Managing aggression in autism spectrum disorder: A cerebellar neuroscience approach

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Abstract (219 words)

Background: Understanding the neurological processes underpinning the elevated aggression rate in autism spectrum disorder may be the key to more effective treatment. Previous research implicates the cerebellum in aggression, specifically lobules right Crus I and II and VIIIA/B.

Objective: This study investigated the relationship between cerebellar grey matter volumes and aggression in children with ASD and neurotypical children, and verbal IQ as a possible moderator.

Methods: Volumetric data from 200 3T MRI scans of children with ASD and neurotypical children, ages 8-13, was used. The aggression measures were extracted from the Child Behavior Checklist.

Results: The stepwise regression analysis showed a significant relationship between the grey matter volume of right lobule VIIIA and aggression scores in children with ASD. Verbal IQ had no moderation effect.

Discussion: Aggression in children with ASD may stem from impaired somatosensory processing since overstimulation can lead to aggression. This may explain the implication of right lobule VIIIA as it plays a role in sensorimotor processing. The effect was found in the right posterior area of the cerebellum, which corroborates the contralateral association with the frontal cortex, where aggression correlates with relatively higher activity in the left hemisphere.

Conclusion: This explorative study yielded many leads for future research on the implication of the right posterior cerebellum in aggression, its treatment in children with ASD, and the role of impaired somatosensory processing.

Keywords: Autism spectrum disorder, aggression, cerebellum, lobular grey matter volumes, verbal IQ

Abbreviations

ASD	–	Autism Spectrum Disorder
ADHD	–	Attention Deficit Hyperactivity Disorder
ODD	–	Oppositional Defiant Disorder
NT	–	Neurotypical
sMRI	–	Structural Magnetic Resonance Imaging
fMRI	–	Functional Magnetic Resonance Imaging
ABIDE	–	Autism Brain Imaging Data Exchange
CBCL	–	Child Behavior Checklist
VIQ	–	Verbal Intelligence Quotient
WISC	–	Wechsler Intelligence Scale for Children
WASI	–	Wechsler Abbreviated Scale of Intelligence
SNR	–	Signal To Noise Ratio
ICV	–	Intracranial Volume
MANOVA	–	Multivariate Analysis Of Variance
MANCOVA	–	Multivariate Analysis of Covariance

Introduction

Autism Spectrum Disorder (ASD) is a developmental disorder with a heterogeneous presentation of clinical symptoms (Lord, Elsabbagh, Baird, & Veenstra-Vanderweele, 2018). The main diagnostic criteria include impairments in social interaction and restricted, repetitive behaviors (American Psychiatric Association, 2013). Psychiatric comorbidity is prevalent in ASD and includes social anxiety disorder, attention deficit hyperactivity disorder (ADHD), and oppositional defiant disorder (ODD) (Simonoff et al., 2008).

ASD and its comorbid disorders ADHD and ODD have been linked to deficits in emotion regulation (Schoorl, Rijn, Wied, Goozen, & Swaab, 2016). This impaired emotion regulation increases the likelihood of aggressive behavior. In under-regulation of emotion, the individual doesn't sufficiently contain a difficult emotion, resulting in impulsive and non-constructive behavior. Contrarily, over-regulation is the use of emotion regulation strategies to stop the individual from experiencing or displaying difficult emotions, resulting in high physical, emotional, and social costs. In under-regulation, there is a decreased coping ability, while in over-regulation there is an increased, but dysfunctional coping ability (Roberton, Daffern, & Bucks, 2012). Both over- and under-regulation of emotions have previously been found in people with ASD and can lead to aggression (Mazefsky et al., 2013).

Aggression in its broadest sense it can be defined as hostile, injurious, or harmful behavior resulting from frustration. It can be classified in numerous ways, for example in impulsive and premeditated aggression (Siever, 2008). Premeditated aggression is a planned behavior with a clear goal and has not been linked to ASD by previous research (Stanford, Houston, Villemarette-Pittman, & Greve, 2003). Contrarily, impulsive aggression is behavior resulting from negative emotions or stress and has been identified and addressed as a therapeutic target in ASD (Jensen et al., 2007).,

The importance of aggression as an objective for treatment in children with ASD is underlined by its adverse effects. Increased aggression rates found in children with ASD negatively affect social relationships and the quality of the support they receive (Fitzpatrick, Srivorakiat, Wink Ernest V Pedapati, & Erickson, 2016). Aside from its direct adverse effects, increase aggression also has secondary harmful effects. For example, research has shown that anger-focused rumination is more prevalent in adolescents with ASD. Rumination can be defined as unyielding thoughts revolved around a negative emotion or situation, in this case, anger. The adverse effects of this increased anger-focused rumination include poorer functioning, more depression symptoms, and overall emotional and behavioral dysregulation (Patel, Day, Jones, & Mazefsky, 2017). These findings emphasize the clinical relevance of researching anger and aggression in children and adolescents with an ASD diagnosis.

An interesting research direction is the implication of language ability in aggression among children with ASD. Language ability refers to language-related skills, like mechanics, vocabulary, and expression (Petersen et al., 2013). The language-aggression hypothesis (Montare & Boone, 1973) proposes that children with poorer language skills exhibit more aggression as opposed to children with better language skills. The researchers suggested that improving language proficiency can reduce aggression. Recent studies also implicate language delays in aggressive behavior (Clark, Menna, McAndrew, & Johnson, 2020; Gremillion & Martel, 2014; M. V. Wang, Aarø, & Ystrom, 2018). A study by Clark et al. from 2020 specifically suggests decreased or delayed self-awareness and self-regulation resulting from the decreased language ability as the cause of the aggression. This implication of self-regulation links back to the association between aggression and emotion regulation ability. The relationship between language ability and aggression was also found

specifically in children and adolescents with ASD (Kanne & Mazurek, 2011), solidifying the relevance of this research angle for this specific clinical population.

Currently, language ability is not a specific target in the treatment of aggression in children with ASD. Instead, non-pharmacological treatment options revolve mostly around increasing self-awareness and self-regulation to divert aggressive behavior to more appropriate and productive behavior, which is associated with language ability, as suggested by Clark et al., 2020. Pharmacological treatments include multiple medication options, like first- and second-generation antipsychotics, antiepileptic medications, and mood stabilizers (Fitzpatrick et al., 2016). The neurobiological background of these symptoms, and by extension the working mechanism of these medications, is not well understood. Therefore, understanding the neurological processes underpinning the elevated aggression rate in ASD may be the key to more effective pharmacological treatment of this issue.

Previous research into the neurobiological background of aggression has established that dysregulation in a corticolimbic network is associated with aggressive behavior (Siever, 2008). The inadequate regulation of the amygdala by the prefrontal cortex increases the likelihood of aggression (Coccaro, Sripada, Yanowitch, & Phan, 2011). Anger after provocation results in enhanced amygdala activation in healthy subjects (Yu, Mobbs, Seymour, Rowe, & Calder, 2014). Lateral prefrontal cortex activation has an opposite effect as it decreases aggressive reactions in anger-provoking situations (Achterberg, van Duijvenvoorde, Bakermans-Kranenburg, & Crone, 2016). Another study showed a reduced blood flow to the prefrontal cortex in an unrestrained aggressive scenario in healthy volunteers (Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000). Structural data also supports the implication of the corticolimbic network in aggression. Reduced grey matter volumes in the amygdala and prefrontal cortex were linked to antisocial traits, including aggression (Ermer, Cope, Nyalakanti, Calhoun, & Kiehl, 2012; Gregory et al., 2012). Based on substantial previous research, the functioning of the amygdala-cortical network seems crucial to the prevention of aggressive behavior.

In addition to the amygdala-cortical centered models, there is a growing body of evidence implicating the cerebellum in aggression, though its specific role is not yet completely understood. Aside from its functional connectivity to the previously mentioned brain areas (Habas et al., 2009), evidence for the relationship between the cerebellum and aggression is also found in lesion studies (Schmahmann, 2000; Schmahmann, Weilburg, & Sherman, 2007). These studies show that damage to the cerebellum, specifically the vermis, increases aggressive and impulsive behavior. Multiple brain stimulation studies in animals (Jackman et al., 2020; Lisander & Martner, 1971; Zanchetti & Zoccolini, 1954), as well as humans (Heath, Dempesy, Fontana, & Meyers, 1978; Heath, Llewellyn, & Rouchell, 1980), also indicate a role for the cerebellum in aggression.

These indications of the involvement of the cerebellum in aggression from lesion and brain stimulation research, are also found in fMRI research. A recent meta-analysis of 28 previous studies by Klaus & Schutter from 2021 showed multiple activation clusters from fMRI scans in the cerebellum associated with anger and aggression. For anger, significant activation clusters were found in the right cerebellar hemisphere, specifically in Crus I and II ($P < .001$). A lower threshold of $P < .01$ yielded activation clusters in the bilateral Crus I and II, right regions of lobule VI, and left regions of lobules VIIIA, VIIIB, and X. Three significant ($P < .001$) activation clusters in the bilateral anterior cerebellum were found in the aggression condition. The more lenient analysis ($P < .01$) revealed an additional cluster in the right hemisphere of Crus II and lobule VIIB.

There are also volumetric indicators for aggression in the cerebellum suggested by previous studies. However, the findings are variable, possibly due to the challenges of testing in psychiatric populations, like small samples and possible covariates. Multiple studies in violent offenders found

larger grey matter volumes in the right cerebellum and smaller volumes in the left cerebellum (Bertsch et al., 2013; Sajous-Turner et al., 2020; Tiihonen et al., 2008). Another study on aggressive versus non-aggressive schizophrenia patients showed reduced grey matter volumes bilaterally in the cerebellum (Puri et al., 2008). No studies on cerebellar volumes and aggression were found with an ASD-diagnosed study population.

However, multiple previous studies do show structural differences in the cerebellum between people with ASD and neurotypical (NT) people (Hashimoto et al., 1995; Piven, Saliba, Bailey, & Arndt, 1997; Stoodley, 2014, 2016; Stoodley & Schmahmann, 2010; Verhoeven, Cock, Lagae, & Sunaert, 2010). One specific study showed a reduced grey matter volume in the right Crus I/II and an increased grey matter volume in the vermis VIIIA/VIIIB in children aged 8 to 13 with an ASD diagnosis (D'Mello, Crocetti, Mostofsky, & Stoodley, 2015). Especially the structural difference in the right Crus I/II is interesting since this region is also associated with anger and aggression (Klaus & Schutter, 2021).

In summary, previous research showed a link between aggression and the cerebellum, the cerebellum and ASD, and ASD and aggression, but these three factors have not been explored together. Additionally, verbal IQ may be a moderating factor in this relationship.

Research aims

Primary research aim

To explore the relationship between the lobular grey matter volumes of the cerebellum and aggression in ASD-diagnosed and NT children.

Secondary research aims

1. To investigate the differences in grey matter volumes of cerebellar regions of interest between ASD-diagnosed and NT children.
2. To examine the relationship between the differences in cerebellar lobular volumes found in secondary aim 1 and aggression.
3. To explore verbal IQ as a moderating factor in the relationships between lobular grey matter volumes and aggression.

Hypotheses

Based on the study by D'Mello, Crocetti, Mostofsky, & Stoodley from 2015 with children of similar ages, the researchers expect to find a reduced grey matter volume in right Crus I/II and an increased grey matter volume in lobules VIIIA/VIIIB. These lobules are designated regions of interest for the statistical analysis. As an exploratory aspect, volumetric data from other lobules was also assessed for between-group differences.

Since Crus I and Crus II have previously been implicated in aggression responses, an inverse relationship between the grey matter volumes of these lobules and aggression is anticipated.

Lastly, VIQ is expected to show a moderating effect on the relationship between lobular grey matter volumes and aggression scores, because a higher VIQ increases the capacity for self-expression and self-regulation, which decreases aggression.

Methods

The data from this study stems from the Autism Brain Imaging Data Exchange (ABIDE) initiative. ABIDE is a repository where datasets of ASD brain research from more than 24 research sites are combined to create large collections of data available for analysis (Martino et al., 2017). Our sample was from the second ABIDE data collection.

The two sites our subjects were sampled from were Georgetown University and Kennedy Krieger Institute. There were no relevant or notable differences in their in- and exclusion criteria, method of recruitment, and scanning procedure. Georgetown University used a Siemens Trio 3-T scanner and the Kennedy Krieger Institute used two Philips 3T scanners to obtain the images.

Participants

In total, data from 100 subjects with ASD and 100 NT subjects was analyzed. The selection was made based on the availability of measures for the Autism Diagnostic Observation Scale (ADOS), Child Behavior Checklist (CBCL), and Wechsler Intelligence Scales. Subjects without verbal IQ scores (n=2) and aggression scores (n=1) were excluded from analyses involving these scores.

Participants with an autism spectrum disorder diagnosis were given this diagnosis by a master's level or higher psychologist. The diagnosis was confirmed through the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, Le Couteur, & Free Hospital, 1994) and the Autism Diagnostic Observation Schedule — Generic (ADOS-G; Lord et al., 2000) module 3.

Descriptive variables of the sample are shown below in table 1. The ASD group has significantly higher aggression scores, as was anticipated. The sample of children with ASD also consisted of more males and as males generally have larger heads, had larger intracranial volumes.

*Table 1 Descriptive analysis of the sample. Significant results are indicated with a *.*

Variable	**ASD**	**NT**	**Between-group difference**
Age	M=10.58; SD=1.56	M=10.41; SD=1.51	t(198)=0.922, p=0.358
Sex (males/females)	M: 79; F: 21	M: 50; F: 50	$X^2(1)=18.364$, p<0.001*
Combined aggression score	58.84 (8.43)	51.94 (3.84)	t(138.573)=7.436, p<0.001*
VIQ	114.87 (16.97)	118.72 (14.48)	t(191.289)=-1.717, p=0.088
Intracranial volume in cm^3	1484.91 (123.73)	1436.27 (134.55)	t(198)=2.661, p=0.008*
males	1514.27 (114.70)	1504.52 (123.74)	
females	1374.43 (90.86)	1368.02 (108.44)	
Total cerebellar volume in cm^3	134.67 (12.99)	133.92 (12.96)	t(198)=0.408, p=0.683
Left cerebellar hemisphere volume in cm3	67.54 (6.54)	67.11 (6.37)	t(198)=0.468, p=0.640
Right cerebellar hemisphere volume in cm3	67.13 (6.50)	66.80 (6.62)	T(198)=0.347, p=0.729

Aggression score

Aggression scores were extracted from the Child Behavior Checklist (CBCL), which is a standardized list, where parents can indicate for 64 behaviors whether their child exhibits this often (2), sometimes (1), or not at all (0). These behaviors are divided into six categories, and their points add

up to form a total score for these categories. Aggression is one of these categories. The scores can fall in a normal range (T score of 50-67), borderline range (T score of 67-70), or clinical range (T score of 70-100) (Thomas M. Achenbach, 2011).

The aggressive behavior scale of the CBCL has a high test-retest reliability (Cronbach's α=0.94). Additionally, the stability is high, with Pearson correlations of 0.82 for a 12-month interval and 0.81 for a 24-month interval (Achenbach & Rescorla, 2000). For the specific population of people with ASD, the test had a similarly high reliability score (Cronbach's α=0.89) (Dill, Pandolfi, & Magyar, 2009). The aggression scores from the CBCL mainly indicate impulsive aggression (Ducharme et al., 2011).

The CBCL is also used to calculate a score for oppositional defiant problems (Thomas M Achenbach, Dumenci, Rescorla, & College, 2001). As most of the diagnostic criteria are related to aggressive or angry behavior (American Psychiatric Association, 2013) and the oppositional score has a significant correlation with the aggression score ($r(199)=0.920$, $p<0.001$), the aggression and oppositional scores were combined to form the combined aggression score used in the analysis.

Verbal Intelligence

Three different versions of the Wechsler Scales of Intelligence were used to obtain verbal IQ (VIQ) scores; the Wechsler Intelligence Scale for Children-4 (WISC-IV) (n=108), WISC-V (n=1), and Wechsler Abbreviated Scale of Intelligence (WASI) (n=90). They are individually administered, standardized procedures consisting of different sets of subtests to assess different elements of intelligence. Scores range from 40-160 with a mean of 100 and a standard deviation of 15. Scores between 40 and 54 are classified as 'moderate mental retardation' and scores higher than 130 are considered 'very superior' (Luiselli et al., 2013).

Image data extraction

3T MRI scans were processed with the Ceres 1.0 pipeline of volBrain, an automatic MRI brain volumetry system (Manjón & Coupé, 2016). Ceres 1.0 is a patch-based multi-atlas segmentation tool that uses a training library of manually segmented cerebellar data to automatically segment new cases (Romero et al., 2017). The volumetric data is segmented in the different cerebellar lobules as depicted in Figure 1 A and B. Figure 1 C shows an illustration of a sMRI scan of one of the subjects, oriented to show the cerebellum and visualized with the program 3D slicer (Fedorov et al., 2012).

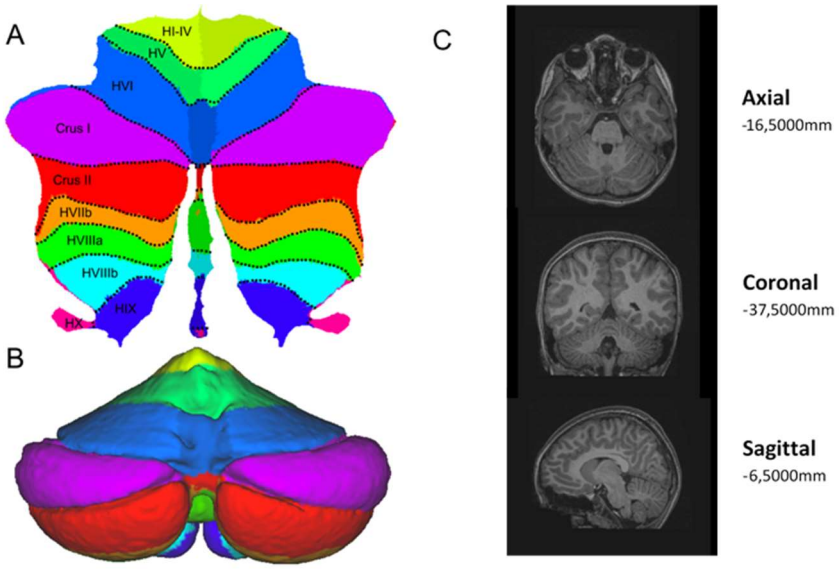

Figure 1 Atlas of the cerebellar lobules (A) Cerebellar lobules projected on a flatmap (B) The data from the flatmap projected on a posterior view of the cerebellum (Diedrichsen & Zotow, 2015) (C) example of a scan visualised with 3D slicer

For the total cerebellum and its separate lobules, the volumetric data extraction yielded measures for total volumes (grey and white matter combined), cortical thickness, and grey matter volumes. In these measures, a distinction was made between the total area and the left and right hemispheres. The output was expressed in volume (cm^3), percentage (%), and asymmetry in the lobule. In the analysis, only the grey matter volumes in cm^3 were used.

Data analysis

Statistical analysis was conducted using SPSS (IBM Corp., 2020). First, qualitative checks were conducted by assessing the signal-to-noise ratio of the scans. Between-group and between-site differences in SNR were evaluated with an independent sample t-test, to determine whether SNR must be included in the covariate analysis. A Levene's test for equal variances was conducted to determine whether to report the output assuming equal or unequal variances. If Levene's test yields a significant result, the corrected results of the t-test are reported, indicated by a decimal number for df.

Cerebellar volumes are correlated to the total brain volume. The ASD group consisted of more men and men generally have a bigger head, and therefore a larger brain volume. Therefore, intracranial volume (ICV) as a proxy for total brain volumes was used to control for the main effect of the between-group differences in sex. Since this is not the only possible effect from the higher amount of men in the ASD sample, sex was also included separately in the covariate analysis.

To assess between-group differences in lobular grey matter volumes of the determined regions of interest, Crus I/II and VIIIA/B, a multivariate analysis of variance (MANOVA) analysis was conducted. Levene's test for equal variances was used. Findings were controlled for possible covariates found before. A similar procedure was followed for the explorative analysis of the remaining lobules. Due to the exploratory nature of this study, no correction for multiple testing was applied. The possibility of ICV, SNR, and sex being covariates was checked using a multivariate analysis of covariance (MANCOVA).

To examine the relationship between the differences in cerebellar lobular volumes found in the MANOVA analysis and aggression, a stepwise linear regression analysis was conducted. Data from the NT group was excluded because there was not sufficient variation in the aggression score to establish a reliable analysis (refer to table 1). The assumption of normality was confirmed with a one-sample Kolmogorov-Smirnov test ($D(100) = 0.06$, $p = 0.200$).

A similar procedure was followed for the explorative analysis of the lobules that showed no significant between-group differences in grey matter volume. The found relationships between lobular grey matter volumes and aggression scores were controlled for covariates ICV, SNR, sex, and VIQ scores.

Lastly, a moderation analysis was conducted to investigate VIQ as a possible moderator in any significant lobular grey matter-aggression relationship.

Results

Qualitative checks

All scans had a signal-to-noise ratio (SNR) of higher than 5, the cut-off value for an acceptable scan (Jose Manjon, personal communication, 6/3/2021). There was a significant difference between sites in SNR (t(144.367)=6.103, p< 0.001). Scans from Georgetown University had a higher SNR (M=9.86; SD=1.37) compared to the Kennedy Krieger Institute (M=8.13; SD=2.44), indicating that the Georgetown University scans were of better quality as compared to the Kennedy Krieger Institute scans.

There was also a significant between-group difference. SNR is approximately half a point higher in the ASD group (M=9.34; SD=2.04) compared to the NT group (M=8.74; SD=2.19). This difference is statistically significant; t(198)=2.019, p=0.045. Therefore, SNR was added as a covariate in the between-group analyses.

Volumetric differences between ASD and NT

Regions of interest

Results of the analysis of the lobular volumetric data can be found in Table 2. The statistical analysis of the volumetric data showed no significant differences in Crus I and II, nor in lobule VIIIA.

*Table 2 Results of the statistical comparison of volumetric data from de ASD and HC groups. Significant results are indicated with a * and results that stayed significant after the covariates analysis are indicated by **. Only results of the ROI and statistically significant results are displayed.*

Lobule		**ASD Mean (SD)**	**HC Mean (SD)**	**Between-group difference**
Crus I	*Right*	11,90 (1,71)	11,76 (1,63)	t(198)= 0,598, p=0,551
Crus II	*Right*	7,84 (1,26)	8,13 (1,41)	t(198)= -1,550, p=0,123
VIIIA		10,97 (1,52)	10,81 (1,57)	t(198)=0,726, p=0,469
	Left	5,55 (0,82)	5,51 (0,87)	t(198)=0,337, p=0,736
	Right	5,42 (0,80)	5,30 (0,80)	t(198)=1,037, p=0,301
VIIIB		7,38 (1,09)	7,02 (1,10)	t(198)=2,338, p=0,020 *
	Left	3,66 (0,59)	3,53 (0,59)	t(198)=1,565, p=0,119
	Right	3,72 (0,58)	3,49 (0,59)	t(198)=2,789, p=0,006 *
I-II		0,077 (0,030)	0,066 (0,023)	t(198)=2,771, p=0,006 *
	Left	0,035 (0,015)	0,030 (0,013)	t(198)=2,618, p=0,010 **
	Right	0,042 (0,017)	0,036 (0,012)	t(180,47)=2,567, p=0,011 *
X		1,12 (0,19)	1,05 (0,17)	t(198)=2,805, p=0,006 *
	Left	0,57 (0,10)	0,53 (0,084)	t(198)=2,578, p=0,011 *
	Right	0,55 (0,11)	0,51 (0,090)	t(198)=2,625, p=0,009 *

Analyses showed that grey matter volumes of the total and right side of lobule VIIIB were significantly higher in de ASD as compared to the NT group. This effect remained significant for the right side of the lobule after controlling for ICV (F(1,197)=4.075, p=0.045) and SNR (F(1,197)=6.175, p=0.014). However, it disappeared after controlling for sex (F(1,197)=2.625, p=0.107). For the total volume the significant difference disappears when controlled for ICV (F(1,197)=1.882, p=0.172), SNR (F(1,197)=3.809, p=0.052) and sex (F(1,197)=0.887, p=0.347).

Explorative analysis of other lobules

Total, right, and left grey matter volumes of lobule I-II were significantly larger in the ASD group than in the control group. This effect remained significant after controlling for SNR for total

(F(1,197)=7.438, p=0.007), right (F(1,197)=6.290, p=0.013) and left grey matter volume of lobule I-II (F(1,197)=6.734, p=0.010). ICV was not a covariate either for total (F(1,197)=5.124, p=0.025), right (F(1,197)=3.959, p=0.048) and left volume (F(1,197)=5.020, p=0.026). However, after controlling for sex, the significant difference disappears for total (F(1,197)=3.623, p=0.058) and right grey matter volume (F(1,197)=2.114, p=0.148). For the left hemisphere the difference stayed significant (F(1,197)=4.457, p=0.036).

Additionally, the grey matter volumes of the total, right, and left side of lobule X were significantly higher in the ASD group. This effect remained significant after controlling for SNR for total (F(1,197)=5.769, p=0.017), right (F(1,197)=5.221, p=0.023) and left grey matter volume (F(1,197)=4.643, p=0.032). ICV was not a covariate either for total (F(1,197)=4.684, p=0.032) and right grey matter volume (F(1,197)=4.221, p=0.041). It was for left grey matter volume (F(1,197)=3.762, p=0.054). However, after controlling for sex, the significant difference disappears for total (F(1,197)=3.190, p=0.076), right (F(1,197)=2.750, p=0.099) and left grey matter volume (F(1,197)=2.703, p=0.102).

Relationship lobular grey matter volumes and aggression

The volumetric data of the left hemisphere of I-II yielded no significant relationship with aggression scores (the excluded variables from the stepwise regression can be found in appendix 1). Only the grey matter volume of the right VIIIA showed a significant effect on aggression in the ASD group (F(1,98)=12,793, p=0,001, R^2=0,115). The beta is -0.340, meaning that when VIIIA volume goes down with 0,34 cm^3, aggression scores go up by 1 point or vice versa.

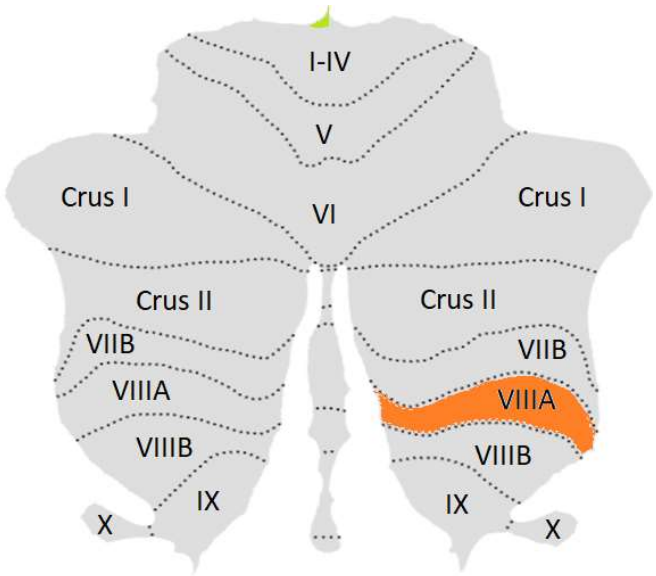

Figure 2 Flatmap of the cerebellum showing left lobule I-II that showed significant volumetric differences between ASD and NT children in green and right lobule VIIIA that had a significant relationship with aggressions cores on ASD children in orange.

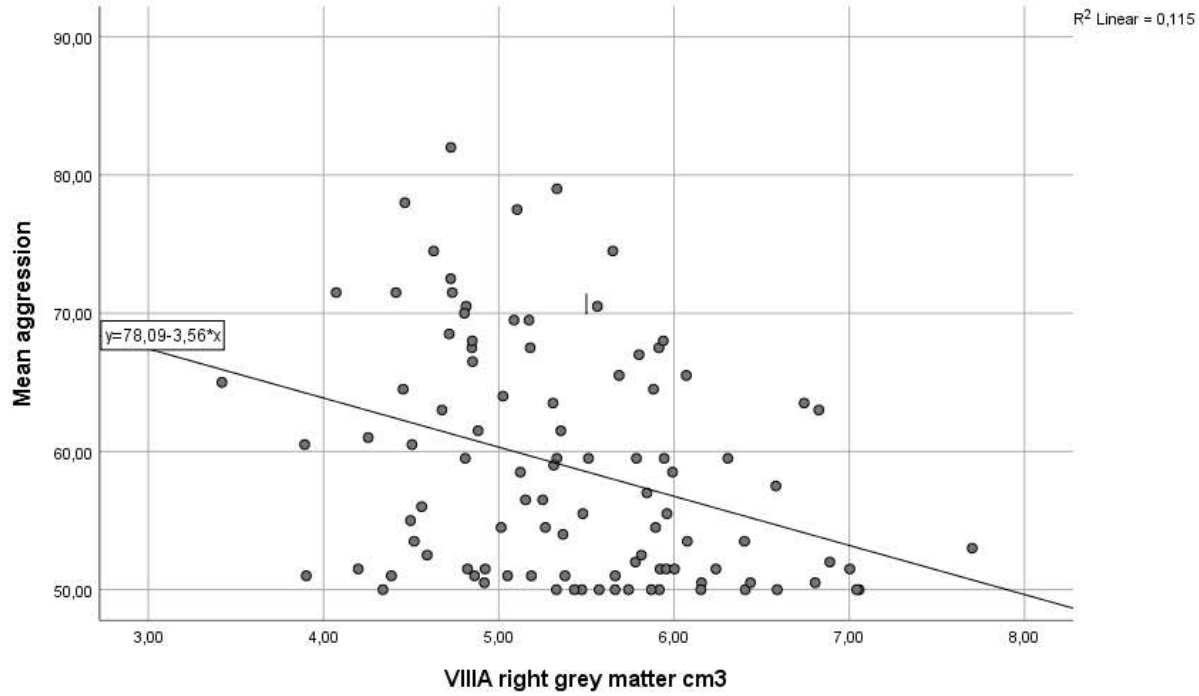

Figure 3 Regression plot of the relationship between VIIIA right grey matter volume and aggression score in children with ASD

The analysis for covariates showed the relationship between VIIIA right grey matter volume and aggression scores is still significant when controlling for ICV (r(97)= -0.329, p=0.001), SNR (r(97)= -0.341, p=0.001), sex (r(97)= -0.313, p=0.002), and VIQ score (r(96)=-0.340, p=0.001).

Verbal IQ as moderating factor

The lack of effect of VIQ score on the relationship between VIIIA grey matter volume and aggression scores found in the partial correlation analysis suggested that there was no moderation effect. Additionally, a moderation analysis was conducted, which again showed no significant effects ($F(3,193)=1,0343$, $p=0,3785$, $R^2=0,0158$).

Discussion

The main aim of the study was to explore the relationship between aggression and cerebellar grey matter volumes in ASD-diagnosed and NT children. The researchers first looked at between-group differences in the lobular grey matter volumes of the cerebellum. Then the relationship between grey matter volumes and aggression was assessed and lastly, VIQ was explored as a potential moderating factor in the relationship between cerebellar grey matter volumes and aggression.

Firstly, our hypothesis that we would find a reduced volume in right Crus I/II and an increased volume in lobules VIIIA/VIIIB (D'Mello, Crocetti, Mostofsky, & Stoodley, 2015) was partially confirmed. While no volumetric differences were found in lobules Crus I, Crus II, and VIIIA. The previous finding of an increased grey matter volume in lobules VIIIB was replicated. In particular, the total and right volume. However, this effect disappeared after controlling for the covariates ICV, SNR, and sex. An additional analysis for differences in other lobules showed a significant difference in lobules I-II and X. The only lobular grey matter volume that remained significant after controlling for ICV, SNR, and sex was left lobule I-II.

The fact that there was no overlap between our findings and the findings of D'Mello, Crocetti, Mostofsky, & Stoodley could be due to a difference in the sample. The participants were similar in age range, but D'Mello, Crocetti, Mostofsky, and Stoodley had a smaller sample (n=65) of only boys, whereas in our study we used a larger sample (n=200) of both boys and girls. The inclusion of females in our sample may explain the different findings. A recent meta-analysis (Walsh, Wallace, Gallegos, & Braden, 2021) focussed on the sex-based differences in the neurodevelopment of children with ASD and showed distinct patterns in the neurological development of females with ASD. For example, female youth had decreased inferior cerebellar volumes and increased Crus I volumes compared to male youth, while inverse patterns were found in adults, suggesting a difference in the developmental trajectory. Indications for the sex-based differences in neurodevelopment were especially found in limbic, cerebellar, and striatal regions. Since most studies collapse the ages, more lifespan-based research is needed to explore these distinct neurodevelopment patterns for females. In this study we did not conduct separate analyses for the ages, therefore the larger age range may have masked any age-specific volumetric differences between ASD-diagnosed and NT children.

Secondly, a relationship between the significant between-group difference in grey matter volume of left lobule I-II and aggression scores was explored. This yielded no significant results, yet through an explorative analysis of the other lobular grey matter volumes, a significant relationship with right lobule VIIIA was found. This indicates that higher aggression scores were associated with smaller grey matter volumes of the right hemisphere of lobule VIIIA.

Lobule VIIIA has previously been implicated in sensorimotor tasks, predominantly right-lateralized (Stoodley & Schmahmann, 2009). The overall sensorimotor abilities are impaired in children with ASD, as well as specifically fine and gross sensorimotor abilities. These abilities are shown to improve with age, but there does not seem to be a link with symptom severity. (Coll, Foster, Meilleur, Brambati, & Hyde, 2020). Sensorimotor ability is linked to sensory gating, which is the filtering of non-important sensory stimuli to prevent overstimulation (D. L. Braff, Swerdlow, & Geyer, 1999; D. Braff et al., 1978). Sensorimotor gating function is significantly impaired in children with ASD, but not in adults (Cheng, Chan, Hsu, & Liu, 2018). This is in line with the notion that sensorimotor abilities improve over time. The decreased gating ability can increase the risk of sensory overstimulation, which can in turn trigger violent behavior. Impairments in sensory processing ability and aggression have been linked in children (Bitsika et al., 2017; Mazurek, Kanne, & Wodka, 2013) and adults with

ASD (van den Boogert et al., 2021). The relationship that was found between grey matter volumes of the right hemisphere of lobule VIIIA and aggression is therefore in line with previous research.

The fact that the association was found specifically in the right side of the cerebellum is also in line with p findings. EEG and brain stimulation studies show that in the frontal cortex, aggression correlates with relatively higher activity in the left frontal cortex (Kelley, Hortensius, Schutter, & Harmon-Jones, 2017; Peterson, Shackman, & Harmon-Jones, 2008). The cerebellum is contralaterally associated with the frontal cortex (Krienen & Buckner, 2009). This right lateralization was found to be strongest in the posterior lobe, which includes lobule VIIIA (D. Wang, Buckner, & Liu, 2013). The association between aggression and the right posterior cerebellum has also previously been shown in a functional context (Klaus & Schutter, 2021). Having found a similar association in structural data shows promise for further research in this field.

Lastly, VIQ was considered as a protective factor in the relationship between right VIIIA grey matter volume and aggression. The hypothesis was that this would be the case since VIQ could help express anger more constructively than with aggression. This hypothesis was rejected since no moderation effect of VIQ on the relationship between right VIIIIA grey matter volume and aggression was found. This suggests that this cerebellar area is not involved in language ability or VIQ in any way that may explain the relationship with aggression.

Strengths and limitations

This study used a large sample size, which means more reliable results. Additionally, there was a thorough assessment of the covariates.

The exploratory nature of this study does not allow for conclusions on causality. To explore causal relations, brain stimulation studies need to be conducted. Fortunately, the posterior cerebellum is easy to stimulate with non-invasive methods, for example with TMS (Ferrari, Fiori, Suchan, Plow, & Cattaneo, 2021)of tDCS (Ferrucci, Cortese, & Priori, 2014). These studies could also provide information about the working mechanism of the cerebellum in aggression like TMS research has done for movement disorders like Parkinson's disease and dystonia (Shukla & Vaillancourt, 2014). Non-invasive brain stimulation of the posterior cerebellum should also be explored as a possible treatment method of aggression in children with ASD.

Whether the relationship between the grey matter volume of the right posterior cerebellum and aggression is exclusive to people with ASD could not be determined, since the aggression scores in the NT group didn't show enough variation to establish a regression line. This was to be expected since high aggression scores are a sign of psychopathology and would therefore generally not occur in the NT group. However, since lobule VIIIA didn't show significant differences in grey matter volume between the two groups, it is possible. Future research with a different variable for aggression, more suited to NT people, is needed.

Conclusion

This study found that the grey matter volume of right lobule VIIIA is associated with aggression in children with ASD. Sensorimotor abilities are impaired in children with ASD, which this area of the cerebellum is implicated in. Lack of sensory gating ability can lead to overstimulation and this can trigger aggression. The right lateralization is in line with the contralateral cortico-cerebellar connection. Future research is needed to solidify and expand on these findings with a lifespan-based and sex-specific approach.

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Appendix 1

Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	I-II grey matter cm3	-,083[b]	-,865	,389	-,087	,989
	I-II right grey matter cm3	-,059[b]	-,618	,538	-,063	,993
	I-II left grey matter cm3	-,098[b]	-1,026	,307	-,104	,985
	III grey matter cm3	-,038[b]	-,398	,691	-,040	,980
	III right grey matter cm3	-,046[b]	-,481	,632	-,049	,972
	III left grey matter cm3	-,028[b]	-,287	,775	-,029	,989
	IV grey matter cm3	-,059[b]	-,593	,554	-,060	,906
	IV right grey matter cm3	-,047[b]	-,475	,636	-,048	,926
	IV left grey matter cm3	-,060[b]	-,601	,549	-,061	,915
	V grey matter %	-,106[b]	-1,106	,271	-,112	,983
	V right grey matter %	-,095[b]	-,992	,324	-,100	,983
	V left grey matter %	-,101[b]	-1,053	,295	-,106	,987
	VI grey matter cm3	-,053[b]	-,523	,602	-,053	,901
	VI right grey matter cm3	-,080[b]	-,800	,426	-,081	,897
	VI left grey matter cm3	-,019[b]	-,192	,848	-,019	,919
	Crus I grey matter cm3	-,003[b]	-,033	,973	-,003	,871
	Crus I right grey matter cm3	,006[b]	,058	,954	,006	,875
	Crus I left grey matter cm3	-,012[b]	-,118	,906	-,012	,883
	Crus II grey matter cm3	,140[b]	1,379	,171	,139	,870
	Crus II right grey matter cm3	,122[b]	1,244	,216	,125	,935
	Crus II left grey matter cm3	,144[b]	1,370	,174	,138	,809
	VIIB grey matter cm3	,095[b]	,811	,419	,082	,657
	VIIB right grey matter cm3	,138[b]	1,222	,225	,123	,706
	VIIB left grey matter cm3	,022[b]	,188	,851	,019	,673
	VIIIA grey matter cm3	,137[b]	,527	,600	,053	,134
	VIIIA left grey matter cm3	,074[b]	,527	,600	,053	,456
	VIIIB grey matter cm3	-,006[b]	-,059	,953	-,006	,765
	VIIIB right grey matter cm3	-,009[b]	-,079	,937	-,008	,760
	VIIIB left grey matter cm3	-,003[b]	-,030	,976	-,003	,831
	IX grey matter cm3	,079[b]	,780	,437	,079	,874
	IX right grey matter cm3	,045[b]	,447	,656	,045	,890
	IX left grey matter cm3	,114[b]	1,117	,267	,113	,863
	X grey matter cm3	-,037[b]	-,378	,706	-,038	,937
	X right grey matter cm3	-,051[b]	-,510	,611	-,052	,927
	X left grey matter cm3	-,017[b]	-,175	,861	-,018	,965

a. Dependent Variable: Mean_aggression
b. Predictors in the Model: (Constant), VIIIA right grey matter cm3