Correlating MRI-Based Brain Volumetry and Cognitive Assessment in Down Syndrome Patients

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Article

Keywords: Down syndrome, Language, Memory, MRI, Cognition, Hippocampus

Posted Date: December 2nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1125604/v1

Abstract

INTRODUCTION: Down syndrome (DS) is the most common genetic cause of intellectual disability. Here, we use magnetic resonance imaging (MRI) on children and adults with DS to characterize changes in the volume of specific brain structures involved in memory and language and their relationship to features of cognitive-behavioral phenotypes.

METHODS: Thirteen children and adults with the DS phenotype and 12 age- and gender-matched healthy controls were analyzed by MRI and underwent a psychological evaluation for language and cognitive abilities.

RESULTS: The neuropsychological profile of DS patients showed deficits in different cognition and language domains in correlation with reduced volumes of specific regional and subregional brain structures.

CONCLUSIONS: The memory functions and language skills affected in our DS patients correlate significantly with the reduced volume of specific brain regions, allowing us to understand DS's cognitive-behavioral phenotype. Our results provide an essential basis for early intervention and the design of rehabilitation management protocols.

Introduction

As the most common genetic cause of mental retardation, DS affects approximately one in every 700 live births (Parker, Mai et al. 2010). Although intellectual disability is the most well-known feature of the DS cognitive-behavioral phenotype (Gibson 1978), research has indicated a profile of relative strengths and weaknesses that characterizes children with DS compared to younger, typically developing peers matched on the developmental level and same-age peers with other forms of intellectual disability (Fidler, Most et al. 2008). Those with DS have deficiencies in several domains of language functioning that outweigh their overall cognitive limitations. Furthermore, difficulties with explicit memory are common and outnumber global impairments (Jarrold, Baddeley et al. 2007, Hamner, Udhnani et al. 2018).

To date, neuroimaging studies of children with Down syndrome development have limits due to low resolution, small group size, and limited age range (Pinter, Eliez et al. 2001).

A better understanding of the developing brain with DS using a developmental approach will illuminate important neurological principles of DS in children and shed light on the foundations of adult phenotypes, particularly the increased risk of early Alzheimer's disease (Zigman and Lott 2007).

Thus, the current study seeks to fill this gap and provide new data on structural neuroimaging of DS children compared to children in the context of normal brain development and cognitive-behavioral phenotype. These deficits in DS-related research are probably due to problems attributable to the successful execution of development-oriented neuroimaging.

However, it is still unclear why previous reports did not adopt a similar method for the neuroimaging of children with DS as in other cognitive impairment-related neurodevelopmental disorders (e.g., Fragile X syndrome, Williams's syndrome, microdeletion syndrome 22q11), although such studies used modern imaging technologies and analyses and could expect common difficulties with imaging such groups (Hamner, Udhnani et al. 2018). To make progress in this field, there is a need for a boost in increased neuroimaging research, especially with a focus on early childhood, using advanced neuroimaging techniques and best practice guidelines for neuroimaging in children (Raschle, Zuk et al. 2012). The study depends on the hypothesis that children and adults with DS have language and memory problems as they age. These problems are related to brain development, particularly neuroanatomical changes associated with these behavioral changes. To test these hypotheses, we will examine the relationship between different brain regions and cognitive scores for memory and language in children and adults with DS. Therefore, our study will analyze the volumes of the hippocampal areas involved in explicit memory deficits (dentate gyrus, Ammon's horn, and subiculum).

Furthermore, we will consider structures such as the superior temporal gyrus and temporoparietal junction structures underlying impaired speech performance (e.g., angular gyrus, supramarginal gyrus, and occipitotemporal structures (e.g., fusiform gyrus)) (Hickok and Poeppel 2004, Friederici and Gierhan 2013) and characterize them in more detail using neuroimaging with volume analysis. We used high-resolution MRI acquisition techniques and advanced segmentation and image processing protocols to obtain more accurate quantitative image data in children with DS. We studied brain areas that previous studies have not considered, such as some regions in the temporal and parietal lobes, or not adequately investigated as hippocampal and parahippocampal gyrus areas. By studying these areas of interest radiologically and comparing their volumes with the psychological results, we can approach language and memory problems in people with DS and provide a basis for further research, including early interventions. Furthermore, the study of the early stage of AD as DS can be a model for understanding AD pathology and clinical features at an early age.

In general, we compared the imaging data on brain areas between different ages of DS and between the different genders in this group. We also compared DS samples and normal controls. We correlated neuroanatomical data and neuropsychological scores of DS samples based on age and sex between DS and normal controls. We described and analyzed the volumes of different brain regions in detail, focusing on areas associated with language and memory. We examined areas such as the temporal lobes, parietal lobes, and hippocampus entirely and subregionally. The focus has also been on some regions, such as the superior temporal gyrus, angular gyrus, supramarginal gyrus, fusiform gyrus, and hippocampal subregions (Dentate gyrus, Ammon's horn, and Subiculum).

Some regions, such as the corpus callosum, are also of interest but will not be explored here and will be considered in future studies by the authors.

Methods

Subjects

We recruited our DS participants from Down syndrome care centers in Sudan and selected control samples from our DS sample family members and hospital records. Thirteen children and adults with DS (eight males and five females, mean age=15 years, SD=5.9, range=6.0–25) and twelve healthy controls (eight males and four females, mean age=14 years, SD=6.8, range=4.0–25) underwent MRI scans at Aliaa Specialist Hospital, Khartoum, Sudan. All DS samples and four control samples were assessed for IQ (intelligence quotient), including working memory by applying the IQ test (The Stanford Binet Scale, the fifth picture of intelligence) and for language by using a language test (Luttas Language Development Test Scale) by a consultant medical psychologist and speech rehabilitation specialist at the Women & Child Health Development Organization, Khartoum, Sudan. Additionally, we designed parents' questionnaires to assess the psychosocial status and related clinical problems of the family and the participant and evaluated the cognitive level and the psychosocial risk factors that affect the participant's cognition. DS subjects were assessed clinically by a pediatrician to exclude cardiac defects and any contraindications for sedation. The diagnosis of DS was established at birth or in early infancy and childhood by clinical examination with one karyotype diagnosis case. We explained all the procedures in detail to all subjects and parents before enrollment in the study. Written informed consent was obtained from all parents and, when possible, orally by subjects before participation. This study was reviewed and accepted by the Ethics Committee of the Faculty of Medicine - University of Heidelberg, Heidelberg, Germany and National Health Research Ethics Committee, Ministry of Health, Khartoum, Sudan.

Imaging

Magnetic resonance imaging (MRI) is a radiographic sectional imaging technique that allows the imaging of different levels of the body with high soft-tissue contrast. In contrast to computed tomography or conventional X-ray imaging, MRI is based on a different magnetization of the body by the magnetics of MR tomography. MRI does not include X-rays so that children can obtain a safe examination. MRI is a very patient-friendly method that generally requires no special preparation. With the latest generation devices using a magnetic field strength of 1.5 Tesla (T) and 3.0 T, the entire body can receive the examination in less than 20 minutes. The most used MR scanners are either 1.5 T (Tesla) or 3 T systems. Both systems allow the quantification of global and regional brain structures. However, 3 T systems offer an increased resolution of the contrast agent between the tissues (i.e., increased visualization of the boundaries between gray matter, white matter, and cerebrospinal fluid (CSF)). MR scans on 1.5 T systems are sufficient to quantify relatively small brain structures such as the hippocampus (Keller and Roberts 2009).

In Sudan, a 3D structure MRI technique with a 1.5 T Siemens scanner is common in Khartoum hospitals, 3D Slicer 2.6 is available for volume measurement.

MRI Protocol

Subjects had MRI scans using a 1.5 Tesla Siemens, Syngo, MR system at the Radiology and Medical Imaging Department, Aliaa Specialist Hospital, Khartoum, Sudan. Some children have sedation to be stable and restrained from movement.

The main sequence: 1) 3 plain localizer + sagittal 3D auto-align localizer, TR: 4.52, TE: 2.3, matrix: 160×160×110.4, time: 24 sec, 2) Axial T2 BLADE, TR: 3300, TE: 107, matrix: 320×320, time: 1:59 min, 3) Axial T1, TR: 1340, TE: 7.3, matrix: 256 ×256, time: 1:30 min, 4) Axial T2 FLAIR, TR: 8000, TE: 77, TI: 2372, matrix: 168×256, time: 1:54 min, 5) Axial Diffusion-Weighted Image, TR: 4150,TE: 79 matrix: 100×100, time: 1:54 min, 6) Sagittal T1, TR: 333, TE:8.9, matrix: 245×320, time: 1:25 min, 7) Coronal T2, TR: 3000, TE: 81, matrix: 225×320, time: 1:05 min.

The whole brain has a scan with a 3d T1 space sequence in a sagittal plane, with slice thickness: 1mm, TR: 550, TE: 8.5, AVERAGE: 1, matrix: 256×256×204.8, time: 4:02 min.

Measurement and segmentation of total brain volume and hippocampal volume

To measure the volumes of different brain regions, we used the volBrain online system (http://volbrain.upv.es), an online MRI brain volumetry system that provides free automated brain analysis and segmentation for different brain structures in a short time with accurate and detailed results. To use this system, users should first register by providing personal information such as the email address, name, and name of the institution to which they belong. The user submits a single anonymized compressed MRI T1w Nifti file in a web interface to analyze the imaging data, and the webserver accepts requests. After approximately 12 minutes, the results will be ready and downloaded as a pdf file and received via email (Manjón and Coupé 2016). We used two pipelines available on the online system to measure our data: 1) the HIPS pipeline (see figure 1a and 1b), which is a pipeline for automatic hippocampal subfield segmentation from monospectral (T1) images using the Kulaga-Yoskovitz segmentation protocol (Kulaga-Yoskovitz, Bernhardt et al. 2015), and 2) the vol2Brain pipeline (see figure 2a and 2b), which provides automatic brain segmentation dividing the volume into 135 structures. It also provides tissue, macrostructure, and lobe segmentations as well as cortical thickness. Researchers have compared this brain volumetry system with other software packages that provide subcortical brain segmentation. They found it more reproducible and accurate. Therefore, it can be considered one of the first few platforms that offer hippocampal segmentation, which will help diagnose and study AD (Manjón and Coupé 2016).

Neuropsychological assessment

We assessed all DS samples and four controls with the Stanford-Binet Intelligence Scales, Fifth Edition (SB5), to measure memory and cognitive abilities. Additionally, we applied the Luttas Language Development Test Scale to measure different language development scales among DS samples and healthy controls.

We selected these tests to comply with the study's goal of correlating brain area anatomy, cognitive status, and language abilities considering the community standards and environment. Some children with special needs cannot acquire all the skills and abilities to respond to the applied test early. These selection criteria and limitations might explain the failure to include children under five years in this study, as they do not have enough skills to carry on with the tests.

Stanford Binet Intelligence Scale, Fifth Edition (SB5)

The Stanford Binet occurred as an intelligence test in 1916. The recent version (published 2003) is the Stanford-Binet Intelligence Scales, Fifth Edition (SB5), a self-administered intelligence and cognitive abilities test for people aged 2 to 85 years and older. The SB5 provides early childhood assessments and is valuable for psychoeducational purposes and plans and later career development to detect various developmental disorders (Roid and Pomplun 2012). It is an IQ test that measures five cognitive abilities in both nonverbal and verbal formats: fluid reasoning, knowledge, quantitative reasoning, visuospatial processing, and working memory. Because it is effective with so many diverse groups independent of gender, race, culture, religion, area, or socioeconomic level, the SB-5 is considered one of the most extensively utilized intelligence tests.

Luttas Language Development Test Scale

The goal of the test is to assess the child's language development level and extract the child's expressive linguistic age and the child's receptive linguistic age. It can define the child's language weaknesses and strengths and develop an appropriate rehabilitation program for language development for each child separately. This test is available for use on an individual basis by assessing the child's capacity to recognize the internal language, name and identify implicit groups, understand, and express object functions, understand and express linguistic context, and identify expression only for the melodic and pragmatic structure. The test is available in Arabic and developed in Egypt but has been found to be suitable for use in other countries, such as Sudan. The test measures expressive language, receptive language, and overall language scores.

Data Analyses

We carried out this investigation as a pilot study. Therefore, we conducted a purely exploratory data evaluation, and the p-values obtained are interpreted purely descriptively and have no confirmatory value. All data collected were analyzed using descriptive statistics (indicating absolute and relative frequencies or mean and standard deviation). All volumetric data met the requirement for different parametric tests, and normality was confirmed with Kolmogorov-Smirnov and Shapiro-Wilk tests and variance homogeneity with the Levene test. We performed descriptive statistics and analysis of variance (ANOVA) to compare total brain volumes (TBVs) between our study groups and separately to compare related neuropsychological test scores between groups. Analyses of covariance (ANCOVA) were performed for all comparisons while controlling for total brain volume. We employed paired t-tests and repeated measures analysis of variance to observe any significant changes in structural brain region volumes over time. To

explore the correlation between age and brain region volumes (TBV, hippocampus, parietal lobe, temporal lobe, superior temporal gyrus, parahippocampal gyrus, angular gyrus, supramarginal gyrus, and fusiform gyrus) and between the same regions and related neuropsychological test scores, we used the Spearman correlation test because the scores were not normally distributed. We used partial correlations to assess this relationship while controlling for age and total brain volume. We carried out regression analyses for each brain region volume with the scores as predictors. We defined a significant difference to have a P value less than 0.05 for two-tailed tests. We conducted statistical calculations with IBM SPSS STATISTICS for Windows Version 28.0.0.0 (190).

Results

Neuroanatomy of DS

As shown in Table 1 and Figure 1, the DS samples' mean total brain volume was 20% smaller than that of the control samples (F=3.1, df=14, p <0.001). Some regions also showed significant group differences, such as the cerebrum (F=3.4, df=14, p <0.001), frontal lobe (F=4.3, df=14, p <0.001), parietal lobe (F=5.3, df=14, p <0.001), fusiform gyrus (F=3.6, df=14, p <0.001), superior temporal gyrus (F=3.2, df=14, p <0.001) and occipital lobe (F=3.2, df=14, p <0.001). Other regions, such as the temporal lobe (F=2.6, df=14, p =0.06) and parahippocampal gyrus (F=2.6, df=14, p =0.06), approached significance in the difference between groups. When measured with ANCOVA, hippocampal volume was not significantly different between groups while controlling for age and total brain volume (F=0.9, df=14, p =0.54). No significant age-related changes in different brain regions in either the DS or control groups (see Tables 2 and 4) were observable. However, some areas, such as the parietal lobe (r= -0,54, p= 0.06) and parahippocampal gyrus (r = -0,52, p= 0.07), approached significance and correlated negatively with age in the DS group when partially correlated while controlling for total brain volume (see table 5). As presented in Table 3, we compared regional brain volumes in males and females of both groups. We found more significant brain region volumes in males with DS than females in regions such as the total brain, cerebrum, frontal lobe, parietal lobe, temporal lobe, occipital lobe, and parahippocampal gyrus. The control group indicated no significant difference.

Neuropsychology of DS

Language test scores are shown in Table 6, which indicates that the total language score in the DS sample was 40% lower than that in the control group (F=8.2, df=16, p <0.001). The expressive language score in the DS group was 50% lower than that in the control group (F=7.6, df=16, p <0.001). The receptive language score in the DS group was 35% lower than that in the control group and approached significance in the difference between the two groups (F=3.3, df=16, p =0.08). Table 7 presents Stanford Binet Intelligence Scale (Fifth Edition) scores in the DS and control groups. These scores included total IQ, which was 36% lower in the DS group than in the control group (F=51.7, df=16, p <0.001). The total IQ has two divisions: Non-Verbal IQ, which is low in DS by 32 % than the control group (F=28.1, df=16, p <0.001), and verbal IQ, which is also low in DS by 40 % than the control group (F=55.0, df=16, p <0.001). Other test

scores such as fluid reasoning is low in DS by 25 % than control (F=12.3, df=16, p <0.001), knowledge is low in DS by 35 % than control group (F=20.1, df=16, p <0.001), quantitative reasoning is low in DS by 36 % than control group (F=39.1, df=16, p <0.001), visuospatial processing is low in DS by 39 % than control group (F=47.5, df=16, p <0.001) and working memory which is also low in DS by 37 % than control group (F=35.7, df=16, p <0.001). We compared language test scores in males and females of the DS group and control group, as shown in Table 10, and found that the mean total language score in males of DS was lower than that in females compared to the control group. The mean scores of expressive and receptive language were also lower in males with DS than in females but showed no difference from the control group. The Stanford Binet Intelligence Scale (Fifth Edition) scores in males and females of the DS group and control group, as shown in Table 11, indicated no significant difference between males and females of DS. However, the DS males have low scores than females. There was a considerable difference between males and females in the control group, and males had lower scores than females.

Association between neuroanatomy and neuropsychology of DS

Using the Spearman correlation test, we correlated DS samples' total brain volume and IQ, working memory, and total language scores. We observed a significant correlation between the whole brain and working memory ($r = 0.68$, $p< 0.001$), and the correlation between the total brain and total IQ approached significance ($r = 0.53$, $p = 0.06$). The correlation between the whole brain and total language was not significant.

We also correlated parietal lobe volume with total IQ, working memory, total language, and visuospatial processing scores for DS samples. We discovered a significant correlation between the parietal lobe and working memory ($r = 0.62$, $p< 0.001$) and visuospatial processing ($r = 0.55$, $p< 0.001$). The correlation between the parietal lobe and total IQ approached significance ($r = 0.49$, $p = 0.08$). We observed no significant correlation between the parietal lobe and total language.

We correlated temporal lobe volume and total IQ, working memory, whole language, and visuospatial processing scores for DS samples. We found a significant correlation between the temporal lobe and working memory ($r = 0.68$, $p< 0.001$), the correlation between the temporal lobe and total IQ approached significance ($r = 0.48$, $p = 0.09$) and no significant correlation between the temporal lobe and whole language and visuospatial processing.

We correlated hippocampal volume and whole IQ, working memory, and whole language scores for DS samples. We discovered a significant correlation between the hippocampus and whole language ($r = 0.59$, $p< 0.001$), and the correlation between the hippocampus and working memory approached significance ($r = 0.51$, $p = 0.07$). The correlation between the hippocampus and total IQ was not significant.

We correlated parahippocampal gyrus volume with whole IQ, working memory, and global language scores for DS samples. We observed a significant correlation between the parahippocampal gyrus and working memory ($r = 0.57$, $p< 0.001$) and no significant correlation between the parahippocampal gyrus and total IQ and total language.

We correlated superior temporal gyrus volume and global IQ, working memory, and whole language scores for DS samples. We observed a significant correlation between the superior temporal gyrus and working memory ($r = 0.57$, $p < 0.001$) and no significant correlation between the superior temporal gyrus and total IQ and total language.

We applied partial correlations between superior temporal gyrus volume and nonverbal and verbal IQ and expressive and receptive language scores for DS samples while controlling for age and total brain volume. We found a negative correlation between the superior temporal gyrus and expressive language that approached significance ($r = -0.58$, $p = 0.07$), while the correlation between the superior temporal gyrus and other scores was insignificant.

We correlated angular gyrus volume with total IQ, working memory, and whole language scores for DS samples. We observed that the correlation between the angular gyrus and working memory approached significance ($r = 0.55$, $p = 0.05$) and no significant correlation between the angular gyrus and total IQ and total language.

We correlated DS samples' supramarginal gyrus volume with global IQ, working memory, and whole language scores. We observed no significant correlation between the supramarginal gyrus and any of these scores.

We applied partial correlations between supramarginal gyrus volume and nonverbal and verbal IQ and expressive and receptive language scores for DS samples while controlling for age and total brain volume. There was a significant negative correlation between the supramarginal gyrus and expressive language ($r = -0.71$, $p < 0.001$). The correlation between the supramarginal gyrus and other scores was not significant.

We correlated fusiform gyrus volume and total IQ, working memory, and whole language scores for DS samples. We observed a significant correlation between the fusiform gyrus and global IQ ($r = 0.60$, $p < 0.001$) and working memory ($r = 0.73$, $p < 0.001$) and no significant correlation between the fusiform gyrus and total language.

We correlated fusiform gyrus volume and fluid reasoning, knowledge, quantitative reasoning, and visuospatial processing scores for DS samples. We observed a significant correlation between the fusiform gyrus and visuospatial processing ($r = 0.65$, $p < 0.001$). The correlation between the fusiform gyrus and other scores was not significant.

We correlated DS samples' hippocampal subregion (dentate gyrus) volume and total IQ, working memory, and whole language scores. We discovered a significant correlation between the dentate gyrus and whole language ($r = 0.64$, $p < 0.001$) and no significant correlation between the dentate gyrus and working memory and total IQ.

We correlated dentate gyrus volume with fluid reasoning, knowledge, quantitative reasoning, and visuospatial processing scores for DS samples. We found no significant correlations between the dentate

gyrus and any of these scores.

We correlated DS samples' hippocampal subregion (Ammon's horn) volume and total IQ, working memory, and whole language scores. We observed that the correlation between Ammon's horn and global IQ approached significance ($r = 0.50$, $p = 0.07$) and that there was no significant correlation between Ammon's horn and other scores.

We correlated Ammon's horn volume and fluid reasoning, knowledge, quantitative reasoning, and visuospatial processing scores for DS samples. We found no significant correlation between Ammon's horn and any of these scores.

We correlated hippocampal subregion (subiculum) volume and total IQ, working memory, and whole language. We found a significant correlation between the subiculum and global IQ ($r = 0.59$, $p< 0.001$) and working memory ($r = 0.61$, $p< 0.001$) and no significant correlation between the subiculum and total language.

We correlated subiculum and fluid reasoning, knowledge, quantitative reasoning, and visuospatial processing. We found a significant correlation between the subiculum and visuospatial processing ($r = 0.62$, $p< 0.001$), that the correlation between the subiculum and quantitative reasoning approached significance ($r = 0.49$, $p = 0.08$) and that there was no correlation between the subiculum and other scores.

Discussion

We investigated regional brain volumes in children and adults with DS to identify the pathophysiological mechanisms related to their cognitive features. We collected imaging data from the participants with DS and the controls and correlated the MRI data of the DS group with cognitive functions evaluated using neuropsychological battery assessments. We applied different neuropsychological tasks to investigate cognitive domains, such as global cognition, memory, and language, and we correlated the results to various regional brain volumes.

Our results confirmed that DS subjects had reduced total brain, cerebrum, cerebellum, brainstem, hippocampus, frontal lobe, parietal lobe, temporal lobe, occipital lobe, and parahippocampal gyrus volumes compared to controls.

These findings, except for parahippocampal gyrus volume, are consistent with the results of previous neuropathological and neuroimaging studies (Jernigan, Bellugi et al. 1993, Kesslak, Nagata et al. 1994, Raz, Torres et al. 1995, Aylward, Habbak et al. 1997, Pinter, Eliez et al. 2001, White, Alkire et al. 2003, Menghini, Costanzo et al. 2011, Mullins, Daly et al. 2013, Hamner, Udhnani et al. 2018). In contrast to the findings by Kesslak, Nagata et al. (1994) and Raz, Torres et al. (1995) of larger parahippocampal gyrus volume in DS subjects compared to controls, our study showed smaller parahippocampal gyrus volume in DS than controls.

Furthermore, our results indicated reduced white matter and grey matter of the total brain, hippocampal subregions (Dentate gyrus, Ammon's horn, and Subiculum), angular gyrus, supramarginal gyrus, fusiform gyrus, and superior temporal gyrus volumes in DS participants compared to controls. Our study did not indicate any age-related changes in brain areas in either the DS or control groups. According to our results, DS males have more significant volumes of different brain regions than females compared to controls.

The neuropsychological profile of DS patients showed deficits in different cognition and language domains in our study group. Our study results confirmed the findings of previous studies that impairments in expressive language are more remarkable than deficits in receptive language (Abbeduto, Pavetto et al. 2001, Pulina, Vianello et al. 2019).

Our study group showed a mean IQ of 65, which is consistent with previous studies that confirmed that most people with DS have an IQ between 30 and 70 (Abbeduto, Warren et al. 2007). Our DS group showed a higher nonverbal IQ than verbal IQ compared to the Evans and Uljarević (2018) study. This study described that children and adolescents with DS have a higher verbal IQ than nonverbal IQ (assessed with the Stanford-Binet Intelligence Scale fourth edition).

We also confirmed deficits in working memory, which is consistent with the finding by Couzens, Haynes et al. (2012). Although the cognitive profile of DS shows relative strength in visuospatial processing skills (Pinter, Eliez et al. 2001), our study group showed impairment in visuospatial processing compared to controls. Additionally, this deficit is remarkable when compared with other verbal and nonverbal abilities. A review by Yang, Conners et al. (2014) also described visuospatial working memory as a weak area in DS. Other domains, such as fluid reasoning, knowledge, and quantitative reasoning, show impairment in our study group.

Raz, Torres et al. (1995) found no relationship between total brain volume and cognitive variables. Nevertheless, our results showed an association between total brain volume reduction and deficits in whole IQ and working memory. This finding confirms previous reports that found a positive association between brain volume and intelligence in the general population (McDaniel 2005, Ritchie, Booth et al. 2015). There is evidence for the association between the parietal lobe and visuospatial processing skills (Pinter, Eliez et al. 2001). This relationship depends on the finding of preserved parietal lobe volume associated with the relative strength in visuospatial processing by previous reports (Pinter, Eliez et al. 2001). However, our results of reduced parietal lobe volume and impaired visuospatial processing with a positive correlation contrast with these reports.

Additionally, we observed a correlation between the reduction in parietal lobe volume and deficits in working memory, which Menghini, Costanzo et al. (2011) confirmed. Our study could not confirm the association between reduction in the parietal lobe volume and deficits in linguistic abilities. No similar research has reported the relationship between reduced parietal lobe volume and deficits in language skills. The relationship between the decrease in parietal lobe volume and low total IQ approached

significance. Nevertheless, there is evidence of the correlation between the parietal lobe and intelligence in the general population (Yoon, Shin et al. 2017).

Our study results confirmed the association between temporal lobe volume reduction and deficits in working memory, ensuring the temporal lobe's role in memory function (Galaburda and Schmitt 2003, Pennington, Moon et al. 2003, Vicari 2006, Menghini, Costanzo et al. 2011).

Our results could not confirm the involvement of the temporal lobe in language deficits. Nevertheless, in contrast to a study by Pinter, Eliez et al. (2001), which reported larger corrected volumes of temporal lobe volume, our results showed the reduced volume of the temporal lobe in DS participants.

This result provides neuroimaging evidence for the hypothesis of disproportionately smaller temporal lobe volumes associated with language deficits in DS. The relationship between the reduced temporal lobe volume and low total IQ approached significance. Nevertheless, there is evidence of the correlation between the temporal lobe and intelligence in the general population (Yoon, Shin et al. 2017).

Our study confirmed the link between hippocampal volume reduction and deficits in language and working memory, and this has been reported widely by previous studies (Raz, Torres et al. 1995, Krasuski, Alexander et al. 2002, Pennington, Moon et al. 2003). These findings reflect the role of the hippocampus as an essential biomarker for AD and one of the regions that are severely affected by the neuropathological changes of AD (Aylward, Li et al. 1999).

We found no significant correlation between age and hippocampal volume. This finding is consistent with previous studies by Raz, Torres et al. (1995) and Aylward, Li et al. (1999), who failed to find a correlation between age and hippocampal volume, but contrasts with the study by Kesslak, Nagata et al. (1994), who found a significant correlation between age and hippocampal volume. The age range of these reported studies is between 22-50 years, and our study group's age range is between 6-25 years. This comparison confirms the suggestion that the significant decrease in hippocampal volume before age 30 remains stable and then decreases later when dementia occurs in DS subjects (Aylward, Li et al. 1999). This decrease in hippocampal volume with increased age is related to changes in the neural pathway associated with memory and learning problems that start at infancy and continue throughout childhood (Kates, Kaufmann et al. 1997).

The most exciting finding in our study is the reduced volume of the parahippocampal gyrus, which contrasts with the results of Raz, Torres et al. (1995), who reported enlargement of this structure that is severely affected by AD.

We suppose that the parahippocampal gyrus volume follows DS's known neuroanatomical, neurodevelopmental, and pathological pathways.

Another interesting finding related to parahippocampal gyrus volume is the association between this structural volume reduction and deficits in working memory. There was no association between parahippocampal gyrus volume reduction and deficits in total IQ and total language. This result contrasts

with that of Raz, Torres et al. (1995), who found a negative correlation between parahippocampal gyrus volume and IQ in DS subjects.

Our results significantly support the suggestion of narrowness of the superior temporal gyrus (Nadel 1999), although some related studies could not confirm this (Kesslak, Nagata et al. 1994, Pinter, Eliez et al. 2001). The superior temporal gyrus is part of the language network (Friederici and Gierhan 2013). It contributes to the perceptual analysis of the speech signal during auditory word processing and production and comprehension of spoken words (Zevin 2009). Our statistical finding of a negative correlation between superior temporal gyrus volume and expressive language when applying partial correlation while controlling for age and total brain volume, which approached significance, confirms superior temporal gyrus function. There was a correlation between a reduction in superior temporal gyrus volume and deficits in working memory. We did not find an association between reduction in superior temporal gyrus volume and scores of total IQ and total language.

We tried to include other specific brain regions related to deficits in language and memory in DS, such as the temporoparietal junction (e.g., angular and supramarginal gyri) and occipitotemporal structures (e.g., fusiform gyrus), which are parts of the language network (Hickok and Poeppel 2004, Friederici and Gierhan 2013, Hamner, Udhnani et al. 2018). We could not confirm the relationship between angular gyrus volume and language deficits. We found a correlation that approached significance between angular gyrus volume and deficits in working memory. This result confirms the role of the angular gyrus in verbal working memory and other complex cognitive functions (Seghier 2013). We observed a significant negative correlation when we applied partial correlation between supramarginal gyrus volume and expressive language while controlling for age and total brain volume.

This finding means that the supramarginal gyrus plays a similar role in language processing skills as the superior temporal gyrus.

The reduced volume fusiform gyrus, also known as the occipitotemporal gyrus, is related to deficits in total IQ and working memory.

An interesting finding is an association between reduced fusiform gyrus volume, a parietal lobe subregion, and impairment in visuospatial processing skills. This finding supports our link between reduced parietal lobe volume and deficits in visuospatial processing skills.

As part of our study of hippocampal formation, we studied three hippocampal subregions (Dentate gyrus, Ammon’s horn, and Subiculum) to understand their role in the cognitive and language skills of DS.

We observed an association between reduced dentate gyrus volume and deficits in total language skills. Dentate gyrus function in the production of long-term memory is evident by studying impaired neurogenesis in DS fetuses and Ts65Dn DS mouse models (Contestabile, Fila et al. 2007).

We found an association between reduced Ammon’s horn volume and deficits in total IQ, which confirms reports indicating this hippocampal subregion's role in cognition (Pang, Kiecker et al. 2018).

Interestingly, reduced subiculum volume is associated with deficits in total IQ, working memory, visuospatial processing, and quantitative reasoning skills.

We suppose that the subiculum plays a significant role in cognition and memory processing in DS compared to other hippocampal subregions.

The subiculum plays an essential role in the hippocampal circuit. Nevertheless, little is known about its function, although some reports indicate a critical but ill-defined role in spatial navigation and mnemonic processing (O'Mara, Commins et al. 2001)

This study is the first to study and assess the neuroanatomy and neuropsychology of DS in detail using high-resolution neuroimaging techniques, considering the limitations of previous related studies. Our results confirm earlier reports regarding overall patterns of brain volumes in individuals with DS and provide new evidence for abnormal volumes of specific regional and subregional brain volumes associated with language and memory domains. Our sample's small size dampens confidence in the observed pattern of neuroanatomic abnormalities. The difficulty in recruiting children and adults with DS and convincing their families to participate in the study, the cost, and the time-consuming nature of radiological and psychological examinations limit the number of subjects included. Additionally, we could not have children under five years of age, which is not due to the rarity of samples but because the skills of the children are not enough to perform the neuropsychological assessment and respond to its content. Although understanding the neuropathological nature of DS deserves to be pursued, studying the relationship between abnormal neuroanatomy and deficits in memory and language is of greater scientific and practical importance. The findings of this study indicate that the brains of subjects with DS show a well-defined pattern of abnormalities. The correlational analysis presented in the results section of this study provides excellent evidence that represents firm conclusions. Within the studied group of intellectually disabled individuals, the degree of the global reduction in brain volume predicts the general level of intellectual performance and memory function. Additionally, a decrease in the parietal lobe volume may be a significant predictor of cognitive disabilities in DS, especially those associated with visuospatial processing skills. Similarly, reduced volumes of the temporal lobe and hippocampus may significantly predict cognitive functions in DS, especially those associated with memory and language skills. The parahippocampal gyrus volume was smaller in DS subjects than in normal controls and was related to deficits in working memory function. Therefore, the phenomenon of parahippocampal gyrus enlargement, indicated twice by independent researchers (Kesslak, Nagata et al. 1994, Raz, Torres et al. 1995), and its specificity to DS, when compared with normal aging and AD contrasted by our study and these results, maybe due to bias occurred by manual measurement of brain regions. Other neuroanatomic abnormalities could also be important markers because of their association with cognitive deficits. These markers include the superior temporal gyrus, which is related to expressive language. Additionally, regions such as the angular gyrus, supramarginal gyrus, and fusiform gyrus are interesting to understand the language network and their association with memory functions. Hippocampal subregions (Dentate gyrus, Ammon’s horn, and Subiculum) are essential to understand the role of hippocampal formation and its association with the memory domain. A more extensive and

longitudinal study is needed to study neuroanatomical and behavioral changes with increasing age while applying interventional rehabilitation programs to observe the effects of these methods to improve cognitive skills or prevent a greater decline with time. From a practical standpoint, these data can provide educational psychologists and teachers invaluable information for developing rationally grounded interventions to understand and alleviate these individuals' learning difficulties and social problems.

Declarations

ACKNOWLEDGMENT

This research project was made possible through funding by the Friedrich-Naumann Foundation for Freedom (Scholar-Number: 8683 / P611, 2021). We express our gratitude to children and adults with DS, their parents, and their educational institutions. We gratefully acknowledge the cooperation of the Women & Child Mental Health Development Organization and Aliaa Specialist Hospital, Khartoum, Sudan, and their valuable help. We thank our families for their outstanding support and patience during the data collection and analysis.

References

Abbeduto, L., M. Pavetto, E. Kesin, M. D. Weissman, S. Karadottir, A. O'Brien and S. Cawthon (2001). "The linguistic and cognitive profile of Down syndrome: evidence from a comparison with fragile X syndrome." Downs Syndr Res Pract **7**(1): 9-15.

Abbeduto, L., S. F. Warren and F. A. Conners (2007). "Language development in Down syndrome: from the prelinguistic period to the acquisition of literacy." Ment Retard Dev Disabil Res Rev **13**(3): 247-261.

Aylward, E. H., R. Habbak, A. C. Warren, M. B. Pulsifer, P. E. Barta, M. Jerram and G. D. J. A. o. n. Pearlson (1997). "Cerebellar volume in adults with Down syndrome." **54**(2): 209-212.

Aylward, E. H., Q. Li, N. A. Honeycutt, A. C. Warren, M. B. Pulsifer, P. E. Barta, M. D. Chan, P. D. Smith, M. Jerram and G. D. J. A. J. o. P. Pearlson (1999). "MRI volumes of the hippocampus and amygdala in adults with Down's syndrome with and without dementia." **156**(4): 564-568.

Contestabile, A., T. Fila, C. Ceccarelli, P. Bonasoni, L. Bonapace, D. Santini, R. Bartesaghi and E. J. H. Ciani (2007). "Cell cycle alteration and decreased cell proliferation in the hippocampal dentate gyrus and in the neocortical germinal matrix of fetuses with Down syndrome and in Ts65Dn mice." **17**(8): 665-678.

Couzens, D., M. Haynes and M. Cuskelly (2012). "Individual and environmental characteristics associated with cognitive development in Down syndrome: a longitudinal study." J Appl Res Intellect Disabil **25**(5): 396-413.

Evans, D. W. and M. Uljarević (2018). "Parental education accounts for variability in the IQs of probands with Down syndrome: A longitudinal study." Am J Med Genet A **176**(1): 29-33.

Fidler, D., D. Most and A. Philofsky (2008). "The Down syndrome behavioural phenotype: Taking a developmental approach."

Friederici, A. D. and S. M. Gierhan (2013). "The language network." Curr Opin Neurobiol **23**(2): 250-254.

Galaburda, A. and J. Schmitt (2003). "Neuroanatomical Considerations Specific to the Study of Neurogenetics."

Gibson, D. (1978). Down's Syndrome: The Pshychology of Mongolism, CUP Archive.

Hamner, T., M. D. Udhnani, K. Z. Osipowicz and N. R. J. J. o. t. I. N. S. Lee (2018). "Pediatric brain development in Down syndrome: a field in its infancy." **24**(9): 966-976.

Hickok, G. and D. Poeppel (2004). "Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language." Cognition **92**(1-2): 67-99.

Jarrold, C., A. D. Baddeley and C. Phillips (2007). "Long-Term Memory for Verbal and Visual Information in Down Syndrome and Williams Syndrome: Performance on the Doors and People Test." Cortex **43**(2): 233-247.

Jernigan, T. L., U. Bellugi, E. Sowell, S. Doherty and J. R. Hesselink (1993). "Cerebral morphologic distinctions between Williams and Down syndromes." Arch Neurol **50**(2): 186-191.

Kates, W. R., W. E. Kaufmann and A. L. Reiss (1997). "Neuroimaging of developmental and genetic disorders." Child and Adolescent Psychiatric Clinics **6**(2): 283-304.

Keller, S. S. and N. Roberts (2009). "Measurement of brain volume using MRI: software, techniques, choices and prerequisites." J Anthropol Sci **87**: 127-151.

Kesslak, J. P., S. F. Nagata, I. Lott and O. Nalcioglu (1994). "Magnetic resonance imaging analysis of age-related changes in the brains of individuals with Down's syndrome." Neurology **44**(6): 1039-1045.

Krasuski, J. S., G. E. Alexander, B. Horwitz, S. I. Rapoport and M. B. J. A. J. o. P. Schapiro (2002). "Relation of medial temporal lobe volumes to age and memory function in nondemented adults with Down's syndrome: implications for the prodromal phase of Alzheimer's disease." **159**(1): 74-81.

Kulaga-Yoskovitz, J., B. C. Bernhardt, S. J. Hong, T. Mansi, K. E. Liang, A. J. van der Kouwe, J. Smallwood, A. Bernasconi and N. Bernasconi (2015). "Multi-contrast submillimetric 3 Tesla hippocampal subfield segmentation protocol and dataset." Sci Data **2**: 150059.

Manjón, J. V. and P. Coupé (2016). "volBrain: An Online MRI Brain Volumetry System." Frontiers in Neuroinformatics **10**(30).

McDaniel, M. A. (2005). "Big-brained people are smarter: A meta-analysis of the relationship between in vivo brain volume and intelligence." Intelligence **33**(4): 337-346.

Menghini, D., F. Costanzo and S. J. B. g. Vicari (2011). "Relationship between brain and cognitive processes in Down syndrome." **41**(3): 381-393.

Mullins, D., E. Daly, A. Simmons, F. Beacher, C. M. Foy, S. Lovestone, B. Hallahan, K. C. Murphy and D. G. Murphy (2013). "Dementia in Down's syndrome: an MRI comparison with Alzheimer's disease in the general population." J Neurodev Disord **5**(1): 19.

Nadel, L. (1999). "Down syndrome in cognitive neuroscience perspective." Neurodevelopmental disorders: 197-221.

O'Mara, S. M., S. Commins, M. Anderson and J. Gigg (2001). "The subiculum: a review of form, physiology and function." Prog Neurobiol **64**(2): 129-155.

Pang, C., C. Kiecker, J. O'Brien, W. Noble and R. Chang (2018). "Ammon's Horn 2 (CA2) of the Hippocampus: A Long-Known Region with a New Potential Role in Neurodegeneration." The Neuroscientist **25**: 107385841877874.

Parker, S. E., C. T. Mai, M. A. Canfield, R. Rickard, Y. Wang, R. E. Meyer, P. Anderson, C. A. Mason, J. S. Collins, R. S. Kirby, A. Correa and N. National Birth Defects Prevention (2010). "Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006." Birth Defects Res A Clin Mol Teratol **88**(12): 1008-1016.

Pennington, B. F., J. Moon, J. Edgin, J. Stedron and L. Nadel (2003). "The neuropsychology of Down syndrome: evidence for hippocampal dysfunction." Child Dev **74**(1): 75-93.

Pinter, J. D., S. Eliez, J. E. Schmitt, G. T. Capone and A. L. Reiss (2001). "Neuroanatomy of Down's syndrome: a high-resolution MRI study." Am J Psychiatry **158**(10): 1659-1665.

Pulina, F., R. Vianello and S. Lanfranchi (2019). Chapter Three - Cognitive profiles in individuals with Down syndrome. International Review of Research in Developmental Disabilities. S. Lanfranchi, Academic Press. **56:** 67-92.

Raschle, N., J. Zuk, S. Ortiz-Mantilla, D. D. Sliva, A. Franceschi, P. E. Grant, A. A. Benasich and N. Gaab (2012). "Pediatric neuroimaging in early childhood and infancy: challenges and practical guidelines." Ann N Y Acad Sci **1252**: 43-50.

Raz, N., I. J. Torres, S. D. Briggs, W. D. Spencer, A. E. Thornton, W. J. Loken, F. Gunning, J. McQuain, N. R. Driesen and J. D. J. N. Acker (1995). "Selective neuroanatornic abnormalities in Down's syndrome and their cognitive correlates: Evidence from MRI morphometry." **45**(2): 356-366.

Ritchie, S. J., T. Booth, M. d. C. Valdés Hernández, J. Corley, S. M. Maniega, A. J. Gow, N. A. Royle, A. Pattie, S. Karama, J. M. Starr, M. E. Bastin, J. M. Wardlaw and I. J. Deary (2015). "Beyond a bigger brain: Multivariable structural brain imaging and intelligence." Intelligence **51**: 47-56.

Roid, G. H. and M. Pomplun (2012). The stanford-binet intelligence scales, The Guilford Press.

Seghier, M. L. (2013). "The angular gyrus: multiple functions and multiple subdivisions." The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry **19**(1): 43-61.

Vicari, S. (2006). "Motor development and neuropsychological patterns in persons with Down syndrome." Behav Genet **36**(3): 355-364.

White, N. S., M. T. Alkire and R. J. J. N. Haier (2003). "A voxel-based morphometric study of nondemented adults with Down Syndrome." **20**(1): 393-403.

Yang, Y., F. A. Conners and E. C. Merrill (2014). "Visuo-spatial ability in individuals with Down syndrome: is it really a strength?" Res Dev Disabil **35**(7): 1473-1500.

Yoon, Y. B., W.-G. Shin, T. Y. Lee, J.-W. Hur, K. I. K. Cho, W. S. Sohn, S.-G. Kim, K.-H. Lee and J. S. Kwon (2017). "Brain Structural Networks Associated with Intelligence and Visuomotor Ability." Scientific Reports **7**(1): 2177.

Zevin, J. (2009). Word Recognition. Encyclopedia of Neuroscience. L. R. Squire. Oxford, Academic Press**:** 517-522.

Zigman, W. B. and I. T. Lott (2007). "Alzheimer's disease in Down syndrome: neurobiology and risk." Ment Retard Dev Disabil Res Rev **13**(3): 237-246.

Tables

Tables 1-11 are available in the Supplementary Files section.

Figures

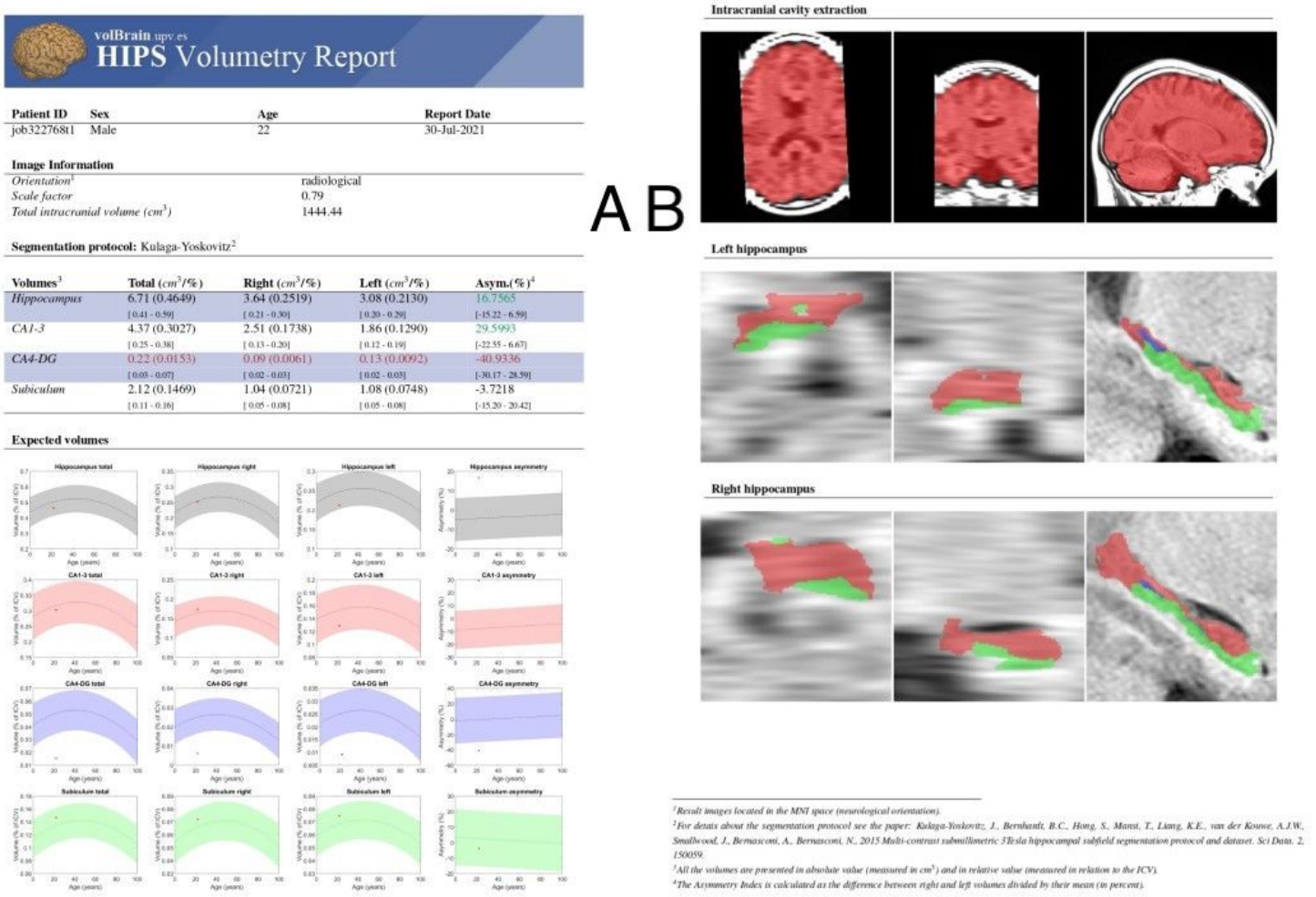

Figure 1

1a: A report generated by the volBrain hippocampal pipeline (HIPS) showing the segmentation of three hippocampal subregions (CA1-3 (Ammon's horn, CA4-DG (Dentate Gyrus), Subiculum) and their expected volumes from the brain of a 22-year-old male with DS. 1b: A report generated by the volBrain hippocampal pipeline (HIPS) showing the segmentation of three hippocampal subregions (color-coded: CA1-3 (Ammon's horn), CA4-DG (Dentate Gyrus, Subiculum) and their volumes from the brain of a 22-year-old male with DS. Upper panels left to right: Planes of section (horizontal, transverse, sagittal) used to obtain the corresponding images below. Middle panels left-side hippocampus and its horizontal, transverse, and sagittal planes are from left to right. Lower panels, right side hippocampus, and its parts, horizontal, transverse and sagittal planes from left to right.

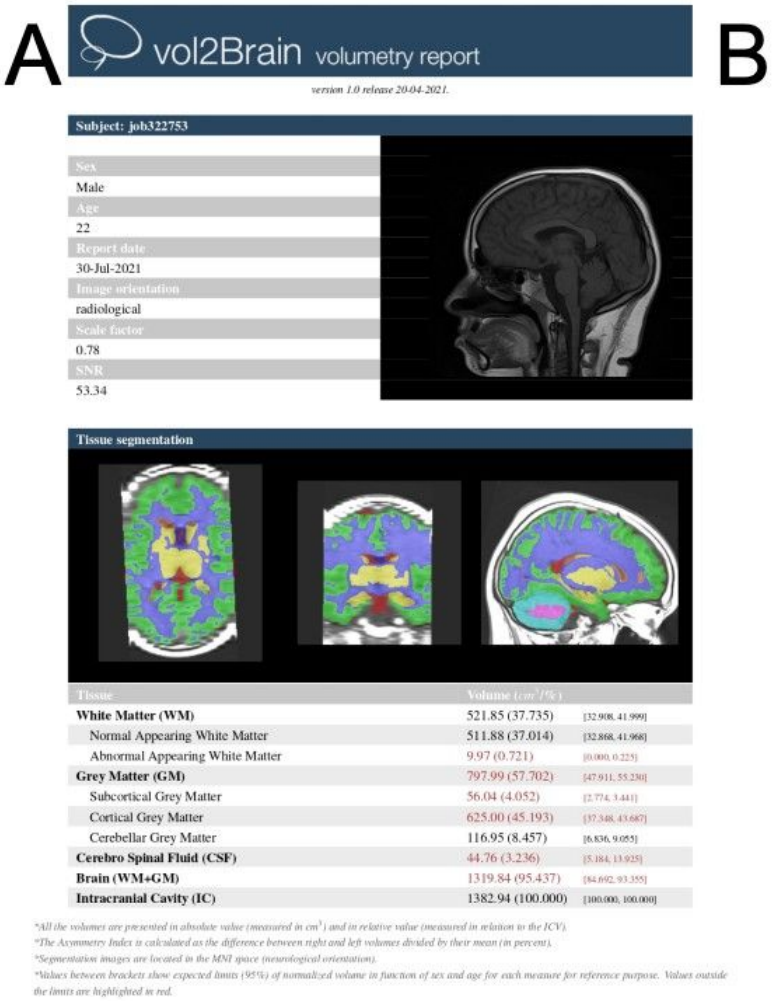

Figure 2

2a: Volumetry report generated by the vol2Brain pipeline. Results of global tissue estimation (GM, WM, IC, and CSF) in a 22-year-old male with DS. 2b: Volumetry report generated by the vol2Brain pipeline. Results of macrostructure tissue estimation (Cerebrum, Cerebellum, Vermis, and Brainstem) in a 22-year-old male with DS.

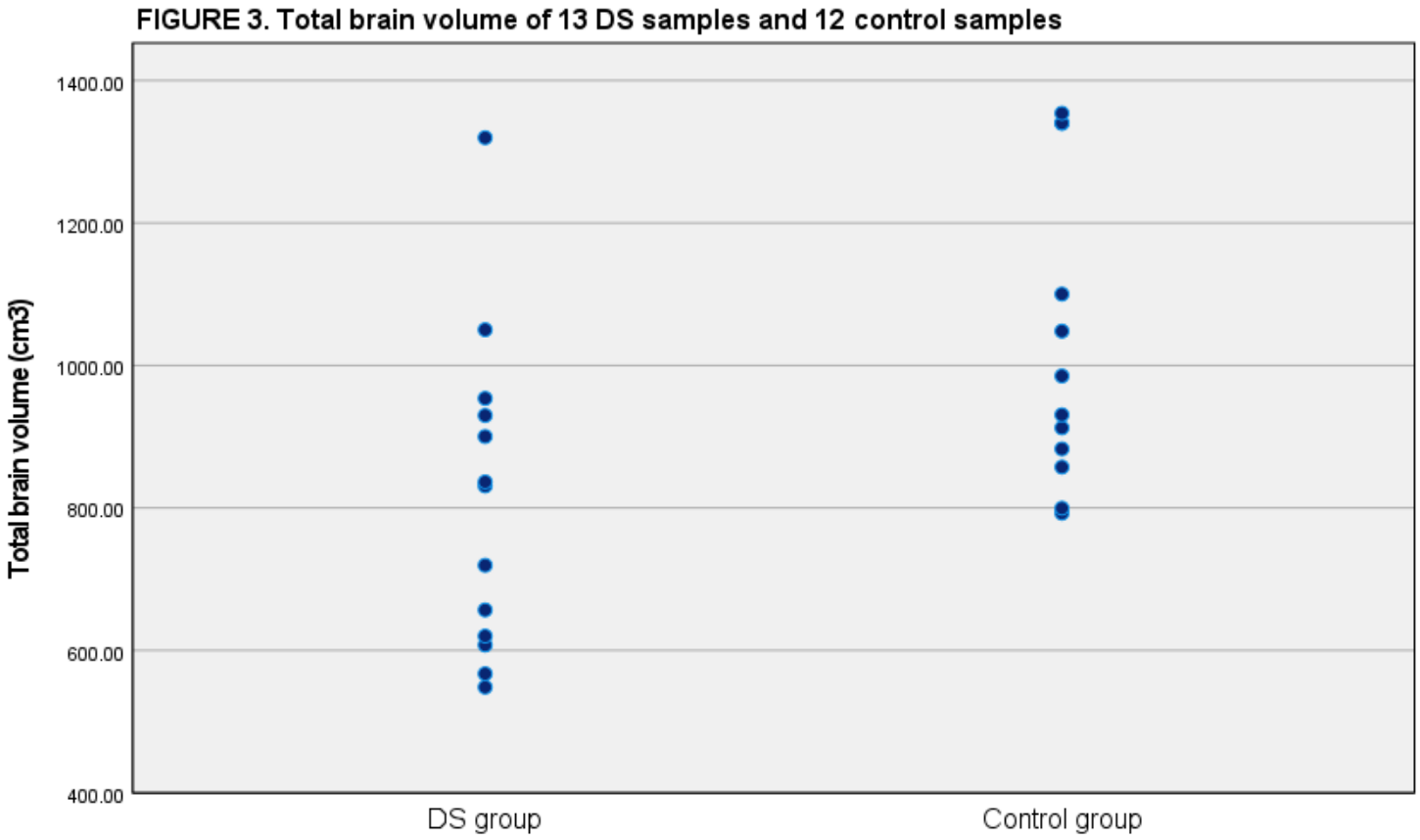

Figure 3

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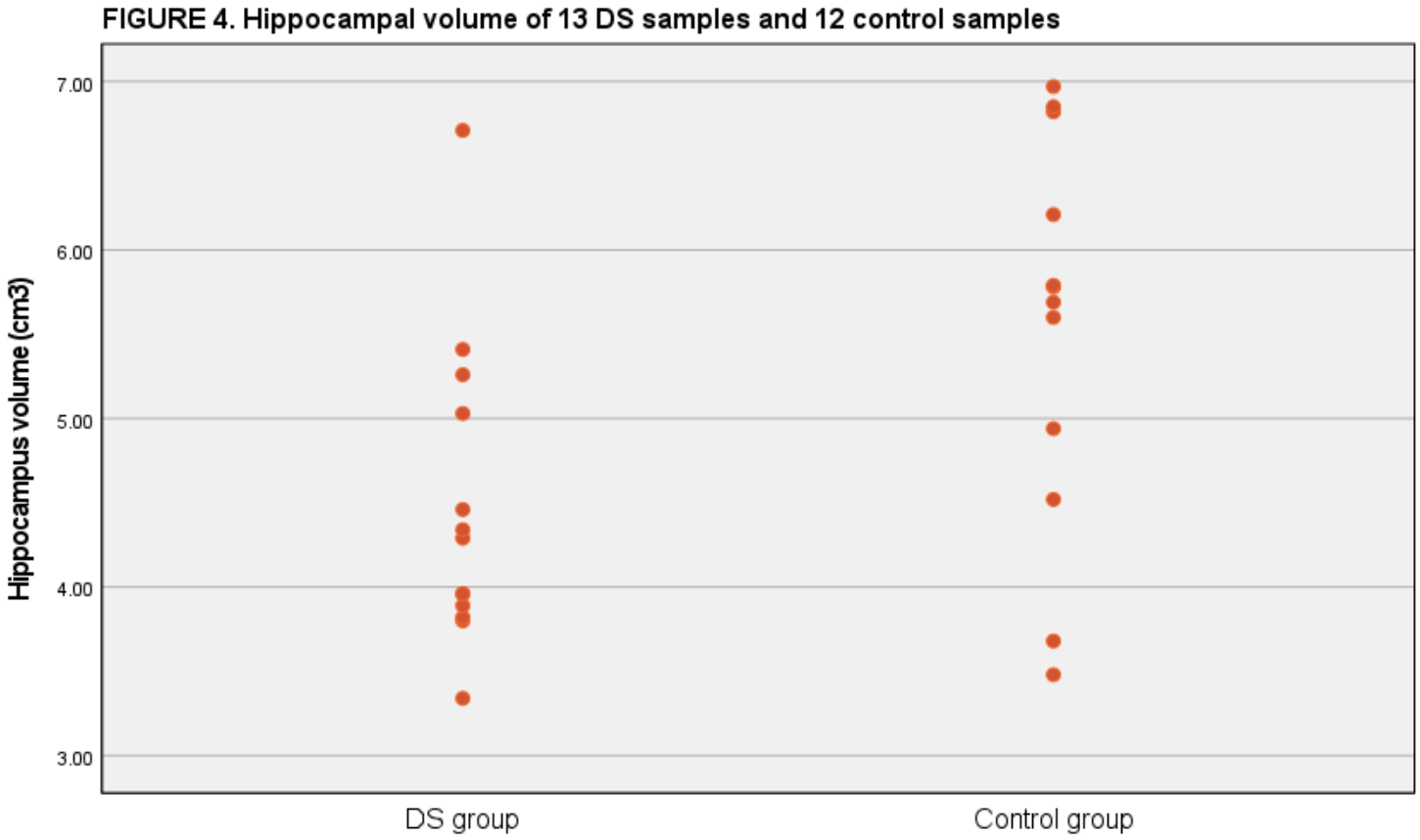

Figure 4

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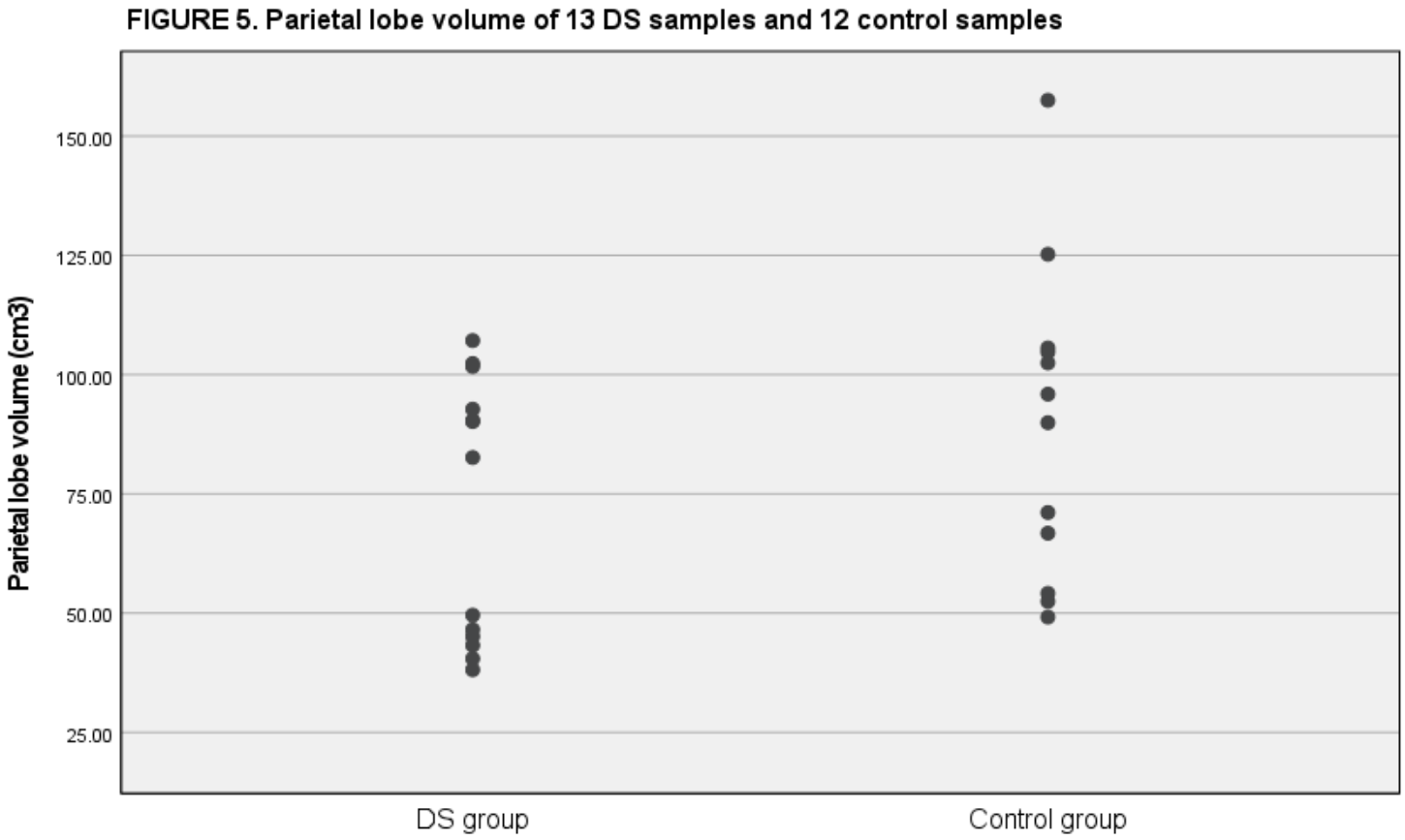

Figure 5

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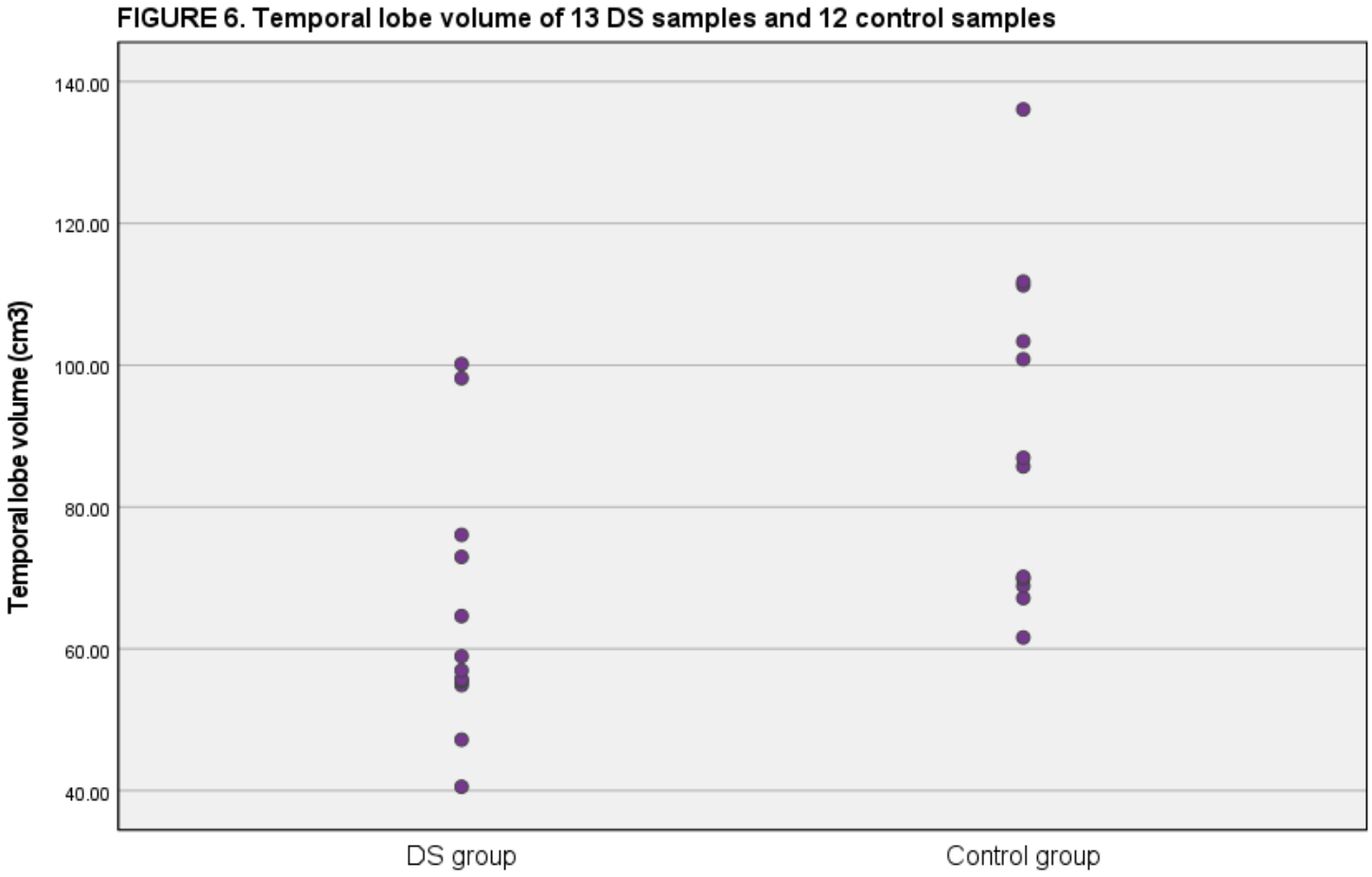

Figure 6

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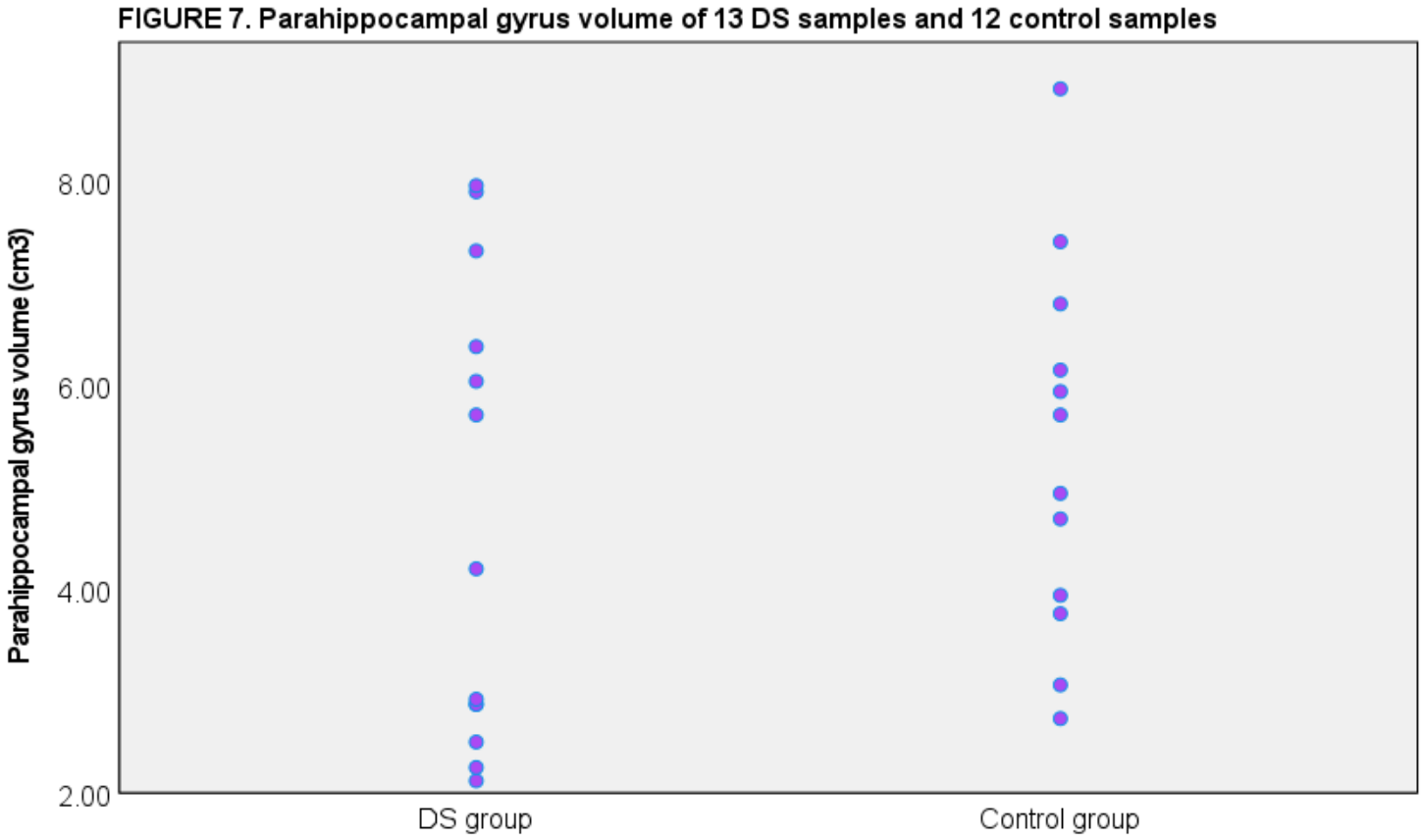

Figure 7

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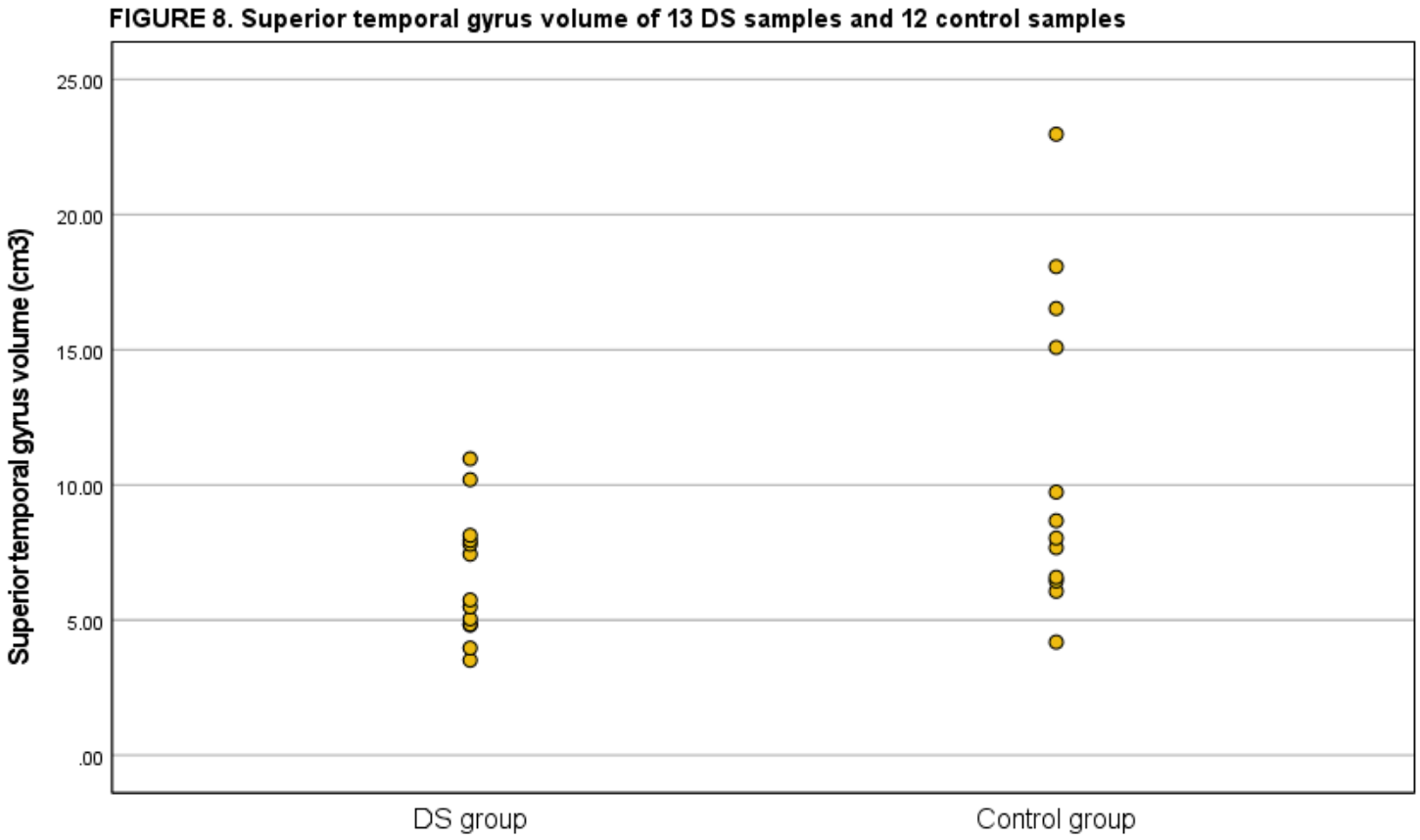

Figure 8

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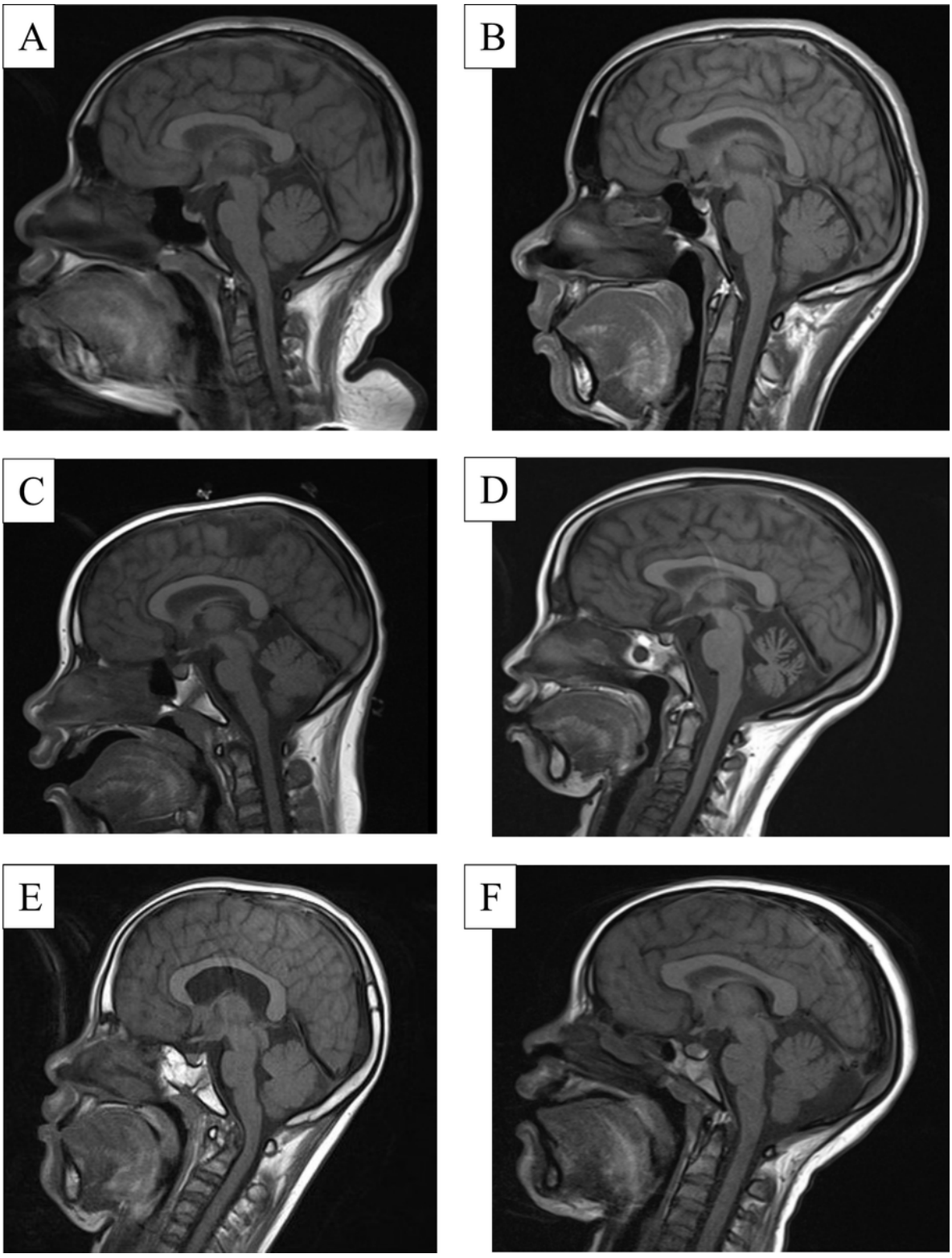

Figure 9

Sagittal T1 / SE MRI view of A) 25-year-old adult male with DS, B) 25-year-old male control sample, C) 12-year-old female with DS, D) 12-year-old female control sample E) 14-year-old male with DS, F) 14-year-old female with DS for comparison between DS and control samples as well as between DS males and females.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx