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Review

A systematic review of frontal lobe volume in autism spectrum disorder revealing distinct trajectories

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Abstract

Frontal lobe volume has been extensively researched in individuals with Autism spectrum disorder (ASD), though findings are yet to be summarised to explain the developmental trends of frontal lobe volume. The aim of the present study is to consolidate all existing frontal lobe volume and age data of autistic individuals below 30 years of age, and compare this data to non-autistic (N-ASD) controls. Following a systematic review, frontal lobe volume data were obtained from seven papers. Raw data, or the means and standard deviations of frontal lobe volume, and age, were obtained from the studies giving 372 autistic and 190 N-ASD participants. Data were plotted and analysed. Findings revealed that regression lines of fit for ASD ($R^2_{Linear} = 0.33$; $R^2_{Quadratic} = 0.52$) and N-ASD ($R^2_{Linear} = 0.14$; $R^2_{Quadratic} = 0.39$) were significantly different by diagnosis (linear $p = 0.002$, quadratic $p = 0.02$) with quadratic models providing significantly better fit within ASD ($p < 0.001$) and N-ASD ($p < 0.001$). Additional analyses revealed that frontal lobe volume was greater in autistic individuals than N-ASD between two and four years ($F_{(1,31)} = 12.965$, $p < 0.005$, $\eta^2 = 0.291$). In the present study, there were distinct developmental trends for frontal lobe volume between ASD and N-ASD.

Keywords: Autism spectrum disorder; Frontal lobe volume; Development; Systematic review

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder usually diagnosed by age three years [1], with an estimated prevalence among US children about 1.7% [2], while the estimated prevalence of autism among US adults is 2.21% [3]. Global estimates put the estimated prevalence of autism in children between 1 and 2% [4].

Herein the term ASD will be used to cover all prior nomenclature for autism such as autism, Asperger's disorder, Kanner's autism, high functioning autism, etc., as detailed in the fifth version of the Diagnostic and Statistical Manual (DSM-5; American Psychiatric Association [APA], 2013 [5]). Additionally, in line with community wishes [6,7] we will use identity-first language, such as 'autistic person', where appropriate.

While over the last three decades, ASD has been heavily researched [8], the neurobiological underpinnings of are not yet elucidated [9]. The brain's frontal lobe is implicated in a range of abilities relevant to ASD, including social cognition and executive function [10]. Because behavioural evidence suggests that frontal lobe volume may be atypical in individuals with ASD [11], an examination of aspects of this region may provide some insight into the complexities of ASD. While studies have demonstrated atypical frontal lobe volume in those with ASD relative to neurotypical individuals [12], these findings do not explain the developmental trend of frontal lobe volume in individuals with ASD. Consequently, the status of the frontal lobes in individuals with ASD remains poorly understood. To date, no study has yet analysed frontal lobe data in autistic individuals over the age span. Because the relationship between head circumference and brain volume are dynamic over age within ASD, investigating the frontal lobe in ASD over age would be useful.

While the relationship between frontal lobe volume and autism diagnosis is difficult to discern, should such a relationship exist, it is likely that it is moderated by age [12]. For examples, there is evidence that between two to four years of age, autistic participants, compared to controls, have larger frontal lobe volume [12,13]. The literature between childhood and young adulthood then tends to conclude that ASD diagnosis does not affect frontal lobe volume [12,14,15]. Similarly, during adulthood frontal lobe volume does not differ between ASD and N-ASD groups [16]. The majority of frontal lobe volume studies in the ASD literature include small to moderate samples of autistic participants. Considering the frequent cases of extreme brain volume identified in autistic individuals [17], the findings of studies with small sample sizes may not explain the entire variance of frontal lobe volume among those with ASD.

No investigation of the relationship between ASD and frontal lobe volume, can be conducted without considering biological sex. Piven *et al.* [14] observed smaller frontal lobe volume in autistic females compared to non-autistic (N-ASD) females, but no difference in frontal lobe volume between autistic and N-ASD males. Notably, there was no analysis by age. Hence, separating data on the basis of bio-

logical sex when investigating frontal lobe volume in ASD seems warranted.

As previously mentioned, the ASD literature is yet to analyse frontal lobe volume using a large sample. These issues are often resolved via a meta-analytic approach. However, a meta-analysis does not properly account for outliers, which can be simultaneously high and low, counterbalancing each other, and not therefore reflected in the mean [18]. Simple effects of confounding variables also cannot be explored. Collecting and re-analysing data within biological sex and across age is a more effective method of improving understanding rather than summarising effect sizes (i.e., meta-analytic approach). This enables comparisons in frontal lobe volume between autistic and N-ASD participants for males and females separately at varying age groups. Additionally, re-analysis of frontal lobe volume data would allow for control of confounding effects, such as age, rather than simply summarising effect sizes (i.e., meta-analytic approach), Re-analysing data will incorporate the effects of more extreme cases, improving understanding. The present study collected mostly individual data points from all suitable studies of frontal lobe volume in autistic and in neurotypical individuals, and compared these while simultaneously controlling for the effects of age. This allows a comparison of cases to controls, simultaneously accounting for variance due to age. This more clearly facilitates the analysis of neurophysiological parameters, which vary over age, rather than reliance upon small comparisons that were not controlled for age. Hence the aim of the current study is to re-analyse existing data to establish the trend in frontal lobe volume among data from ASD participants.

Given the inconclusive findings outlined above, we deemed it necessary to more fully investigate comparisons in frontal lobe volume between ASD and N-ASD groups across age and sex. It was hypothesised that frontal lobe volume would be greater in autistic than N-ASD participants between ages two to four years, and not different between ASD and N-ASD groups above four years of age. Additionally, due to the dearth of literature concerning the role of biological sex on frontal volume in autism, we form no hypothesis concerning this. We will explore the effect of biological sex on frontal lobe volume in ASD.

2. Method

A systematic search of the literature was undertaken for studies measuring frontal lobe volume in ASD. Relevant data for N-ASD participants in these studies were also harvested. Inclusion criteria of the present study were that the authors provided raw or mean frontal lobe and age data. Authors were contacted directly to obtain data. However, raw data were not obtained via this method as no author responded to our requests for data necessitating estimation or data capture techniques be used (see [19]). In short, raw data were obtained via data capture techniques [20] from published reports, and from published data sets [12,21].

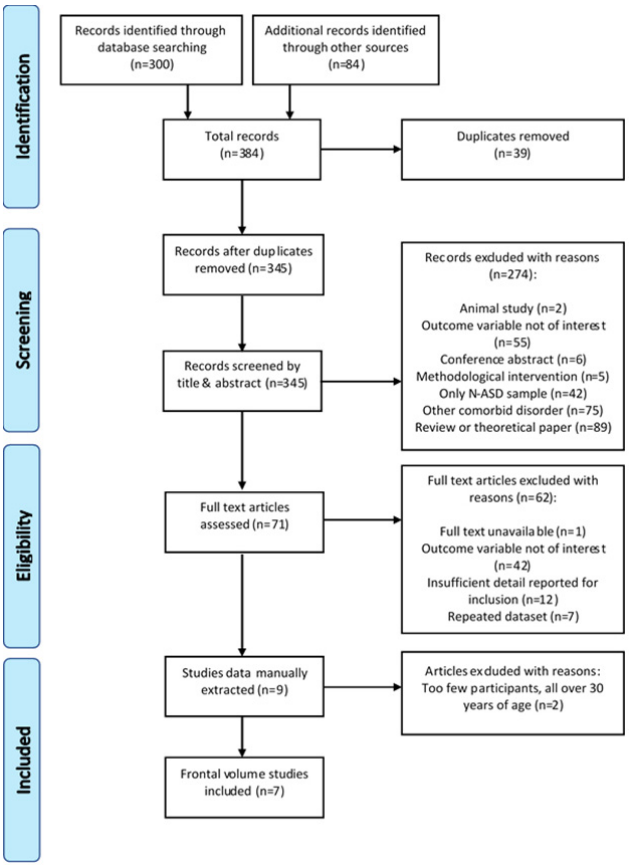

Fig. 1. PRISMA flow chart. ASD, Autism spectrum disorder; N-ASD, non-autistic.

The data capture approach involved transferring figures from publications to be viewed via DataThief vIII^{TM}. We used the figure axes as published and then recorded the co-ordinates of each data point in the figure. We were able to replicate the original results in all instances. In cases where raw data could not be obtained, we statistically modelled these data as the reported mean weighted by the number of cases. Further details of the analysis are published elsewhere [19].

A systematic database search was conducted in April, 2020 on CINAHL Complete, Psychinfo, Embase, MEDLINE Complete, PubMed, Scopus, and Web of Science to retrieve all relevant publications and theses. Databases were searched using the following search string: [("frontal lobe volume" OR "frontal volume" OR "frontal lobe size" OR "frontal size") AND (Autis* OR ASD OR Asperger* OR ASC)]. In addition, Google Scholar and reference lists were searched by scanning titles that included words relating to 'Autism' and 'Frontal lobe volume'.

Including searching reference lists of 84 studies, the systematic search produced 384 results (see Fig. 1). After the removal of duplicates ($n = 39$), various articles were excluded on the basis of title and abstract ($n = 274$). Exclusion criteria included: animal studies ($n = 2$), an outcome variable not of interest ($n = 55$), conference abstract ($n = 6$),

Table 1. Summary of included studies of frontal lobe volume (*n* = 7).

No.	Author & country	Sample size & participant details	Diagnostic criteria	MRI Scanner type	Findings & Effect Size (Cohen's *d*)	Risk of bias
1	Carper, Moses, Tigue and Courchesne (2002) USA [12]	*n* = 77 ASD (*n* = 38) 38 m *M (SD)* = 5.7 (2.2) years N-ASD (*n* = 39) 39 m *M (SD)* = 6.5 (2.5) years	DSM-IV Confirmed using ADI-R and ADOS	GE Signa 1.5-T	ASD >N-ASD[a] at 2–3 years (d = 1.85). NS[a] at 4–7.5 (*d* = 0.28) and 7.5–11 years (*d* = 0.37)	Number of raters of brain scans not reported No report of medication status of participants No report if participants were sedated Male only sample Only PIQ was reported Differing IQ methods between groups MRI scanner only 1.5-T Autistic participants had seizure history (*n* = 7)
2	Hazlett *et al*. (2011) USA [25]	*n* = 95 ASD (*n* = 95) 83 m, 12 f Mean age: 3.5 years	DSM-IV Confirmed using ADI-R and ADOS-G	GE Signa 1.5-T 2D FSE	No comparisons to report	Single rater used to interpret brain scans Medication status of participants not reported Sedation used only for Autistic participants M:F ASD ratio not representative of the general population MRI scanner only 1.5-T Comorbid disorders not in exclusion criteria
3	Miller (2004) USA [21]	*n* = 45 ASD1 (*n* = 28) 28 m *M (SD)* = 14.6 (6.2) years ASD2 (*n* = 14) 14 m *M (SD)* = 12.6 (4.1) years N-ASD1 (*n* = 22) 22 m *M (SD)* = 13.7 (5.2) years N-ASD2 (*n* = 8) 8 m *M (SD)* = 12.6 (3.3) years	DSM-IV Confirmed using ADI-R and ADOS-G	Philips Marconi 1.5-T 3D FSE	NS for ASD1 vs N-ASD1 (*d* = 0.09) and ASD2 vs N-ASD2 (d = 0.76)	Number of raters of brain scans not reported Head motion control not reported on Medication status not reported on Some, not all, participants were sedated Only males included in sample Only PIQ was reported PIQ was significantly different between groups MRI scanner only 1.5-T Other developmental disabilities not included in exclusion criteria
4	Mitchell *et al*. (2009) USA [15]	*n* = 28 ASD (*n* = 14) 12 m, 2 f *M (SD)* = 8.8 (2.6) years N-ASD (*n* = 21) 12 m, 2 f *M (SD)* = 8.4 (2.6) years	DSM-IV Confirmed using ADI-R and ADOS-G	GE Signa 1.5-T 3D SPGR	NS (*d* = 0.60)	Head motion control not reported on Participant medication status not reported Sedation status of participants not reported M:F ASD ratio not representative of the general population IQ differed significantly between groups MRI scanner only 1.5-T Comorbid disorders of ASD not included in exclusion criteria

Table 1. Continued.

No.	Author & country	Sample size & participant details	Diagnostic criteria	MRI Scanner type	Findings & Effect Size (Cohen's *d*)	Risk of bias
5	Nordahl *et al*. (2013) USA [13]	*n* = 45 ASD1 (*n* = 121) 121 m *M (SD)* = 39.8 (5.9) mths ASD2 (*n* = 10) 10 m *M (SD)* = 39.1 (6.0) mths N-ASD (*n* = 50) 50 m *M (SD)* = 39.1 (5.5) mths	DSM-IV Confirmed using ADI-R and ADOS-G	Siemens Tim Trio 3.0-T	ASD1 >N-ASD (*d* = 0.33) and ASD2 >N-ASD (*d* = 1.53)	Number of raters of brain scans not reported Medication status not reported on Only Autistic participants sedated (*n* = 10) Male only sample Other developmental disabilities not included in exclusion criteria
6	Palmen *et al*. (2004) The Netherlands [26]	*n* = 42 HFA (*n* = 21) 19 m, 2 f *M (SD)* = 20.1 (3.1) years N-ASD (*n* = 21) 20 m, 1 f *M (SD)* = 20.3 (2.2) years	DSM-IV Confirmed using ADI-R	Philips NT 1.5-T 3D FFE	HFA >N-ASD (*d* = 0.63)	Participant sedation not reported M:F ASD ratio not representative of the general population MRI scanner only 1.5-T ASD diagnosis not confirmed by ADOS Chromosomal abnormalities related to ASD were not controlled
7	Piven, Arndt, Bailey and Andreasen (1996) USA [14]	*n* = 71 AD (*n* = 35) 26 m and 9 f *M (SD)* = 18.0 (4.5) years N-ASD (*n* = 36) 20 m, 16 f *M (SD)* = 20.2 (3.8) years	DSM-III-R Confirmed using ADI	1.5-T scanner 3D SPGR	NS (*d* = 0.10)	Medication status not reported on M:F ratio was significantly different between groups Only non-verbal IQ was reported MRI scanner only 1.5-T Type of MRI scanner not reported ASD diagnosis not confirmed by ADOS Superseded diagnostic instruments used (ADI and DSM-III-R) Brief exclusion criteria for comorbid disorders

Note. [a] Raw data either provided by the original authors or captured from publication by DataThief vIII^{TM}; AD, Autistic disorder; ADI, Autism Diagnostic Interview; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ADOS-G, Autism Diagnostic Observation Schedule-Generic; ASD, Autism spectrum disorder; Aut, autism; DSM, Diagnostic and Statistical Manual of Mental Disorders; f, female; FSE, Fast Spin Echo; GE, General Electric; m, male; M:F, Male-to-Female ratio; MRI, Magnetic Resonance Imaging; mths, Month(s); N-ASD, Non-Autistic; NS, Non-significant difference; PIQ, Performance IQ; SPGR, Spoiled Gradient Recalled Echo.

studies based on methodology or an intervention (n = 5), studies including only N-ASD participants (n = 42), or participants with another disorder (n = 75), a review or theoretical study (n = 89). Consequently, 71 sources were examined in full-text. Reasons for exclusion at full-text included being unavailable for review (n = 1) as the work was not available where it was referenced as being, and we were not able to otherwise locate it, not measuring frontal lobe volume (n = 42), measuring frontal lobe volume but not providing raw data to be included in the present study (n = 12), or, finally, for using a dataset reported in another study otherwise included in here (n = 7). Data were manually extracted from nine studies. However, due to very limited data in two studies with cases above 30 years of age, there was insufficient data to extract, forcing us to impose a cut-off at 30-years of age. Consequently, an additional two studies were removed, and seven studies remained to be included in the present study.

Where multiple reports were based upon a single dataset, the study reporting the largest sample was used. In cases where raw data were not available, the study that split mean data into smaller groups was selected, giving multiple means, this gave a better approximation of the overall data. Where smaller groups had not been used, and therefore multiple means were not available, but the study had relied upon the data published elsewhere, again, only the study with the largest sample was included. For repeated publications that could not be differentiated on these criteria, those publications with the clearest and most detailed description of recruitment method, frontal lobe volume measurement, and data source were used.

Case severity was considered. However, as severity has been measured in a different manner over different versions of the DSM, this represented a considerable problem. Additionally, as no papers detailed any measure of severity, we were unable to evaluate or control for severity.

The captured and statistically modelled data collected herein were plotted into separate figures for autistic and N-ASD participants. Circles in the figures represent raw data while triangles represent weighted mean values. Figures of only female participants were not included due to insufficient data. Quadratic model fits (SPSS v27, IBM, Chicago, IL, USA) were found to be stronger than loglinear, linear or cubic alternatives, having larger effect sizes and more centrally fitting the data than the other options. Differences between ASD and N-ASD linear and quadratic models were also derived.

Analysis of diagnosis covaried with age was undertaken as an ANCOVA. However, tests of homogeneity of variance-covariance were undertaken, and age was found to violate this assumption. Hence, age was recoded into blocks or grouping [22,23] of approximately equal sample sizes distributed over approximate developmental levels [24] and analysed, and analysed together with its interaction with diagnosis. Thereafter, diagnostic group and age were analysed as independent variables, in a two-way ANOVA.

3. Results

Raw data, or the means and sample sizes of frontal lobe volume and age, were obtained from seven studies of autistic (n = 372), six of which included N-ASD participants (n = 190). A description of each data set is provided in Table 1 (Ref. [12–15,21,25,26]). All autistic individuals had received a formal diagnosis as reported by the authors before participating in the included studies. Each study's initial diagnostic criteria for participants are presented in Table 1. Diagnoses were made by mental health or medical professionals using either DSM-III-R (n = 1) or DSM-IV (n = 6). N-ASD participants were also screened for inclusion in the present study. Of the six studies with N-ASD participants, five screened participants for psychiatric and neurologic disorders [12,13,15,21,26], while one did so briefly (i.e., [14]). Piven *et al*. [14] did not specify that any of the N-ASD participants had disorders, and so were included in the present study. Biological sex compositions of studies were either only male participants [12,13,21], a male-to-female ratio greater than 4:1 [15,25,26] or a male-to-female ratio smaller than 4:1 [14]. Participants' ages ranged either between or within early childhood and younger age groups [13,25], childhood and younger age groups [12], childhood and early adolescence [15], childhood and adulthood [21], or adolescence and adulthood [14,26].

Of the studies that reported technique used to measure brain volume, a 1.5-T scanner (n = 6), or a 3.0-T scanner (n = 1) were employed. The types of 1.5-T scanners were either General Electric Signa (n = 3), Phillips Marconi (n = 1), Philips NT (n = 1), or not reported (n = 1). The 3.0-T scanner was a Siemens Trim Trio. Data was analysed via either Silicon graphic workstations [12], the Expectation Maximization Segmentation image processing tool [25], ANALYZE® biomedical image processing software [21], BrainImage [15], Freesurfer 5.1 (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging. Harvard University, Boston, MA, USA) and Analyze 11.0 software (AnalyzeDirect, Inc. Overland Park, KS, USA) [13], Hewlett Packard Unix 9,000 workstations, a computer server and Pentium III-equipped personal computers [26], or BRAINS software on a Silicon Graphics Personal Iris 4-D graphic workstation [14]. Frontal lobe volume in participants with ASD, compared to N-ASD controls, was either greater [13,26], greater in some age ranges but not different in others [12], or not different [14,15,21]. Frontal lobe volume was based on absolute data for all studies but one, in which data was adjusted [25].

Regression models were fitted to the frontal lobe volume data using age (linear models), and age squared (quadratic models; SPSS v.27; IBM, Chicago, IL, USA; Fig. 2 & Table 2). The quadratic of age was used to model the change with increasing age. For instance, the frontal lobe would be expected to slow its growth at some point.

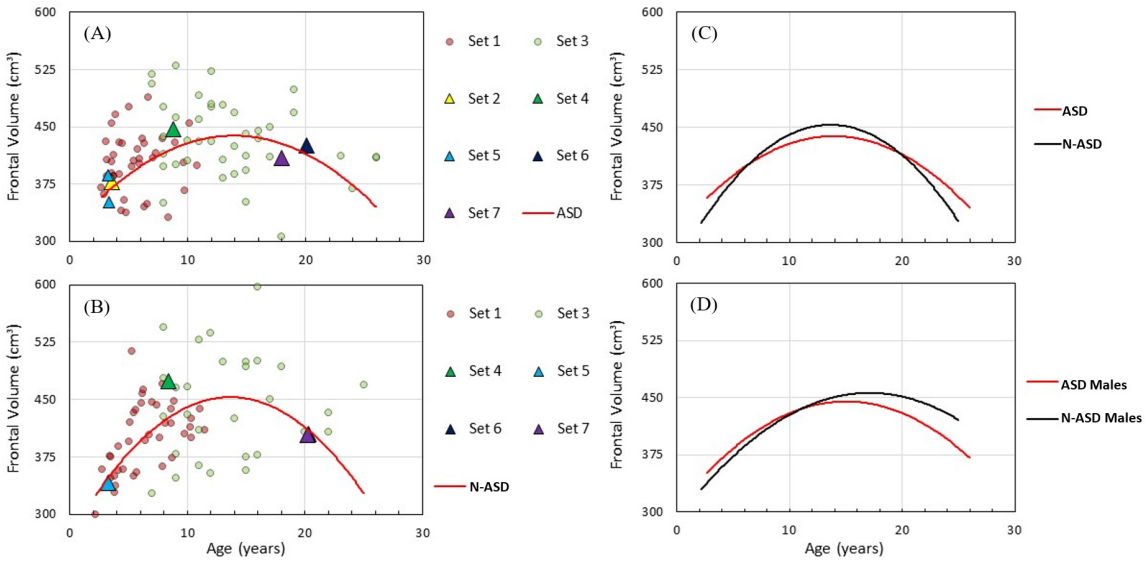

Fig. 2. Raw data (circles) and mean-weighted data (triangles) for frontal lobe volume by age. Set number refers to data in Table 1. Quadratic fits of data are imposed on each figure. (A) ASD; (B) N-ASD; (C) comparison between ASD and N-ASD models; and (D) comparison between models for ASD and NASD males only.

Table 2. Linear and Quadratic model R^2.

				ASD vs N-ASD		Linear vs Quadratic			
						ASD		N-ASD	
Dataset	Model	R^2 ASD	R^2 N-ASD	Z	p	Z	p	Z	p
All data	Linear	0.33	0.14	2.90	0.002	3.48	<0.001	3.28	<0.001
	Quadratic	0.52	0.39	1.98	0.02				
Male only	Linear	0.29	0.30	–0.11	0.46	2.26	0.01	0.69	0.24
	Quadratic	0.46	0.37	1.03	0.15				

A quadratic model enables modelling of this change. A strong quadratic relationship was observed between frontal lobe volume and age for males and females with ASD (R^2 = 0.52), while a moderate to strong relationship was observed for N-ASD data (R^2 = 0.39, Fig. 2A,B). Curve-fits were compared by Fisher's transformations [22,27]. When all data were considered, the curve-fit for ASD differed from the curve-fit from N-ASD data (see Table 2). When male only data was considered the curve-fits for those with ASD did not differ from N-ASD data. Among data for ASD, linear models accounted for significantly less variance than quadratic models in both datasets (all data & male only). In N-ASD data, a difference between linear and quadratic models was only found when all data was used.

Differences in mean frontal lobe volume between the raw data of autistic and NASD participants were also assessed via one-way ANCOVA controlling for age. However, in assumption checking, the covariate age was found to interact with diagnosis ($F_{(1,144)}$ = 5.719, $p < 0.05$, η^2 = 0.038), violating the assumption of homogeneity of regression. Thus, age was blocked into groups (see Table 3) and treated as an additional IV [22]. The groups were chosen

Table 3. Assessment of frontal lobe volume differences between diagnostic groups.

Age group	Data points		F	df	p	η^2
	ASD	N-ASD				
2–4 years	21	12	12.965	1, 31	0.002	0.291
5–8 years	24	26	0.246	1, 48	0.725	0.005
9–12 years	16	17	2.474	1, 31	0.170	0.074
13–17 years	14	10	2.676	1, 22	0.116	0.108
18+ years	9	7	0.642	1, 14	0.260	0.044

on the basis of approximately homogenous developmental periods that would give reasonable sample sizes within each group. Age group and diagnosis were found to interact ($F_{(4,146)}$ = 2.972, $p < 0.05$, η^2 = 0.075), necessitating tests of simple main effects. Prior to these, tests of main effects were examined. Overall, diagnosis was not found to differ by group ($F_{(1,146)}$ = 0.224, p = 0.637, η^2 = 0.002), but a main effect was noted for age group ($F_{(4,146)}$ = 6.133, $p < 0.001$, η^2 = 0.144). Thereafter, tests of simple main effects were evaluated, assessing the effect of diagnosis within each age group, and the effect of age group

within each diagnosis. Age group was significant within autistic data ($F_{(1,79)} = 3.538$, $p < 0.01$, $\eta^2 = 0.152$) and within NASD data ($F_{(1,67)} = 4.117$, $p < 0.005$, $\eta^2 = 0.197$). Diagnosis effects were analysed within age group and are presented in Table 2. The only significant difference by diagnosis within an age group was within the group 2- to 4-years of age ($F_{(1,31)} = 12.965$, $p < 0.01$, $\eta^2 = 0.291$), with autistic data being greater than NASD. For the remaining age groups, frontal lobe volume was not different between autistic and N-ASD participants.

4. Discussion

The aim of the present study was to investigate frontal lobe volume in autistic and NASD individuals over age. In the present study, the inclusion of age provided a unique window into the development of the frontal lobe in ASD. Frontal lobe volume between two to four years was greater in autistic than N-ASD males. For the remaining age groups, frontal lobe volume was not different between autistic and N-ASD participants. The model fits for frontal lobe volume over age were different between autistic and N-ASD participants. Hence, we conclude that the trend of frontal lobe volume over age is different in autistic individuals. These differences in frontal lobe volume are evident early in development and appear to dissipate with age.

The present study highlights multiple developmental aspects of frontal lobe volume that contrast between autistic and N-ASD participants below 30 years of age. First, the ASD and N-ASD lines of fit were significantly different. This suggests that frontal lobe volume in ASD varies from typical development in early ages. Although these lines of fit were based on data older than two years, this finding suggests that frontal lobe volume in autistic individuals during early years is different in size than expected. Measurements of frontal lobe volume for autistic participants under two years of age are yet to be published. Future research should aim to address this research gap. Second, the linear and quadratic lines of fit in the present study were different by diagnosis group; compared to typical development, the rate of frontal lobe volume growth and the change in such growth rate are different in autistic individuals. The differences in linear models reflects the difference in underlying trend between the groups. The differences in quadratic growth between ASD and NASD arose because of the larger frontal lobe volume in ASD than in N-ASD between two to four years of age, which dissipated with age. This single difference is sufficient to cause a difference in change in growth, which is reflected in the quadratic term.

Consistent with past literature [12,13], autistic participants had greater frontal lobe volume than controls between two and four years of age in the present study. Frontal lobes are important for the higher order, top down control that is essential for complex emotional and social interactions, as well as fluid and mature motor control [28]. These functions tend to be impaired in ASD [29,30], and may be more so between two to four years [12]. Additionally, many other neural developmental processes accelerate through two to four years of age. For instance, fibre density and volume in the Corpus Callosum have been found to demonstrate the greatest acceleration in increase though two to four years of age [31]. Others have reported that Corpus Callosal fibre projections reach a peak around 2.5 years of age [32]. Considerable neural reorganisation has been observed though this early period of development as well, with differences between ASD and N-ASD groups, from gene expression, to total brain volume, and including changes in protein folding [33]. Various cognitive processes accelerate in the period two to four years of age. For instance, considerable vocabulary and language development occurs through this period [34]. Limited research highlight that early frontal lobe hypertrophy in toddlers with ASD was largely attributed by prefrontal hypertrophy [12]. Regardless of the specific origin of abnormality, these abilities influenced by the frontal lobe relate to praxis abilities; skilled motor gestures that cannot be explained by fundamental movement skills [35]. Praxis abilities are known to be impaired in autistic children [36], and older children and adolescents [37]. Considering the feasibility and simplicity associated with assessing motor skills during early years [38], this is a particularly important area for researchers to further pursue.

Biological explanations for varying volumes of frontal lobe volume in ASD, compared to typical development, have been published elsewhere [39]. In summary, microglia in autistic individuals are readily activated in the frontal lobe [40]. This may influence neuronal networks, and consequently explain the enlarged volumes in ASD during two to four years of age. For instance, greater density of minicolumns and smaller width between these minicolumns in the frontal lobe have been observed more frequently in autistic than N-ASD post-mortem cases older than four years of age [41,42]. Minicolumns are locally connected neuronal networks with radial neuronal projections that function as an essential cortical information processing unit [43]. Although the present study does not find any support for this finding at that age range, those findings relied upon a small number of cases. Hence, our findings may not explain the entire variance of density and width of minicolumns in the frontal lobe of individuals with ASD. Alternatively, it may be that greater density of, and smaller width between, minicolumns does not necessitate enlarged frontal lobes. Nonetheless, future studies should confirm this speculation and examine the relationship between frontal lobe volume, and the density and number of minicolumns in ASD between two- and four-years of age. It may be asked why this development was limited to the period two to four years of age. The studies noted here indicated the changes peaked in the range two to four years of age, and thereafter reduced. This coincides with the major phase of cognitive development in children, after which neural development is reduced [24].

5. Limitations

In spite of the comprehensive dataset of the present study, limitations were evident. First, high variance was observed in the data within studies, even when investigating males separately. This reduces the effectiveness of the lines of fit to explain data. Although diagnostic status and IQ do not moderate the relationship between ASD diagnosis and frontal lobe volume in adults [16], such variables may explain the variance in other age groups. Some might suggest that the differences in scanners and parameters set within machines and analyses may account for the heterogeneity of the data. However, the issue we highlight here is the consistency of trend across the data, with the only noted difference found between ASD and NASD in the 2- to 4-year age group, which were found within single machines, made apparent by our combining data. Second, there was considerable variance between studies. This is likely due to the different image processing techniques used between studies. Controlling for site of study was not possible herein due to the limited included studies. Additionally, methods for measuring frontal volume were inconsistently reported, and so we were not able to control for this. Consequently, our findings may be influenced by methodological characteristics of previous studies. As each group of researchers implements their own unique method to obtain brain volume data, controlling for imaging acquisition is difficult. We encourage future research to develop a protocol that is feasible and effective, to ensure consistency between studies. Third, frontal lobe volume data were lacking for females and older adults. Consequently, lines of fit and mean brain size could not be analysed in females and older adults. In light of ASD not being the male dominant disorder it was once thought to be [44] and with the aging of the population [45], future research should continue to investigate the relationship between frontal lobe volume and ASD diagnosis in females and older adults. Alternatively, this may have been affected by publication bias. Although the literature was systematically searched, the possibility of relevant studies not being included in the present study should be considered. Fourth, one study included longitudinal data and used adjusted, rather than absolute, data [25]. Consequently, adjusted data with repeated cases were included in the cross-sectional analyses. Considering the large sample size of the present study, and that these data were only included in the line of fit analyses, these cases did not severely influence the findings. Nonetheless, this potential bias should be considered. Last, some of the age range analyses were largely represented by either few studies (i.e., adulthood) or a single study (i.e., mean group comparisons between two- to four-years). The findings of these age ranges may have been influenced by the methodological characteristics of the included studies (i.e., MRI resolution based on mostly 1.5 T scanners). These findings should thus be interpreted cautiously until more data is obtained for these age ranges.

6. Conclusions

The findings of the present study indicate that the relationship between ASD diagnosis and frontal lobe volume is dynamic over age; that is, frontal lobe volume is different in ASD compared to typical development, particularly during infancy. While we suggest continued investigation across neuroimaging datasets in ASD, it will also be important to acquire comprehensive clinical information (e.g., clinical, neuropsychological, and genetic assessment) to determine the likely causes and consequences of these developmental differences in frontal lobe volume.

Abbreviations

AD, Autistic disorder; ADI, Autism Diagnostic Interview; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ADOS-G, Autism Diagnostic Observation Schedule-Generic; ASD, autism spectrum disorder; Aut, autism; DSM, Diagnostic and Statistical Manual of Mental Disorders; f, female; FSE, Fast Spin Echo; GE, General Electric; IQ, Intelligence Quotient; m, male; M:F, Male-to-Female ratio; MRI, Magnetic Resonance Imaging; mths, Month(s); NASD, Non-Autistic; NS, Non-significant difference; PIQ, Performance IQ; SPGR, Spoiled Gradient Recalled Echo.

Author contributions

JC attained and analysed the data of the present study, and prepared the initial manuscript for publication. PGE and CH contributed to the project's conceptions, analysis of data, and preparation of the manuscript. MAS supervised the project throughout its development, directed aspects of statistical analysis, recommended key changes to improve the quality of the present study, and addressed all revisions. All authors read, edited, and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Data accessibility

Data access can be obtained by contacting the corresponding author via email. Data will be provided in all reasonable requests.

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