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Relationship between brain stem volume and aggression in children diagnosed with autism spectrum disorder

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Brain volumes associated with high levels of aggression in male children diagnosed with autism spectrum disorder

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Abstract

Background—Aggressive behaviors are common in individuals diagnosed with autism spectrum disorder (ASD) and may be phenotypic indicators of different subtypes within ASD. In current research literature for non-ASD samples, aggression has been linked to several brain structures associated with emotion and behavioral control. However, few if any studies exist investigating brain volume differences in individuals with ASD who have comorbid aggression as indicated by standardized diagnostic and behavioral measures.

Method—We examined neuroimaging data from individuals rigorously diagnosed with ASD versus typically developing (TD) controls. We began with data from brain volume regions of interest (ROI) taken from previous literature on aggression including the brainstem, amygdala, orbitofrontal cortex, anterior cingulate cortex, and dorsolateral prefrontal cortex. We defined aggression status using the Irritability subscale of the Aberrant Behavior Checklist and used lasso logistic regression to select among these predictor variables. Brainstem volume was the only variable shown to be a predictor of aggression status.

Results—We found that smaller brainstem volumes are associated with higher odds of being in the high aggression group.

Conclusions—Understanding brain differences in individuals with ASD who engage in aggressive behavior from those with ASD who do not can inform treatment approaches. Future research should investigate brainstem structure and function in ASD to identify possible mechanisms related to arousal and aggression.

Keywords

Autism; aggression; imaging; brainstem; structural MRI

Introduction

Aggressive behavior is a common symptom of autism spectrum disorders (ASD) that can be particularly difficult for families to manage (Dominick, Davis, Lainhart, Tager-Flusberg, & Folstein, 2007; Farmer, et al., 2014; Horner, Carr, Strain, Todd, & Reed, 2002; Kanne & Mazurek, 2011; Mazurek, Kanne, & Wodka, 2013). In particular, parents frequently report that aggression in their child is more distressing than poor adaptive skills (Lecavalier, Leone, & Wiltz, 2006).

In typically developing (TD) children, there is mounting evidence that increased aggression is associated with brain functioning in regions of emotional or behavioral control (Lamm, Granic, Zelazo, & Lewis, 2011; Lozier, Cardinale, VanMeter, & Marsh, 2014; Paus, 2005; Sterzer & Stadler, 2009). Particular regions identified include the amygdala, brainstem, orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC) (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; Ducharme, et al., 2011; Kolla, et al., 2015; Rylands, et al., 2012; Saxbe, Del Piero, Immordino-Yang, Kaplan, & Margolin, 2016; Siegel & Victoroff, 2009; Visser, et al., 2014). These regions might also be

associated with increased aggression in children with ASD. Because brain function is linked in some degree to brain structure (Meier et al., 2016; Ponten, Daffertshofer, Hillebrand, & Stam, 2010; Stam et al., 2016), we reasoned that these findings from functional scans would provide a useful starting place for examining structural integrity.

To date, few if any studies exist investigating brain volume differences in individuals with ASD who have comorbid aggression. Because aggression is likely related to brain function in regions of emotional control and occurs in some children with autism but not others, it may be useful to use aggression as an indicator of different subcategories of ASD. This approach may increase the likelihood that researchers will find reliable associations between symptoms and brain regions (Chaste, et al., 2015). Improved understanding of brain correlates with behavioral outcomes could go a long way towards identifying effective interventions (South, Wolf, & Herlihy, 2012). Understanding brain differences in individuals with ASD who engage in aggressive behavior from those with ASD who do not have frequent aggressive behaviors can inform treatment approaches at all levels. The aim of this exploratory study was to determine the nature of relationships between brain structure volumes and parent-reported symptoms of aggression in children with ASD.

Methods

Participants

The data for this project were collected as part of a multifaceted, joint longitudinal project by researchers at Brigham Young University and the University of Utah. The study was approved by Institutional Review Boards at both universities and appropriate signed informed consent was obtained for all procedures. This work was carried out in accordance with the ethical standards of both universities and with the Declaration of Helsinki as revised in 2000. All participants were recruited via community autism support, health care, and educational service providers. In order to enhance homogeneity for this exploratory project, we selected data from a larger sample of over 150 children and adults enrolled in the longitudinal study (Travers, et al., 2015) including 45 male children with ASD who had available scores on the Aberrant Behavior Checklist and imaging data. The participants with available data ranged from 3-13 years old, and so we used comparison data (from the same dataset) of 18 typically developing (TD) male children of the same age range.

For the ASD sample, diagnosis was verified through extensive assessment according to DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1992) criteria based on data collected from the Autism Diagnostic Observation Schedule (ADOS) (Lord, et al., 2000), Autism Diagnostic Interview-Revised (ADI-R) (Lord & Rutter, 1994), and clinical judgment. Binary aggression status was determined from the Irritability subscale of the Aberrant Behavior Checklist, where a cut score ≥ 18 indicates high-aggression (ASD_{HA}) and < 18 for low-aggression (ASD_{LA}) status (Aman, et al., 2010; Aman, Singh, & Stewart, 1985; Brown, Aman, & Havercamp, 2002; Carroll, et al., 2014; Marcus, et al., 2009; Marshburn & Aman, 1992; McCracken, et al., 2002). According to this cutoff, 14 ASD participants were in the “high aggression” group, 31 ASD participants were in the “low aggression” group, and all 18 TD participants were in the “low aggression” group.

TD participants were evaluated using ADOS, IQ, language tests, and parent interview to confirm that all had age appropriate verbal skills and no history of learning, developmental, cognitive, neurological, or neuropsychiatric problems (Alexander, et al., 2007; Allen-Brady, et al., 2010; Jantz, et al., 2015; Prigge, et al., 2013; Travers, et al., 2014). See Table 1 for more detailed descriptions of participant recruitment and characteristics.

Behavioral Measures

ABC-Irritability—The Irritability subscale of the Aberrant Behavior Checklist (ABC) (Aman, et al., 1985) is commonly used as a measure of problematic behavior focused on aggression. It has been used in many studies assessing the effects of various interventions on the maladaptive and aggressive behaviors of children with autism (Aman, et al., 2010; Aman, et al., 2009; Bearss, et al., 2015; McCracken, et al., 2002; Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005). This scale consists of 15 parent-reported Likert-type items rated on a scale of 0 – 3. Items include questions about intentional self-injury; aggression to others; noisy, rough behavior; temper tantrums/outbursts; irritable and whiny behavior; disobedience or difficulty to control; uncooperative behavior; insistence that demands be met immediately; disruptive behavior; stamping or banging; and temper outbursts or tantrums when the individual does not get his/her own way. A score of 18 and above has been used to indicate high-aggression status (Aman, et al., 2010; Aman, Singh, & Stewart, 1985; Brown, Aman, & Haverkamp, 2002; Carroll, et al., 2014; Marcus, et al., 2009; Marshburn & Aman, 1992; McCracken, et al., 2002).

Wechsler Intelligence Scales for Children-Third Edition—IQ was assessed at the initial study visit, using the Differential Abilities Scale (Elliott, 1990) or the Wechsler Intelligence Scales for Children-Third Edition (Wechsler, 1991). As in previous papers from this study (Alexander, et al., 2007; Allen-Brady, et al., 2010; Dominick, et al., 2007; Jantz, et al., 2015; Prigge, et al., 2013; Travers, et al., 2014), we used the most comprehensive IQ score from each measure (i.e., Wechsler Full Scale IQ, DAS General Cognitive Ability score). While IQ scores are reported, we did not use IQ as a covariate in the model. This is because covarying IQ takes away important and meaningful variance that is part-and-parcel of neurodevelopmental disorders (Dennis, et al., 2009).

ADOS—We verified autism diagnoses using the Autism Diagnostic Observation Schedule, administered by research reliable clinicians (Lord, et al., 2000). Although the ADOS Modules are determined by language level, the ADOS was used in our study only as a factor in determining case status, not language ability.

ADI-R—The Autism Diagnostic Interview-Revised was also used to verify case status. In addition, Question 30, which asks “How much speech does ____ have now?” was used to identify verbal language levels. The research reliable interviewer determines the appropriate code based on language abilities including parts of speech used, number of words used, and if other people understand the language of the individual being evaluated. We distinguished a minimally verbal group on the basis of a code fewer than five words total, or does not use speech on a daily basis, from this item.

Imaging procedures

Neuroimaging data were selected for each individual based on the first time point in the longitudinal study where both MRI and behavioral data were available. Participants were scanned using a Siemens Trio 3.0T scanner and an 8-channel, receive-only, RF head coil (Alexander, et al., 2007). Structural scans were sagittal 3D MPRAGE T1-weighted images with $1 \times 1 \times 1$ mm isotropic resolution (inversion time = 1100ms, echo time = 2.93 ms, repetition time = 1800 ms, flip angle = 12° , field of view = 56mm, matrix = $256 \times 256 \times 160$, slice thickness = 1.0mm, 160 slices) (Zielinski, et al., 2014).

Imaging and statistical data analysis

MRI scans were processed using FreeSurfer v5.1.0 (<http://surfer.nmr.mgh.harvard.edu/>) including automated cortical parcellation and region of interest (ROI) definition using the Desikan-Killiany Atlas (Desikan, et al., 2006) resulting in 34 cortical parcellations per hemisphere (Zielinski, et al., 2014). The technical details of the automated parcellation process have been described previously (Fischl et al. 2002). These parcellations were used to examine differences in the mean brain structure ROI of the ASD_{HA}, ASD_{LA}, and TD groups. Age across the three groups (shown in Table 1) was not significantly different ($p = 0.48$). Likewise, mean total intracranial brain volumes were not significantly different across groups ($p = 0.27$). The FreeSurfer-based bilateral ROIs we investigated for contributions to aggression were the amygdala, brainstem (defined from the base of the skull to superior colliculus, excluding the cerebellum), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC), see Table 2.

We used logistic regression, and in particular elastic net regularization (Lockhart, Taylor, Tibshirani, & Tibshirani, 2014; Zou & Hastie, 2005), in conjunction with logistic regression, to simultaneously select informative ROIs and estimate a model for predicting aggression status based on the ROIs. (Tibshirani, 1996) The elastic net is a variation of lasso (least absolute shrinkage and selection operator) (Tibshirani, 1996), both of which are regularization methods that shrink some of the regression coefficients to zero. Remaining non-zero coefficients correspond to variables that are important for prediction. Elastic net regularization is recommended over lasso when the predictor variables are correlated (Zou & Hastie, 2005). The predictor variables included in the analysis were the volumes for the five ROIs, total brain volume, and age at scan (Zou & Hastie, 2005). We selected the appropriate elastic net regularization parameter using cross-validation based on minimizing the binomial deviance. All analyses were done using R version 3.2.3 (R Core Team, 2015), also using the “glmnet” package for elastic net logistic regression (Friedman, Hastie, & Tibshirani, 2010) and the “covTest” package for computing the p-values (Lockhart, Taylor, Tibshirani, & Tibshirani, 2013).

Results

ASD group only

In order to address concerns of possible confounding between ASD diagnosis and aggression, we first ran the elastic net logistic regression using only the 45 ASD participants. Using the regularization parameter that minimized the binomial deviance, the only predictor

that remained with a non-zero coefficient was brainstem volume, which was significant at the 0.05 level (p -value=0.0453). The regression coefficient corresponding to the brainstem was -0.0001. The negative coefficient means that the odds of being in the high aggression group decreases as brainstem volume increases. The coefficient is small because it is the average change in log odds for a 1-cubic millimeter increase in brainstem volume. However, the magnitude of the coefficient is not important, just that its significance indicates that the brainstem can possibly be used as one predictor for aggression. It is unlikely the brainstem would be the only predictor, but our findings suggest a hopeful connection worth future study.

ASD and TD

We obtained very similar results when predicting aggression status based on both the ASD group and the typically developing group. In this later case, we classified all of the TD participants into the low aggression group (since none of the TD participants had an ABC irritability score higher than 18). The elastic net logistic regression again selected only the brainstem as a meaningful predictor (p -value=0.0427). In the logistic regression model, the brainstem coefficient is again -0.0001. These results are suggestive that the brainstem is important in classifying aggression status, although it is unlikely the brainstem would be the only predictor.

Discussion and Implications

Although symptoms of aggression add substantially to the burden of care for individuals affected by ASD, there has been little research regarding the neural mechanisms that underlie this behavior. To our knowledge, this is the first study to directly explore brain volumes as related to aggression in ASD. Our most striking finding is that reduced brainstem volume is associated with the likelihood of being in the high versus low aggression group. We also acknowledge that progress also needs to be made in finding other useful predictors.

Although the brainstem develops from three distinct embryological neural tube vesicles, our finding suggests that at least one of the structures of the brainstem is associated with aggression in ASD. However, our findings with aggression could be explained by functional connectivity (temporal correlation of brain activity) between the brainstem and other regions of the brain. Abnormalities in functional connectivity of the brainstem have been observed in autism (for a review, see Bressler and Menon (2010) and Kirsch, et al. (2005)). The latter study is discussed below. Structural connectivity via white matter tracts are also possible, however, these studies rarely include the brainstem (see Kleinhans, et al. (2012) for an exception). To explore the possibility of brainstem involvement in aggression in autism, there is a need for more specific research that includes the brainstem.

We note that our findings cannot be due simply to differences in intelligence scores. As a reminder, we did not use IQ scores as a covariate. This is because covarying IQ takes away important and meaningful variance that is part-and-parcel of neurodevelopmental disorders (Dennis, et al., 2009). Additionally, the high aggression ASD group did not have lower composite IQ scores than the low aggression ASD group. More participants in the low-

aggression group were verbal (91% vs. 73%) and language skills may logically play a role in ability to express feelings without acting out. However, there were not enough available formal language measures at this point to perform additional analyses, and Maskey, Warnell, Parr, Le Couteur, and McConachie (2013) suggest that language may not play as large a factor in aggression as assumed. Future research should include additional communication measures to explore possible associations with acting out in aggressive children with ASD.

In addition, our study is not the first to identify a potential biological marker for aggression and autism. Anckarsäter (2006) reviews several findings concerning autism and aggression including abnormalities in limbic circuitry and increased dopaminergic relative to serotonergic neurotransmission. Arrested development of serotonergic neurons has been associated with increased aggression in mice (Hendricks, et al., 2003) and this has been proposed as a model for autism (Schaefer, Vorhees, & Williams, 2009). The present study is also consistent with some earlier findings that suggest associations between the brainstem and aggression or between the brainstem and autism. For example, Kirsch, et al. (2005) found that oxytocin (which modulates aggression) (Bosch, Meddle, Beiderbeck, Douglas, & Neumann, 2005) acts on the amygdala, which has both tracts that project to the brainstem (LeDoux, 2000) and functional connectivity with the upper brainstem (including the periaqueductal gray area and the reticular formation). Another region of the brainstem (locus coeruleus) has also been found to be associated with autism (Mehler & Purpura, 2009). In addition, ASD has been associated with reduced volume in the brainstem (Hashimoto, et al., 1992) and with the HOXA1 gene, which is involved in brainstem development (Weidenheim, 2001). While connections between the brainstem and aggression or between the brainstem and autism have been made, our contribution is to connect aggression in ASD with brainstem volume.

This line of research has the potential to improve proactive approaches to aggression in ASD. Understanding what is happening in the brain shortly before an aggressive episode could lead to better interventions. For example, if we knew that it was general physiological arousal that led to the apparent association between the brainstem and aggression (the association that we report in this paper), that could inform better treatments. Some treatments might be in regard to baseline physiological arousal levels and/or modulation of physiological arousal in response to threatening or frustrating situations. For example, individuals with better regulation of physiological arousal in reaction to environmental stimuli may be slower to “default” to aggressive behavior. Improved regulation (by psychopharmacology and/or behavioral methods) may provide a window of opportunity to ameliorate distress before aggressive behavior escalates.

Our findings warrant replication and refinement using larger samples, investigating potential sex differences (our study used only males), exploring variations in development and age, and including other imaging modalities. More fine-grained imaging approaches with larger samples may target structural measures, including volumetrics, and connectivity measures as well as functional activity in the region as a putative area of interest for predicting aggression associated with autism symptoms. Better procedures for a matched control group are also necessary to address issues such as the contribution of IQ to our findings. This exploratory study suggests further work regarding the brainstem and aggression in ASD in

order to improve understanding of neural mechanisms and more specific targets for intervention in this important symptom domain.

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Highlights

- Used structural MRI data from 63 male children, 45 with autism spectrum disorder (ASD).
- Examined brain volume in individuals with ASD with and without comorbid aggression.
- Smaller brainstem volume was associated with odds of higher aggression.

Figure 1. Brainstem volume (in mm³) by group. The boxes represent the median and the first and third quartiles for each group. The whiskers represent the minimum and maximum of all data in each group. The low aggression ASD group is more similar to the control group on brainstem volume.

Table 1
Participant Characteristics

	ASD _{HA}	ASD _{LA}	TD
TOTAL	14	31	18
Race			
# Caucasian	13	31	18
# African American	1	-	-
Language			
# Verbal	10	28	18
# Minimally Verbal	3	1	-
# No language data	1	2	-
	ASD _{HA} <i>M</i> (SD)	ASD _{LA} <i>M</i> (SD)	TD <i>M</i> (SD)
ABC Irritability	23.86 (5.17)	7.10 (4.84)	1.00 (1.57)
(min-max)	(18-33)	(0-17)	(0-5)
BASC Anxiety	52.40 (13.30)	51.50 (11.92)	--
(min-max)	(36-71)	(34-80)	
ADOS	14.57 (3.80)	15.22 (3.95)	1.50 (1.38)
(min-max)	(7-20)	(6-23)	(0-4)
Full Scale IQ	97.43 (27.61)	94.13(20.85)	118.57 (18.11)
(min-max)	(48-136)	(58-137)	(93-144)
Scan age in years	7.93 (3.34)	8.77 (3.22)	9.22 (2.32)
(min-max)	(3-13)	(3-13)	(5-13)
TICV, mm ³	1,575,136 (159,480)	1,610,711 (183,651)	1,513,308 (249,142)
(min-max)	(1,383,898-2,010,302)	(1,179,262-1,942,259)	(1,000,273-2,151,003)

Note. All participants were male. Language category (verbal versus minimally verbal) was determined using quesiton 30 on the ADI-R. Aggression status was determined using Irritability subscale score from the Aberrant Behavior Checklist (ABC). Following McCracken et al. (2002) among others, scores <18 are Low Aggression (ASD_{LA}) and scores ≥ 18 are High Aggression (ASD_{HA}). BASC Anxiety = Anxiety subscale from the Behavioral Assessment Scales for Children. The Composite Intelligence Estimate was calculated from various IQ tests given to different participants following the procedures described below. TICV = Total Intracranial Brain Volume, in mm³.

Table 2
Average brain volumes by region of interest and participant group

	ASD_{HA} <i>M (SD)</i>	ASD_{LA} <i>M (SD)</i>	TD <i>M (SD)</i>
Amygdala	3,325 (492)	3,418 (472)	3,262 (450)
Brainstem	19,869 (2,904)	21,546 (2,953)	21,357 (2,396)
OFC	35,293 (3,918)	35,464 (3,519)	34,783 (4,469)
DLPFC	126,122 (17,312)	129,705 (13,772)	128,103 (13,697)
ACC	11,214 (2,077)	11,171 (2,121)	10,961 (2,184)