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Specific cortical and subcortical alterations for reactive and proactive aggression in children and adolescents with disruptive behavior

Jilly Naaijen[a,b,*], Leandra M Mulder[a,b], Shahrzad Ilbegi[a], Sanne de Bruijn[a,b], Renee Kleine-Deters[c], Andrea Dietrich[c], Pieter J Hoekstra[c], Jan-Bernard C Marsman[d], Pascal M Aggensteiner[e], Nathalie E Holz[e], Boris Boettinger[e], Sarah Baumeister[e], Tobias Banaschewski[e], Melanie C Saam[f], Ulrike M E Schulze[f], Paramala J Santosh[g,h], Ilyas Sagar-Ouriaghli[g], Mathilde Mastroianni[g], Josefina Castro Fornieles[i], Nuria Bargallo[i,j], Mireia Rosa[i,j], Celso Arango[k], Maria J Penzol[k], Julia E Werhahn[l], Susanne Walitza[l], Daniel Brandeis[e,l], Jeffrey C Glennon[a], Barbara Franke[m,n], Marcel P Zwiers[b], Jan K Buitelaar[a,o]

[a] Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Department of Cognitive Neuroscience, Nijmegen, the Netherlands
[b] Radboud University, Donders Institute for Brain, Cognition and Behavior, Centre for Cognitive Neuroimaging, Nijmegen, the Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Child and Adolescent Psychiatry, Groningen, the Netherlands
[d] Cognitive Neuroscience Center, Department of Neuroscience, University Medical Center Groningen, Groningen, the Netherlands
[e] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim /Heidelberg University, Mannheim, Germany
[f] Department of Child and Adolescent Psychiatry/Psychotherapy, University Hospital, University of Ulm, Germany
[g] Department of Child and Adolescent Psychiatry, King's College London, London, UK
[h] Centre for Interventional Paediatric Psychopharmacology and Rare Diseases, South London and Maudsley NHS Foundation Trust, London, UK
[i] Child and Adolescent Psychiatry and Psychology Department, 2014SGR489, Institute Clinic of Neurosciences, Hospital Clinic of Barcelona, CIBERSAM, IDIBAPS, Department of Medicine, University of Barcelona. Villarroel, 170, Barcelona 08036, Spain
[j] Clinic Image Diagnostic Center (CDIC), Hospital Clinic of Barcelona; Magnetic Resonance Image Core Facility, IDIBAPS, Barcelona, Spain
[k] Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón School of Medicine, Universidad Complutense, IiSGM, CIBERSAM, Madrid, Spain
[l] Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Zurich, Switzerland
[m] Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Department of Human Genetics, Nijmegen, the Netherlands
[n] Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Department of Psychiatry, Nijmegen, the Netherlands
[o] Karakter Child and Adolescent Psychiatry University Center, Nijmegen, the Netherlands

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ABSTRACT

Maladaptive aggression, as present in conduct disorder (CD) and, to a lesser extent, oppositional defiant disorder (ODD), has been associated with structural alterations in various brain regions, such as ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), amygdala, insula and ventral striatum. Although aggression can be subdivided into reactive and proactive subtypes, no neuroimaging studies have yet investigated if any structural brain alterations are associated with either of the subtypes specifically. Here we investigated associations between aggression subtypes, CU traits and ADHD symptoms in predefined regions of interest.

T1-weighted magnetic resonance images were acquired from 158 children and adolescents with disruptive behavior (ODD/CD) and 96 controls in a multi-center study (aged 8–18). Aggression subtypes were assessed by questionnaires filled in by participants and their parents. Cortical volume and subcortical volumes and shape were determined using Freesurfer and the FMRIB integrated registration and segmentation tool. Associations between volumes and continuous measures of aggression were established using multilevel linear mixed effects models.

Proactive aggression was negatively associated with amygdala volume (b = -10.7, p = 0.02), while reactive aggression was negatively associated with insula volume (b = -21.7, p = 0.01). No associations were found with CU traits or ADHD symptomatology. Classical group comparison showed that children and adolescents with

disruptive behavior had smaller volumes than controls in (bilateral) vmPFC ($p = 0.003$) with modest effect size and a reduced shape in the anterior part of the left ventral striatum ($p = 0.005$).

Our study showed negative associations between reactive aggression and volumes in a region involved in threat responsivity and between proactive aggression and a region linked to empathy. This provides evidence for aggression subtype-specific alterations in brain structure which may provide useful insights for clinical practice.

1. Introduction

Aggression, overt behavior with the intention of inflicting damage, is a behavioral trait with important roles throughout evolution in defense and predation. However, when expressed in humans in the wrong context, aggression may lead to social maladjustment and crime. Maladaptive aggression is commonly observed across childhood in disruptive behavioral disorders, in particular in conduct disorder (CD) and to a lesser degree in oppositional defiant disorder (ODD). CD is defined as a repetitive and persistent pattern of behavior, which violates the rights of others and major age-appropriate societal rules. ODD is characterized by a frequent and persistent pattern of irritable and angry mood, vindictiveness, and inappropriate and disobedient behavior toward authority figures (American Psychiatric Association, 2013). Both disorders are highly comorbid with attention-deficit/hyperactivity disorder (ADHD), which has been associated with aggressive behavior as well (Saylor and Amann, 2016).

Subtyping of aggressive behavior is considered an important step towards effective prevention and treatment strategies, as currently available treatment options for maladaptive aggressive behavior have limited efficacy (Bakker et al., 2016; Waschbusch et al., 2007). A promising subdivision, derived from animal studies, defines impulsive and instrumental subtypes of aggression, also referred to as reactive and proactive aggression, respectively (Poulin and Boivin, 2000). Reactive aggression is thought to be associated with high arousal, impulsivity, strong emotions and uncontrolled behavior. Animal studies have shown that this form of aggression is mediated by a circuit that is responsive to threat (and frustration) and involves the amygdala (Haller, 2018). Furthermore, this circuit may be regulated by frontal cortical regions, such as the ventromedial prefrontal cortex (vmPFC) and the anterior cingulate cortex (ACC) (Blair, 2013). In contrast, proactive aggression is hypothesized to be goal-directed, planned behavior associated with low arousal and higher levels of callous unemotional and/or psychopathic traits. This form of aggression often goes hand in hand with impaired stimulus-reinforcement learning (which involves the amygdala) combined with impaired prediction error signaling (which involves the striatum), leading to a poor understanding of the value of objects, cues and responses represented in the vmPFC as well as a lower empathy level (Blair, 2013). Although the subdivision of reactive versus proactive aggression is the most prevalent subdivision referred to in literature, it is so far not used clinically and no neuroimaging studies have yet investigated if any structural brain alterations are associated with either of these aggression subtypes specifically in a clinical sample (Yang et al., 2017). Prior research has focused on the presence or absence of callous unemotional (CU) traits and/or childhood versus adolescent onset of CD in subtyping aggression. The strongest evidence from such studies so far points to an involvement of the fronto-limbic-striatal circuitry in aggressive behavior (Blair, 2013).

Several studies have focused on structural abnormalities related to aggression, although not in consistent subgroups of disruptive disorders. Almost all of these performed voxel-based morphometry (VBM) analyses of grey matter associating these measures to either conduct problems, conduct disorder or CU traits (De Brito et al., 2009; Budhiraja et al., 2017; Cohn et al., 2016; Fairchild et al., 2011). A recent meta-analysis of thirteen VBM studies included almost 400 participants (aged 9–21 years) with conduct problems and showed that individuals with conduct disorder/problems compared with controls had smaller grey matter (GM) volumes in the left amygdala, in the bilateral insula

extending to the ventrolateral prefrontal cortex (PFC)/orbitofrontal cortex (OFC) and in the medial superior frontal gyrus extending to the anterior cingulate cortex (ACC) with small-medium effect sizes (Rogers and De Brito, 2016). Another meta-analysis including ODD/CD and ADHD studies (n = 415) reported reduced volumes of the amygdala, insula and frontal regions in ODD/CD as well, with greater reductions in the presence of comorbid ADHD (Noordermeer et al., 2016). However, other studies have not been able to find any group differences in GM volume in these regions between participants with conduct problems and controls or found opposite results with positive associations between CU traits and insula volume and CD symptoms and amygdala volume (Cohn et al., 2016; Holz et al., 2016).

In the present multi-center study, we investigated the association between structural alterations and continuous measures of reactive and proactive aggression as well as CU traits in the largest sample of children/adolescents with disruptive behavior reported so far. We used pre-selected regions of interest based on the previous meta-analyses and thus investigated ACC, insula, vmPFC, amygdala, and ventral striatum. We expected the vmPFC, ACC and insula volume to be associated with reactive aggression. For the ventral striatum and amygdala, associations with proactive aggression were expected. We chose not to perform a whole brain VBM analysis to limit the number of independent tests (Focke et al., 2014), because surface-based morphometry measures have been shown to be more robust across different MR scanners, as used in our multi-site design (Clarkson et al., 2011) and due to its higher sensitivity to capture subtle grey matter changes (Palaniyappan and Liddle, 2012; Winkler et al., 2010). We focused on analyses of the volumes of these regions and subsequently investigated the shape of the subcortical structures for subtler morphological changes and cortical thickness and surface area of the cortical areas.

2. Methods and materials

2.1. Participants

We included 277 participants (n = 176 cases and n = 101 healthy controls) aged 8–18 years who were recruited across nine sites in Europe (see supplementary material for details). Exclusion criteria for all participants were contraindications for MRI, an IQ < 80 and a primary DSM-5 diagnosis of psychosis, bipolar disorder, major depression and/or anxiety disorder. Participants that were included as "cases" were diagnosed with conduct disorder (CD) and/or oppositional defiant disorder (ODD) and/or scored above the clinical cut-off for aggressive behavior and/or rule-breaking behavior as measured with the Child Behavior Checklist (CBCL) completed by parents (Bordin et al., 2013). Within the control group no psychiatric disorders or scores within the clinical range were allowed, as determined by screening questionnaires (CBCL). Participants that were using medication were at a stable dose for at least two weeks. Ethical approval for the study was obtained for all sites separately by local ethics committees. After description of the study written informed consent was given by the participants and/or their parents.

2.2. Phenotypic information

Clinical diagnoses of ODD, CD and possible comorbid ADHD were confirmed by structured diagnostic interviews with both child and parents using the Kiddie Schedule for Affective Disorders and

Schizophrenia (K-SADS; Kaufman et al., 1997). Participants were administered a screening-module, followed, if needed, by application of disorder-specific modules. Aggressive/disruptive behavior was measured by the aggressive behavior and rule-breaking behavior sub-scales of the CBCL (Bordin et al., 2013). The Reactive Proactive Aggression Questionnaire (RPQ; Raine et al., 2006) completed by participants themselves was used to subtype aggressive behavior. The presence of CU traits was assessed by the Inventory of Callous Unemotional Traits (ICU; Kimonis et al., 2008) completed by parents. A continuous measure for ADHD symptoms was derived from the K-SADS by summing the number of inattention and hyperactivity/impulsivity symptoms. IQ was estimated from four subtests (vocabulary, similarities, block design and picture completion) of the Wechsler Intelligence Scale for Children III or IV (Wechsler, 2002). Information about use of medication was collected via parental report on the measurement day.

2.3. MR acquisition and processing

MRI data-sets were acquired on 3 T scanners across nine different sites in Europe (see Table 1 for the scan parameters and Table S2 for Vendor specifications). T1-weighted images were processed with the FMRIB Software Library (FSL; Smith et al., 2004) for subcortical volume and shapes and with Freesurfer v5.3.0 (http://surfer.nmr.mgh.harvard.edu) for measures of cortical volumes and cortical thickness (CT) and surface area (SA; Dale et al., 1999; Desikan et al., 2006). Subcortical segmentation was performed with the automated FMRIB integrated registration and segmentation tool (FIRST; Patenaude et al., 2011) which included affine registration to MNI-space followed by a segmentation procedure integrating both shape and intensity information for accurate segmentation of subcortical structures, including the bilateral ventral striatum and amygdala. Volumes of these respective regions were extracted for statistical analysis. Vertex analysis was performed with FIRST_utils to determine shape. A multivariate Gaussian model of the location and intensity variation of the vertex was used to generate surface meshes. Localized shape differences using the 3D-coordinates of the corresponding vertices with vertex-wise F-statistics were calculated after alignment to the average shape of the cohort and removal of global scaling (useRigidAlign and useScale). Cortical reconstruction was performed in FreeSurfer using the Desikan-Killiany atlas (see Fig. 1). CT was calculated for each vertex on the reconstructed cortical sheet and was defined as the closest distance between the grey/white matter boundary and the GM/CSF boundary (Fischl and Dale, 2000). SA was measured at the geometric middle of the inner and outer cortical surfaces. CT, SA and volume of the ACC, vmPFC and insula were extracted from the parcellations and segmentations using the 'mri_segstats' function.

2.4. Quality control

T1-weighted images and segmentation were all visually inspected and evaluated by an experienced rater (JN). Since images of

participants with externalizing disorders are more prone to motion artefacts, we used a rating system that has been described and thoroughly applied to an MRI data-set of children with ADHD and/or CD before (Backhausen et al., 2016). Segmentation was visually inspected for all Freesurfer and FSL-first output for all scans. Scans of 18 cases and 5 healthy controls were excluded due to anxiety in the scanner (scan-session aborted) or due to poor data quality, which was based on ratings of image sharpness, ringing, contrast to noise ratio of the subcortical structures and of GM/WM. Total GM volume, total brain volume (TBV), amygdala and ventral striatum volumes are compared across in- and excluded participants in Figure S1.

2.5. Statistical analyses

Statistical analyses were performed with the R statistical program (R Team, 2013). Group distributions in sex were tested with Pearson's chi-squared test. Group differences in continuous demographic measures were assessed with one-way analyses of variance (ANOVAs) or Kruskal-Wallis rank sum tests when assumptions of homogeneity of variance and normality of distributions were violated.

We investigated whether volume of the ventral striatum, amygdala, ACC, vmPFC and insula were related to continuous measures of aggression and to CU-traits by using linear mixed effects models in R with a maximum likelihood fit (lme4 package; (Bates et al., 2015)) with effect sizes being presented as "r". For the associations between volumes and continuous measures of aggression, assumptions for linearity, homogeneity of variance and normality of residuals were met. Hemisphere was used as within-subjects' factor and the respective continuous measure as between-subject's variable of interest. Age, sex and TBV were added as possible confounders of non-interest and participant as random factor to account for within subject variability across hemispheres. Since reactive and proactive aggression are highly correlated (r = 0.69 in this sample), any significant associations between either of them with volumes were controlled for the effect of the other. Due to the skewed distribution of reactive and proactive aggression scores in the control group, we additionally repeated analyses with significant results in the cases only group and investigated whether diagnostic group affected the results by adding this to the model.

We also investigated traditional cases-control differences in volume and shape, and post-hoc CT and SA of the same regions to better compare our results to previous studies (with a larger sample), using the same linear mixed effects model replacing the continuous measure of aggression with diagnostic status. As part of the supplemental material we additionally report whole-brain analyses results for these case-control comparisons. All p-values of the continuous measures and diagnostic status on (sub)cortical volumes only are corrected for multiple comparisons using the false discovery rate (FDR) of $q < 0.05$. Analyses of thickness and surface area were considered post-hoc tests and were not corrected for multiple comparisons. Possible effects of scan-site on these analyses are shown in the supplementary material.

Statistical shape analyses based on the vertex-wise F-statistic of the

Table 1
Scan parameters for the T1-scan across the different sites.

| Scanner	Site	TR*/TE/T1 (ms)	Flip angle	Field of view	Matrix RL/AP/slices	Voxel size (mm)	Acceleration factor
Siemens	Nijmegen	2300/2.98/900	9	256	212/256/176	1.0 × 1.0 × 1.2	2
	Mannheim	2300/2.96/900	9	256	212/256/176	1.0 × 1.0 × 1.2	2
	Ulm	2300/2.96/900	9	256	212/256/176	1.0 × 1.0 × 1.2	2
	Barcelona	2300/2.98/900	9	256	212/256/176	1.0 × 1.0 × 1.2	2
	Madrid	2300/2.98/900	9	256	212/256/176	1.0 × 1.0 × 1.2	2
	Rome	2300/2.86/900	9	256	212/256/176	1.0 × 1.0 × 1.2	2
Philips	Groningen	6.69/3.11/900	8	270	256/232/170	1.0 × .1.0 × 1.0	1.8
	Zurich	6.69/3.11/900	9	270	256/232/170	1.0 × 1.0 × 1.0	1.8
GE	London	7.31/3.02/400	11	270	256/256/196	1.0 × 1.0 × 1.2	1.75

* As provided by the manufacturer.
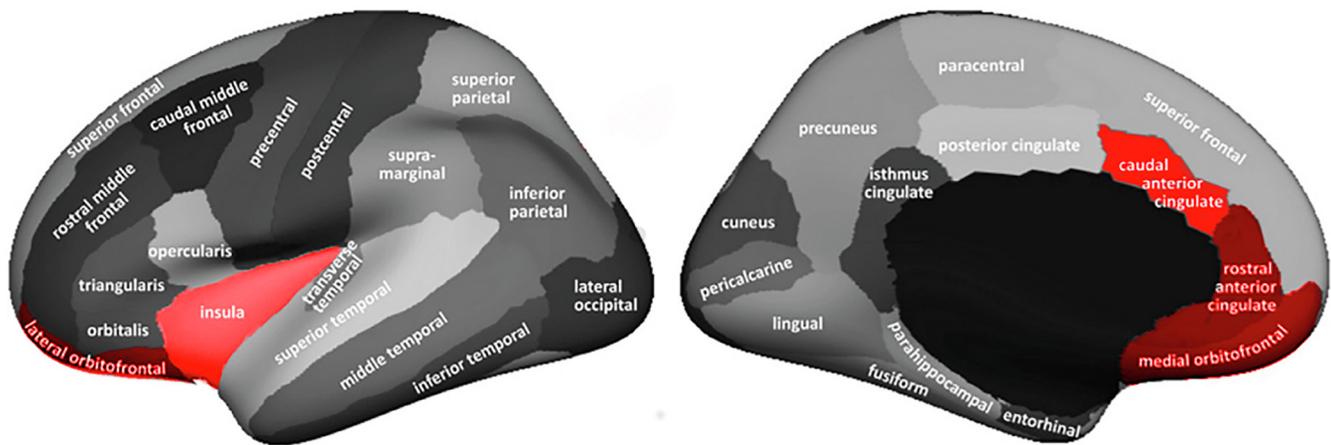
Fig. 1. Regions included in the cortical volume analyses. ACC consisted of rostral and caudal anterior cingulate cortex; vmPFC consisted of lateral- and medial orbitofrontal cortex (Boes et al., 2009).

bilateral ventral striatum and amygdala structures were performed using FSL randomize (Winkler et al., 2014) with 5000 random permutations and threshold-free cluster enhancement (Smith and Nichols, 2009). Bonferroni corrections were used for multiple comparisons corrections for testing the shape of multiple structures ($p_{corrected} = 0.01$). For illustrative purposes, we also performed classical vertex analysis containing vectors displaying the direction of shape alterations.

3. Results

3.1. Demographics

Due to the exclusion of 23 participants, our final sample consisted of 254 participants (n = 158 cases, 130 male; and n = 96 controls, 55 male). Out of the 158 cases, 59 were diagnosed with ODD, 11 with CD and 42 with both ODD and CD. The other 46 participants were included as "case" based on a CBCL aggression and/or rule-breaking behavior subscale T-score of ≥ 70. Among the cases, 44 participants were diagnosed with comorbid ADHD. Table 2 provides a summary of the demographic and clinical information. Table S1 provides demographic information across the different scan-sites.

3.2. Continuous measures

We found an effect of proactive aggression on amygdala volume, where an increase in proactive aggression was associated with smaller amygdala volume (b = -10.7, $\mathbf{t}$(348.3) = -2.27, p = 0.02, r = 0.14) in our entire sample. This association remained present after controlling for reactive aggression (b = -14.1, $\mathbf{t}$(302.7) = -2.29, p = 0.02, r = 0.14). However, when investigating cases only (n = 158), this association became non-significant (b = -9.37, $\mathbf{t}$(219.5) = -1.67, p = 0.09, r = 0.11).

Reactive aggression was associated with the volume of the insula (b = -21.7, $\mathbf{t}$(360.5) = -2.51, p = 0.01 r = 0.13), where more reactive aggression was associated with smaller volumes, also when controlled for the effect of proactive aggression (b = -26.5, $\mathbf{t}$(309.9) = -2.35, p = 0.02, r = 0.13; see Fig. 2). The associations were also present when investigating the cases only (n = 158; b = –32.60, $\mathbf{t}$(218.7) = -2.53, p = 0.01, r = 0.17). Adding diagnostic group to the model did not change the effect of proactive aggression on amygdala volume (b = -11.7, $\mathbf{t}$(331.1) = -2.29, p = 0.02) or the effect of reactive aggression on insula volume (b = –22.82, $\mathbf{t}$(337.2) = -2.27, p = 0.02).

No effect of hemisphere or any interactions between hemisphere and reactive aggression were observed. When investigating CT and SA of the insula separately, we did not find an association with reactive aggression (all p-values > 0.05). There was no effect of CU-traits on any of the cortical or subcortical volumes (all p-values > 0.05). There was also no effect of any of the continuous measures of aggression on ventral striatum or amygdala shape.

The effect of covariates and the model outputs are described in the Supplementary Material (See Table S3 for the proactive aggression model and Table S4 for the reactive aggression model).

Table 2
Demographic and clinical characteristics (n = 254).

	Case (n = 158)	Control n = 96	Test statistic	p-value
	N	*N*		
Sex m/f	130/28	55/41	$\chi^2 = 17.60$	< 0.001
	Mean (SD)	*Mean (SD)*		
Age	13.0 (2.8)	13.5 (2.6)	K-Wχ^2 = 2.33	0.13
[a]**IQ**	99.8 (11.3)	106.5 (10.6)	F = 21.41	< 0.001
Reactive aggression	12.0 (4.6)	5.8 (3.4)	K-Wχ^2 = 93.55	< 0.001
Proactive aggression	4.6 (4.4)	0.8 (1.4)	K-Wχ^2 = 79.42	< 0.001
ICU total score	33.4 (9.9)	21.0 (8.5)	K-Wχ^2 = 77.97	< 0.001
[b]**ODD symptom counts**	3.7 (2.4)	–		
[b]**CD symptom counts**	1.8 (2.4)	–		
[b]**ADHD**				
- Inattention	3.4 (3.0)	–		
- Hyperactivity/ impulsivity	3.0 (2.9)	–		
CBCL Aggression T-score	64.7 (25.9)	46.2 (17.2)	K-Wχ^2 = 72.19	< 0.001
CBCL Rule-breaking T-score	61.7 (17.0)	46.3 (16.7)	K-W χ^2 = 72.53	< 0.001
[c]**Medication use**				
- Stimulants	66	–		
- Antipsychotics	37	–		
- Antidepressants	4	–		
- [d]Other	7	–		

ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist; CD, conduct disorder; ICU, Inventory of Callous Unemotional Traits; K-W, Kruskal-Wallis; m/f, male/female; ODD, oppositional defiant disorder; SD, standard deviation;
a IQ estimated from a subset of the Wechsler Intelligence Scale for Children III (Wechsler, 2002).
b As measured with the K-SADS (Kaufman et al., 1997).
cMedication use was determined by parental report.
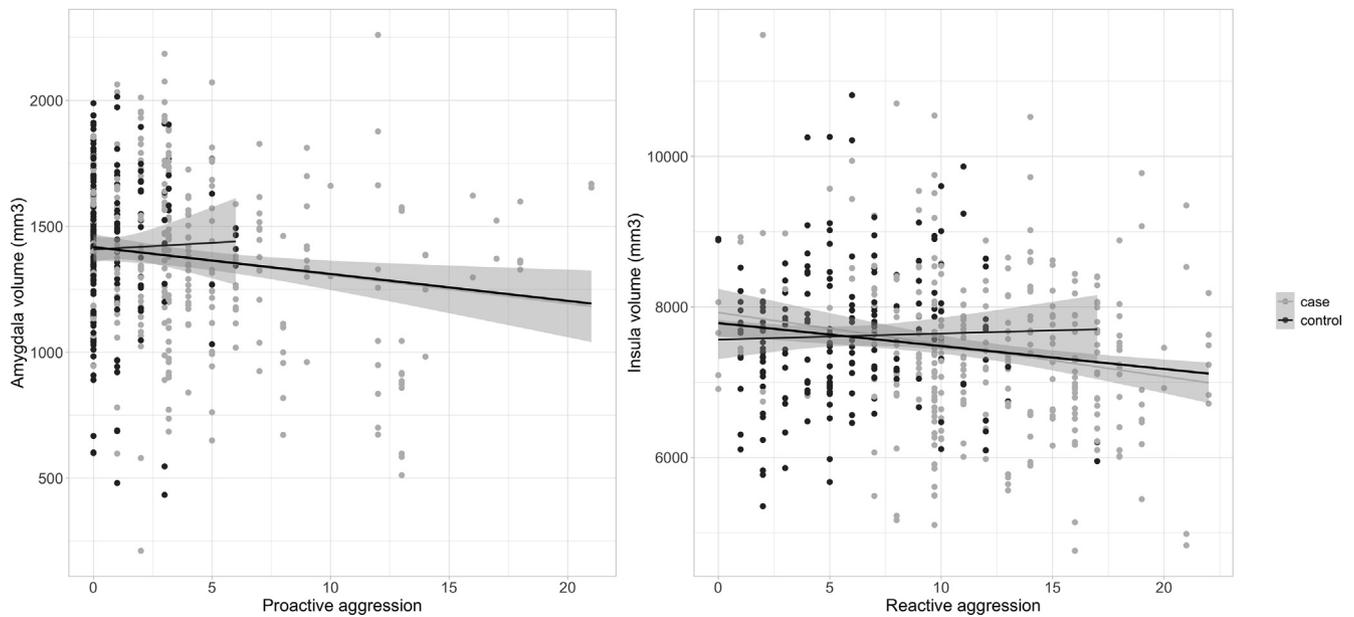d Other medications included mood-stabilizers (Lithium), anti-epileptic medication and benzodiazepines.

Fig. 2. Negative association between proactive aggression and total amygdala volume (A) and between reactive aggression and total insula volume (B). The thick black line represents associations across the entire sample. For illustrative purposes the associations for cases (dark-grey) and controls (light-grey) are shown as well.

3.3. Case-control comparisons

In our case-control comparisons we found that cases showed a significantly smaller volume of the vmPFC than controls (b = 572.4, $\mathbf{t}$ (305.6) = -3.02, p = 0.003, r = 0.17). No other group differences were found regarding volume, CT or SA in any of the regions (all p-values > 0.05). See Table S5 of the model output and the supplemental text for the effects of covariates.

Shape analyses of the subcortical regions revealed differences in the left (but not right) ventral striatum (Fig. 3), showing an overall inward position of the vertices (corrected p-value of 0.005) with the largest

difference in one anterior cluster of voxels (voxel-coordinates: x = 102, y = 143, z = 69, size = 28 voxels). This difference reflects a regional decreased shape of the anterior part of the left striatum in cases compared to controls. No shape differences between cases and controls were found for the amygdala.

4. Discussion

The current study investigated whether structural brain alterations in regions of interest chosen on the basis of two *meta*-analyses were differentially associated with reactive and proactive subtypes of
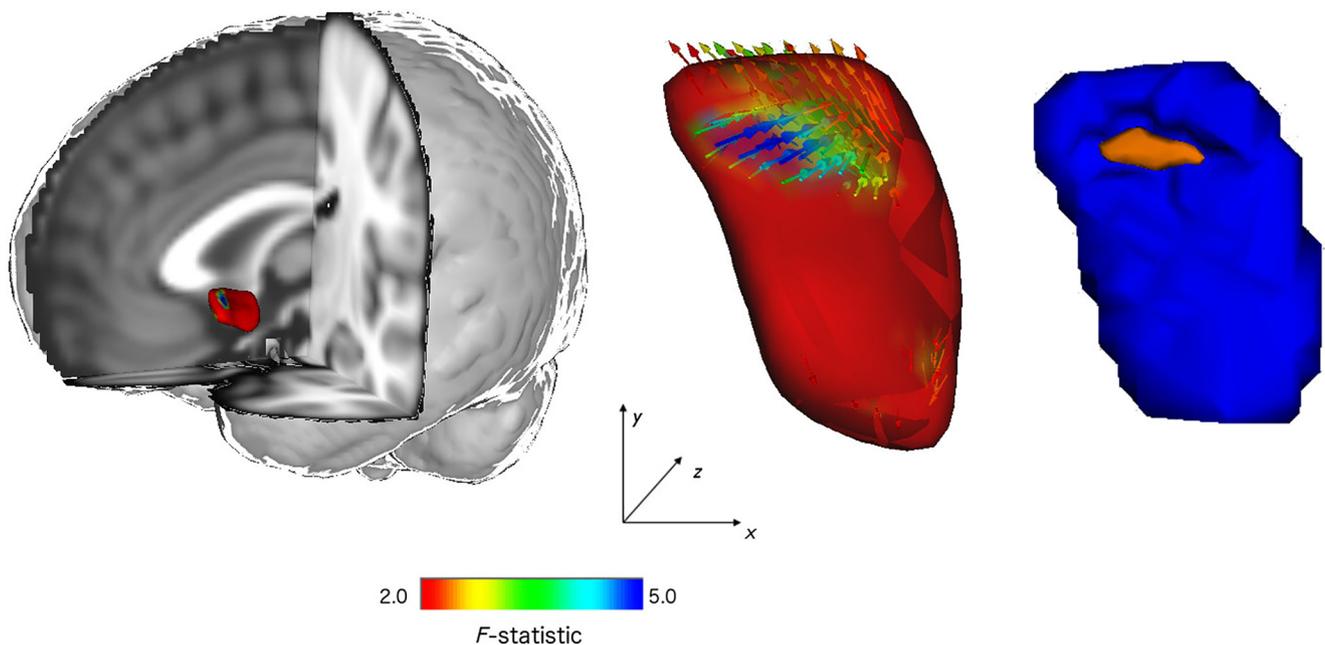

Fig. 3. Vertex analyses of shape alterations in the left ventral striatum. Left panel shows the anatomical location of the area and the local areas exhibiting shape change (alterations in color). The middle panel shows shape changes in the ODD/CD participants compared with controls with vector directions. Inward direction represents relative inward position of the vertices, pointing to regional decreased shapes. The color of the surface and the arrows indicate the Pillai's trace F-statistic in the middle panel. The right panel shows the results analyzed with the vertex-wise F-statistic. The region in orange corresponds to the anterior part of the ventral striatum shown to be smaller in cases than in controls (which resembles the dark blue arrows in the middle panel).

aggression. Our main finding is that we could confirm these differential associations by observing reactive aggression to be associated with smaller insula volume and proactive aggression with smaller amygdala volume, although not with the other regions of interest and with relatively small effect sizes. These associations, however, survived extensive controlling for possible confounding variables. No effects of CU traits were found in any of the regions. In addition, cases showed smaller volume of the vmPFC compared with healthy controls and differences regarding shape of the left ventral striatum. Participants with disruptive behaviour only showed subtle differences with controls. However, small neuroanatomic abnormalities may nevertheless have implications for behavior (Hoogman et al., 2017); here we showed a first association with aggression subtypes, implicating effects on functioning.

Aggression and conduct problems have been associated with several neurocognitive dysfunctions moderated by the presence or absence of psychopathic or CU traits (Blair et al., 2014). Higher levels of conduct problems or CU-traits (often associated with lower empathy) has been linked to reduced amygdala response to fear, sadness and pain (Blair et al., 2004; Jones et al., 2009), and to reduced amygdala volume (Cardinale et al., 2019; Fairchild et al., 2011, 2013; Pardini et al., 2014). However, we did not find an association between amygdala volume and CU-traits, but with proactive aggression, another severe form of aggression often associated with high CU-traits. Despite previous evidence for proactive aggression involving the striatum and vmPFC (Yang et al., 2017), related to impaired prediction error signaling and impaired decision making, we did not find an association between proactive aggression and the volumes of these regions in our sample.

Decision making and empathy are highly dependent on each other, where learning and representing the valence of objects and actions is critical in deciding whether to respond empathically, and is related to dysfunction of not only striatum, amygdala and vmPFC, but also insula (Fanning et al., 2017; O'Doherty, 2012). In the current study, we found a negative relation between reactive aggression and insula volume, a region assumed to be associated with responses to threat and frustration. Our result is in line with studies that report the amygdala to be associated with fear and sadness while the insula is more responsive to angry faces (Fusar-Poli et al., 2009; Passamonti et al., 2010). A reduced insula volume in association with more reactive aggression may explain a deficit in responding to threatening stimuli. Deficits in the insula have also been associated with poor decision making by relating outcome information (reward/punishment) wrongly to responding which in turn increases conduct problems (Blair, 2013; Dambacher et al., 2013; Frick and White, 2008).

Our findings of reduced vmPFC volume in disruptive behaviour are in accordance with the idea of reduced empathy, as this region is associated with responses to distress cues (Dawel et al., 2012). The alterations in the shape of the left ventral striatum has not been reported in aggression before and localizes a possible shape difference to the anterior part of the ventral striatum, although no volume differences were reported. Our differential findings of associations between amygdala and insula volume and respectively proactive and reactive aggression and group differences in vmPFC and ventral striatum reflect possible state (diagnosis) versus trait (continuous measures) effects which need replication in future studies that include both types of analyses.

We did not find any association between the volume of any of our regions of interest and the severity of CU traits. This may be due to the relatively low levels of CU traits in our sample compared to other studies; the group of children and adolescents in our study seem to show more reactive (impulsive) forms of aggression.

Important strengths of the current study are the investigation of reactive and proactive aggression in a large clinical sample in relation to structural brain alterations that was achieved because of a multi-site design. There were, however, also some limitations. First, we included

participants with aggression scores in the clinical range on the CBCL who did not fulfil all diagnostic criteria for ODD and/or CD. Especially the CD group was relatively small. In addition, the amount of ODD and CD symptoms in our cases group were relatively small. This may have caused heterogeneity in our cases, thus reducing symptom severity and may be reflected in our more pronounced findings of reduced volume in areas that are less specific for CU traits and lack of empathy types of aggression (ACC, vmPFC and striatum). However, reducing the sample to only cases with a clinical diagnosis did not change our results. Second, the male/female ratio was different for cases and controls which is inherent to the ratio of males/females that are diagnosed with these types of disorders. There was, however, no effect of sex on any of our results. The variance induced by the multi-site setup may further have diluted some of our findings. However, investigating in multiple centers also allowed us to have a larger sample size compared to many previous studies and facilitated in generalizing our findings. Our sample of controls showed very little variation in aggressive behaviour, possibly reducing our power for dimensional analyses. However, investigating only cases as well as the full sample resulted in the same associations between amygdala volume and proactive aggression (although non-significant) and insula volume and reactive aggression. The two measures of aggression are further highly associated with each other, but controlling the effect of one for the effect of the other did not change our results.

In conclusion, the current study showed a negative relation between proactive aggression and amygdala volume and between reactive aggression and insula volume (after controlling for several confounding variables) and a decreased volume of the vmPFC in children and adolescents with disruptive behaviour compared with controls. Our findings support the idea of subtype-specific impairments in aggression, where different brain regions are involved in empathy, threat response and decision making which are in turn more associated with either proactive or reactive aggression. This may have implications for designing targeted intervention strategies, which needs to be further explored in future studies.

Acknowledgments

Conflict of interest

T Banaschewski served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Medice, NovartisOxford outcomes, PCM scientific, Shire and Viforpharma. He received conference support or speaker's fee by Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire & Viforpharma. The present work is unrelated to the grants and relationships noted earlier. U. Schulze received a speaker's fee from Shire and serves as an unpayed ethics advisor in two EU-funded projects which are not related to the present work. C Arango has been a consultant to or has received honoraria or grants from Acadia, Ambrosseti, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Forum, Instituto de Salud Carlos III, Gedeon Richter, Janssen Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Roche, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovio and Takeda. D Brandeis serves

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102344.

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