations between amygdala and hippocampal volumes with memory tests [79]. While intriguing, it is important to note that our DS sample had a rather narrow range of cognitive ability, which may limit interpretation of this data.

The ASD group showed a negative relationship between brain volume (TCV) and cognitive skills (GCA score) such that larger TCV was associated with poorer cognitive skills. This negative association was also observed across total tissue volume, and total GM volume. Total WM volumes and total tissue volumes were also negatively trending with spatial scores, specifically, on the DAS, in the ASD group only. This suggests that, unlike the positive association between cognitive skills and brain size found in typical development [76–78], at a certain point, larger brains may be disadvantageous for ASD children, particularly in the spatial domain. Research has suggested that early brain overgrowth is a marker of autism in pre-symptomatic infants and toddlers who go on to receive autism diagnoses, highlighting the potential atypicality of larger brains in this population [35].

This study's findings should be interpreted considering several limitations. The research employed the Differential Ability Scales (DAS) [80], the Vineland Adaptive Behavior Scales (VABS) [32], and the Autism Diagnostic Observation Schedule (ADOS-2) [33], to characterize the participants behavioral profiles. It should be noted that the validity of these measures has not explicitly been confirmed in DS samples, as studies have reported floor effects [81–83]. It is possible that the values derived from these metrics are poor representations of the constructs that they intend to reflect. Indeed, none of the children with DS in our study received co-diagnoses of autism; yet more than 30% of the DS sample met cutoffs for autism on the ADOS. Meta-analytic reviews indicate that the specificity of the ADOS ranges from 0.81–0.85 [84], using a sample of non-ASD individuals with varied diagnoses, among which only a small subsample had DS. Nevertheless, the specificity of the ADOS is reportedly better in these mixed samples than we see in our DS-only sample.

The individuals included in this sample, particularly those with available neuroimaging data, may not be representative of the broader populations. For example, individuals with higher cognitive ability and functional

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capacities who can complete an MRI scan while awake and remain still are more likely to be recruited. Specifically, the children with DS with neuroimaging data might represent a subset of children who have higher cognitive skills, fewer hyperactivity symptoms, sensory sensitivities or anxiety related behaviors, than most individuals with DS. Within our neuroimaging data, there is some missing regional information because of participant movement in the scanner. While this data loss is minimal, it is possible that, when using relatively small samples such as ours, these losses of data may affect the power of our sample and subsequent ability to detect differences of significance. This may also be reflected in the ADOS-2 results since we were limited to using data that was not collected during the COVID-19 pandemic, when PPE was in use and invalidated data collection. As such, all results presented here should be replicated in larger samples. Additionally, DS research should strive to include diverse clinical presentations to better understand the range of neurodevelopmental characteristics associated with DS.

DS is a highly underrepresented group in neurobiological studies. This research addresses a gap in the literature comparing the neurobiology of DS to ASD individuals, measured by MRI. Despite the considerable behavioral overlap between these prevalent neurodevelopmental disorders [26], this study represents a crucial initial effort toward understanding the neurobiology of DS using neuroimaging techniques. We reveal differences and similarities in cortical volumes across groups and connect these findings to unique cognitive and adaptive profiles. Our results highlight the unique neurobiological features of DS despite similarities with ASD individuals in behavioral (e.g., adaptive) skills. This study is a steppingstone to future research comparing DS brain and behavioral characteristics to ASD individuals and TD samples, as well as other neurodevelopmental disorders with similar phenotypic presentations.

#### Abbreviations

ABC	Adaptive Behavior Composite
ADOS-2	Autism Diagnostic Observation Scale, Second Edition
ANCOVA	Analyses of Covariance
ANOVA	Analyses of Variance
ASD	Autism spectrum disorder
BCBA	Board-certified behavior analyst
DAS	Differential Ability Scales
DS	Down syndrome
GCA	General Conceptual Ability
GM	Gray matter
IBIS	Infant Brain Imaging Study
ID	Intellectual disability
IQ	Intelligence Quotient
MRI	Magnetic resonance imaging
NDD	Neurodevelopmental disorders
NIRAL	Neuro Image Research and Analysis Laboratories
QC	Quality Control
TCV	Total Cerebral Volume

TD Typically developir	ng
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VABS Vineland Adaptive Behavior Scales WM White matter

## **Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s11689-024-09581-6.

Supplementary Material 1: Supplementary Fig. 1. Gray Matter: Violin Plots by group.\*Comparison between DS and other groups: Stars indicate significant differences between the DS group and both ASD and TD groups (p < 0.001), except for left frontal GM (ASD > DS).

Supplementary Material 2: Supplementary Fig. 2. Violin Plots: White Matter by Group. \*Comparison between DS and other groups: Stars indicate significant differences between the DS group and both ASD and TD groups (p < 0.001).

Supplementary Material 3: Supplementary Table 1. Brain-Behavior Correlations.

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#### Authors' contributions

Drs. Grzadzinski, Hazlett, and Piven conceptualized the study. Dr. Grzadzinski led data cleaning, analyses, and manuscript preparation. Authors A.J., A.B., and K.M. assisted with manuscript preparation, data analyses, and data visualization. Authors D.G., M.S., J.P., T.S.J., L.Z., A.E., A.S., K.B., and N.M. assisted with data collection and manuscript preparation/revisions. Authors R.S., S.D., R.S., M.S., A.E., S.H.K., R.K., and G.G. assisted with neuroimaging processing, cleaning, and data preparation. All authors have approved the final manuscript in its submitted form and have agreed to assume responsibility for all aspects of the work.

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#### Data availability

No datasets were generated or analysed during the current study.

#### Declarations

#### Ethics approval and consent to participate

The research described in this work was approved by the local Institutional Review Board.

#### **Consent for publication**

All authors have reviewed the manuscript and approved it for publication.

#### **Competing interests**

The authors declare no competing interests.

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