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A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy

Philipp Sterzer,[a,c,*] Christina Stadler,[b] Fritz Poustka,[b] and Andreas Kleinschmidt[a,d,e]

[a]*Departments of Neurology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany*
[b]*Departments. of Child- and Adolescent Psychiatry, Johann Wolfgang Goethe University, Frankfurt am Main, Germany*
[c]*Department of Psychiatry, Charité University Hospital, Humboldt University, Berlin, Germany*
[d]*INSERM, Unité 562, F-91191 Gif-sur-Yvette, France*
[e]*CEA, DSV, I²BM, NeuroSpin, F-91191 Gif-sur-Yvette, France*

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The goal of this study was to determine whether brain regions implicated in emotion processing show structural alterations in adolescents with conduct disorder (CD). Using an optimized voxel-based morphometry protocol, we compared grey matter volume in 12 patients with CD and 12 age-, sex-, and intelligence-matched control subjects. Grey matter volume in bilateral anterior insular cortex and the left amygdala was significantly reduced in CD patients compared to healthy control subjects. The insular grey matter abnormalities could be attributed to aggressive behaviour. Moreover, bilateral anterior insular grey matter volume in CD patients correlated significantly with empathy scores. These novel findings point at a joint neuroanatomical substrate underpinning aggressive behaviour and impaired capacity of empathy and suggest a critical role for the anterior insula in regulating social behaviour.

Keywords: Conduct disorder; Voxel-based morphometry; Aggression; Empathy; Insular cortex; Amygdala

Introduction

The problem of juvenile delinquency and violence in modern societies has stimulated the search for factors that may predispose to aggressive behaviour. Despite the undisputable importance of socio-economic and political factors, the understanding of pathological aggression should benefit from identifying its biological basis (Davidson et al., 2000).

The propensity for aggressive and violent behaviour has been proposed to indicate a profound disturbance in an appropriate empathic response to the suffering of another (Blair, 2005; Frick et al., 1994; Miller and Eisenberg, 1988; Pardini et al., 2003; Soderstrom, 2003). Such lack of empathy could result from a dysfunction of neural circuits involved in recognizing emotional expressions that indicate distress in other individuals (Blair, 2001, 2005; Davidson et al., 2000). Functional neuroimaging studies of emotion processing in aggressive and violent individuals indeed support this view by demonstrating functional deficits in brain regions involved in emotion recognition, most notably the amygdala (Birbaumer et al., 2005; Kiehl et al., 2001; Sterzer et al., 2005; Veit et al., 2002). In addition to relying on emotion recognition, empathy may also involve brain structures which in general serve the representation of emotional and bodily states of arousal (Craig, 2002; Critchley, 2005; Damasio, 2003). Accordingly, recent functional neuroimaging studies investigating the mechanisms of empathy for pain (Jackson et al., 2005, 2006; Singer et al., 2004, 2006) and disgust (Wicker et al., 2003) or imitation of emotional facial expression (Carr et al., 2003) support the notion of a central involvement of anterior insular cortex in empathy (for overviews, see de Vignemont and Singer, 2006; Decety and Lamm, 2006; Gallese et al., 2004).

In addition to deficient empathy, it has been proposed that aggressive and antisocial behaviour may arise from functional deficits in brain regions involved in the regulation of emotional behaviour, most importantly orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Adolphs, 2003; Davidson et al., 2000). OFC is thought to constrain affective impulses through its connections with other prefrontal regions and the amygdala, as suggested by evidence from the study of patients with OFC lesions (Anderson et al., 1999) as well as structural (Raine et al., 2000) and functional neuroimaging (Kiehl et al., 2001; Raine et al., 1998) in antisocial and psychopathic individuals. ACC plays an important role in the regulation of cognitive and emotional processes (Bush et al., 2000), and abnormal function in this region has been observed in patients with conduct disorder (Sterzer et al., 2005), antisocial personality disorder (Veit et al., 2002), and in criminal psychopaths (Kiehl et al., 2001). While in normal individuals these brain regions act to constrain the expression of affect, deficits in this

* Corresponding author. Department of Psychiatry, Charité University Hospital/St Hedwig Hospital, Große Hamburger Straße 5 - 11, D-10115 Berlin, Germany. Fax: +49 030 2311 2963.
E-mail address: philipp.sterzer@charite.de (P. Sterzer).
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circuit are hypothesized to increase a person's inclination towards vulnerability to aggressive behaviour (Davidson et al., 2000).

Here, we asked whether aggressive behaviour might be associated with structural deficits in brain regions implicated in emotion recognition, empathy, and emotion regulation. We used structural magnetic resonance (MR) imaging in conjunction with voxel-based morphometry (VBM) to examine grey matter abnormalities in adolescents with conduct disorder (CD). CD is characterized by repetitive and chronic aggressive and antisocial behaviour in which the basic rights of others or major age-appropriate norms or rules of society are violated and that has a variety of implications such as school refusal, social communication problems, and legal involvement (American Psychiatric Association, 1994). CD is often associated with other psychiatric diagnoses, most prominently attention-deficit hyperactivity disorder (ADHD) and anxiety disorders (Loeber et al., 2000). The participants were therefore carefully assessed with respect to symptoms of such co-morbidities, enabling us to test whether any volumetric differences between CD patients and normal control subjects could be attributed to aggressive behaviour. Finally, reduced empathy may be an important factor predisposing to aggressive behaviour, as outlined above. We therefore determined empathy levels psychometrically and probed their association with regional grey matter volume in CD patients.

Materials and methods

Subjects and behavioural measures

Twelve male adolescents with CD recruited from the specialized 'aggression clinics' of the Department of Child and Adolescent Psychiatry and twelve age- and intelligence-matched male control subjects recruited from secondary schools volunteered for the experiment. All participants were white Caucasian and were born and raised in Germany. None of the participants had a history of traumatic brain damage or other neurological diseases. None of the control subjects had any history of psychiatric disease. The experimental protocol was approved by the local ethics committee. All participants' parents gave written informed consent.

All patients underwent a structured clinical interview (Dopfner and Lehmkuhl, 2000) by a trained psychiatrist. The diagnosis of CD was established in accordance with both the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994) and the International Classification of Diseases (ICD-10, http://www.who.int/classifications/apps/icd/icd10online). A standardized symptom checklist according to DSM-IV and ICD-10 (DCL-SSV), which has been proven to be reliable and valid in large samples of children and adolescents (Dopfner and Lehmkuhl, 2000), was used. DCL-SSV is a clinical rating scale and includes oppositional-aggressive and dissocial-aggressive symptoms specified in the DSM-IV and ICD-10. These symptoms are scored by assigning to each symptom a severity estimate on a 4-point scale (i.e., 0 = not at all, 1 = just a little, 2 = pretty much, and 3 = very much). A global CD-score is formed by summarizing items with clinical significance (scoring 2 and 3). In accordance with DSM-IV/ICD-10, a minimum of 4 out of 25 criteria are required for the diagnosis of CD. In the patient group, on average 10.9 ± 0.9 (SEM) criteria were present, compared to 0.4 ± 0.3 in the control group. Out of 10 possible criteria specifying aggressive behaviour to people and animals, on average 3.2 ± 0.5 were present in the patient group, whereas none of the control subjects fulfilled any of these criteria. All patients had childhood-onset CD according to DSM-IV, i.e., onset of at least one criterion characteristic of CD prior to age 10. Seven out of 12 patients also fulfilled the diagnostic criteria (DSM-IV and ICD-10) for ADHD in addition to CD.

In addition to the clinical interview, the Child Behaviour Checklist (CBCL) (Achenbach, 1991) was used as a quantitative measure of psychiatric symptoms. The CBCL is a questionnaire to be completed by parents of 4- to 18-year-olds and can be scored on 8 syndrome scales (see Table 1). The norms and the discriminant validity of the German version of the CBCL are comparable to the original English version (Schmeck et al., 2001). The results of the CBCL are reported and used for further analyses as *t* scores. The Impulsiveness–Venturesomeness–Empathy Questionnaire (IVE) (Eysenck and Eysenck, 1991) was used to further characterize the study groups behaviourally. The IVE is an established self-administered questionnaire for children that was designed to assess impulsiveness (reflecting poor behavioural control and lack of ability to delay gratification), venturesomeness (reflecting sensation-seeking and risk-taking behaviour), and empathy (reflecting sensitivity to the feelings and reactions of others and susceptibility to social cues). It consists of 48 yes/no questions in simple language appropriate for children, which are face-valid measures of impulsivity (e.g., "I often do things on the spur of the moment"), venturesomeness (e.g., "I would enjoy parachute jumping"), and empathy (e.g., "I feel sorry for children who get bullied a lot"). The scale discriminates conduct-disordered children from controls and is predictive of future conduct problems (Luengo et al., 1994). A previously validated German version of the IVE was used (Eysenck et al., 1990; Stadler et al., 2004). Raw scores of the IVE are reported and used for further analyses. Intelligence quotient (IQ) was assessed using the Culture Fair Test (Cattel and Catell, 1973) in a validated German version (Weiss, 1987). The Culture Fair Test is a language-free intelligence test which was chosen because of potential verbal impairments in CD patients (Lynam et al., 1993). Parental socio-economic status was assigned to one of three categories (unskilled/qualified worker, clerk/commercial occupation, and graduate occupation).

Table 1
Demographic and behavioural characteristics of the study groups

	Controls (n = 12)		Patients (n = 12)		
	Mean	SEM	Mean	SEM	p
Age	12.5	0.45	12.75	0.49	0.71
IQ	107.2	3.0	100.6	3.7	0.18
Socio-economic state	2.33	0.19	1.83	0.24	0.12
Child behaviour check list (Achenbach, 1991)					
Social withdrawal	51.7	0.9	61.3	2.8	0.004
Somatic complaints	53.3	2.1	59.8	3.2	0.11
Anxiety/depression	52.3	1.3	61.9	2.5	0.002
Social problems	51.9	1.4	63.9	2.5	<0.001
Thought problems	51.2	0.8	55.9	2.5	0.08
Attention problems	53.4	1.6	62.8	2.1	0.002
Aggressive behaviour	52.7	1.5	75.8	2.4	<0.001
Delinquent behaviour	53.4	1.1	70.5	1.6	<0.001
Impulsiveness–Venturesomeness–Empathy Questionnaire (Eysenck and Eysenck, 1991)					
Impulsiveness	7.3	0.9	11.5	0.8	0.003
Venturesomeness	10.4	1.0	12.3	0.8	0.18
Empathy	8.8	0.8	4.9	0.8	0.009

MR imaging and data analysis

Images were acquired on a 1.5-T scanner (Siemens Vision, Erlangen, Germany), using a T1-weighted 3D MPRAGE sequence (TR 9.7 ms, TE 4 ms, TI 300 ms, flip angle 12°, voxel size 1×1×1 mm). Data analysis was carried out with SPM2 (http://www.fil.ion.ucl.ac.uk/spm) using Matlab 6.5 (MathWorks, Natick, MA, USA). An optimized VBM protocol was applied, the pre-processing steps of which have been described in detail previously (Good et al., 2001). Customized grey and white matter templates for normalization to standard anatomical space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca/brainweb) were created from all subjects' (patients and controls) MR images (Good et al., 2001). Images were smoothed with an 8-mm full-width-at-half-maximum (FWHM) isotropic Gaussian kernel.

We assessed, firstly, regional between-group differences in grey matter, and secondly, grey matter changes correlating with empathy scores as assessed by the IVE questionnaire across the CD patient group. In both analyses, we included global grey matter signal, age, and IQ as confounding covariates. As stated above, the existing literature provides a priori hypotheses regarding the regions involved in emotion recognition (amygdala), empathy (anterior insula), and emotion regulation (ACC, OFC). These regions of interest (ROIs) were defined anatomically and delineated bilaterally on an average normalized brain image (derived from all 24 participants, see Fig. S1) using MRIcro (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). The anatomical boundaries of the ROIs were traced manually in three planes with reference to standard anatomical atlases. The amygdala mask comprised 800 voxels per hemisphere; orbitofrontal cortex mask 9600 voxels; anterior insula mask 2600 voxels; and the anterior cingulate mask 5600 voxels. Statistical testing was restricted to these ROIs and effects are reported if significance reached $p<0.05$, corrected for multiple comparisons using family-wise error correction (FWE) within each ROI (small-volume correction). To not bias our results towards smaller regions, we also report trends within ROIs if significant at $p<0.001$, uncorrected. In addition to the ROI-based analyses, we also tested for exploratory purposes voxel-by-voxel for grey matter differences throughout the entire brain, using a significance threshold of $p<0.05$, FWE-corrected across the whole brain.

CD is associated with attention-deficit and hyperactivity disorder (ADHD) and also with affective symptoms (Loeber et al., 2000). We therefore tested for correlations between the regional maxima of any observed grey matter group differences and relevant behavioural factors as represented by scores for aggressive behaviour, attention problems, and anxiety/depression scales of the CBCL. To determine which of these behavioural factors most strongly predicted the observed group differences in grey matter volume, we first tested for across-subject correlations between behavioural factors and grey matter volume at the peak voxel of each cluster showing a significant group difference and then performed stepwise multiple regression analyses. Due to spatial smoothing with an 8-mm FWHM Gaussian kernel, the peak voxel represents a weighted average of and is thereby representative for the nearby voxels within the range of the smoothing kernel. Separate multiples regression analyses were performed for each region showing significant group differences, using the grey matter value at the peak voxel of each significant cluster (as determined by VBM, see above) as dependent variable. The aggressive behaviour, attention problems, and anxiety/depression scores from the CBCL were used as independent variables. These analyses were performed across all participants (both patients and controls) because their aim was not to detect correlations between behavioural variables and brain structure per se, but to determine the contribution of the behavioural variables to the observed group differences. F probabilities were set to <0.05 to enter and >0.1 to remove variables.

Results

Demographic and behavioural results

Patients and control subjects did not differ significantly in age, intelligence, or parental socio-economic state (Table 1). As expected, CBCL scores for aggressive behaviour and delinquent behaviour, i.e., the diagnosis-defining features in CD, were significantly higher in the patient group (Table 1). Scores for social withdrawal, anxiety/derepression, and attention problems also showed significant group differences. Psychometric testing using the IVE questionnaire revealed significantly lower empathy scores in adolescents with CD compared to controls (Table 1). CD patients had higher impulsiveness scores but did not differ in venturesomeness.

Group differences in grey matter volume

Compared to the control group, grey matter volume in adolescents with CD was significantly reduced in the anterior insula bilaterally (Figs. 1a and b, Table 2). In the right hemisphere, the local maximum in grey matter difference was located slightly more dorsally than in the left hemisphere, at the border between insular cortex and frontal operculum. Grey matter volume was also significantly smaller in the medial part of the left amygdala of CD patients (Fig. 1c, Table 2). Our a priori regions of interest also comprised the ACC and OFC, but no significant grey matter differences or even trends were observed in these cortical regions. We also did not find any significant grey matter differences elsewhere in the brain.

Behavioural differences between the study groups were not limited to aggression, which was the behavioural feature of central interest in our study, but were also present in other behavioural variables that may account for the observed grey matter differences (Table 1). We therefore sought to determine the degree to which the observed grey matter differences could be attributed to any of the relevant behavioural differences between the study groups. In a first step, we assessed the correlations between the local maxima of the grey matter differences and scores on the CBCL scales for aggressive behaviour, but also for attention problems and anxiety/depression as the most relevant confounding variables (Loeber et al., 2000). The correlation matrix (Table 3) revealed that grey matter volume in both anterior insular cortices showed a highly significant correlation with aggressive behaviour. A weaker but significant relationship was also observed for attention problems, but not for anxiety and depressive symptoms. Grey matter volume in the left amygdala correlated significantly with attention problems and aggressive behaviour, and there was a trend towards a significant correlation between left amygdala and scores on the anxiety/depression scale. A subsequent stepwise multiple regression analysis (Table 4) confirmed aggressive behaviour as the strongest predictor for grey matter volume in the left and right

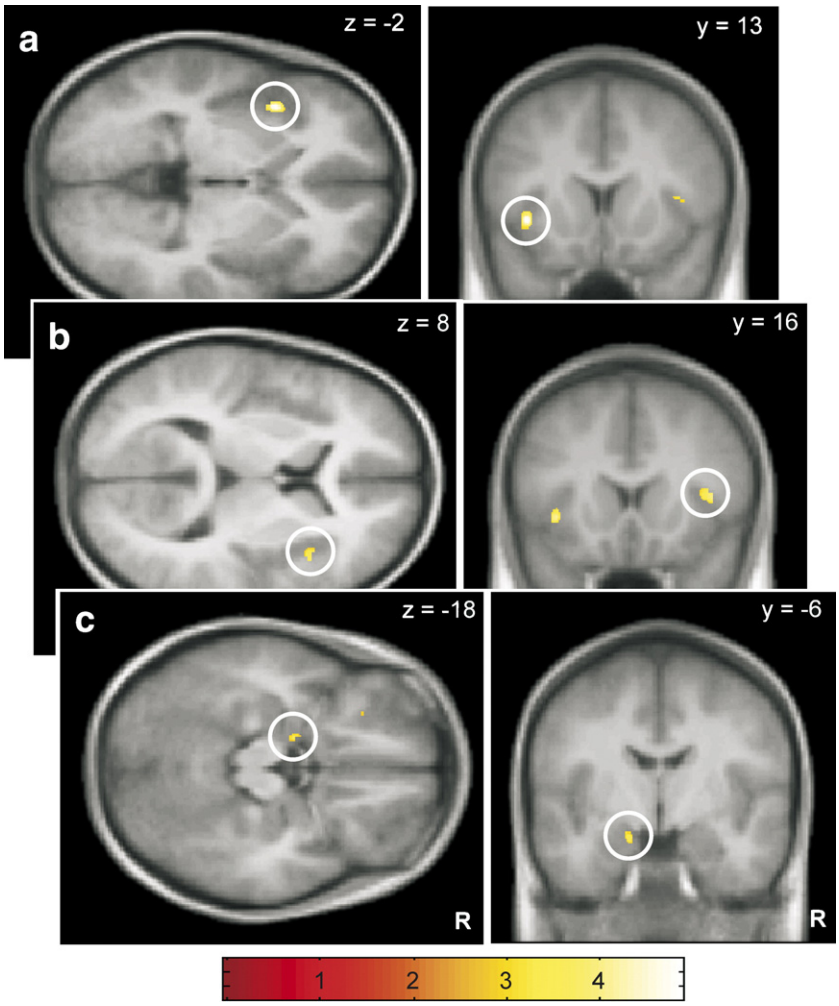

Fig. 1. Areas of reduced grey matter volume in adolescents with conduct disorder compared with age- and IQ-matched controls ($n=12$, respectively) are rendered onto transversal and coronal sections of the mean structural scan of all participants. The scale represents t scores. Significant differences were observed in the left (a) and right (b) anterior insula and in the left amygdala (c; see Table 2).

anterior insula (left: beta=−0.54, $p<0.007$; right: beta=−0.56, $p<0.004$). In the left amygdala, attention problems most strongly predicted grey matter volume (beta=−0.49, $p<0.016$).

Table 2

Region	Coordinates			p (corrected)[a]	p (uncorrected)	t
	x	y	z			
Group differences between adolescents with conduct disorder (n=12) and control subjects (n=12) in grey matter volume						
Right anterior insula	42	16	8	0.04	<0.001	3.92
Left anterior insula	−38	13	−2	0.008	<0.001	4.88
Left amygdala	−16	−6	−18	0.03	0.001	3.46
Regional maxima of correlations between empathy scores and grey matter volume in adolescents with conduct disorder (n=12)						
Right anterior insula	37	15	11	0.049	<0.001	5.90
Left anterior insula	−26	18	10	0.093	0.001	5.01
Right ventral ACC	11	47	8	0.28	0.001	4.46
Left ventral ACC	−8	47	−6	0.17	<0.001	5.19

[a] Family-wise error correction for multiple comparison within region of interest (see Methods and materials).

Correlations between empathy and regional grey matter volume

Anterior insular cortex is known to be involved in emotion processing (Craig, 2002) but has been less in the focus of attention than the amygdala or OFC. Recently, however, neural responses in the anterior insula have been related to the experience of empathy (Carr et al., 2003; Jackson et al., 2005, 2006; Singer et al., 2004,

Table 3
Correlations across all participants ($n=24$) between behavioural factors from the child behaviour checklist (Achenbach, 1991) and grey matter volume at the regional maxima of group differences

		Left anterior insula	Right anterior insula	Left amygdala
Aggressive behaviour	Correlation (r)	−0.54	−0.56	−0.44
	p-value	0.007	0.004	0.033
Attention problems	Correlation (r)	−0.43	−0.42	−0.49
	p-value	0.037	0.042	0.016
Anxiety/ depression	Correlation (r)	−0.36	−0.225	0.40
	p-value	0.085	0.29	0.051

r=Pearson correlation coefficient.

Table 4
Stepwise multiple regression analyses testing which behavioural factors best predict grey matter volume differences

	β	t	p	Partial correlation
Left anterior insula				
Included variables				
Aggressive behaviour	−0.54	−3.0	0.007	
Excluded variables				
Attention problems	−0.26	−0.09	0.93	−0.02
Anxiety/depression	−0.46	−0.2	0.84	−0.04
Right anterior insula				
Included variables				
Aggressive behaviour	−0.56	−3.2	0.004	
Excluded variables				
Attention problems	0.04	0.15	0.88	0.032
Anxiety/depression	0.19	0.85	0.40	0.18
Left amygdala				
Included variables				
Attention problems	−0.49	−2.6	0.016	
Excluded variables				
Aggressive behaviour	−0.15	−0.51	0.62	−0.11
Anxiety/depression	−0.13	−0.48	0.64	−0.10

Probabilities of F to enter ≤0.05 and F to remove ≥0.1.

2006; Wicker et al., 2003). Our behavioural testing had revealed lower empathy scores in adolescents with CD compared to controls, and we hence probed the subject-by-subject relationship between empathy levels and grey matter volume in the CD group. We indeed found a significant correlation between empathy scores and grey matter volume in the right dorsal anterior insular cortex, in virtually the same location as the group difference between patients and controls (Figs. 2a and b, Table 2). A similar correlation was detected at a more lenient statistical threshold ($p<0.001$, uncorrected) at the corresponding location in the left hemisphere. This focus was located slightly more dorsally than the group difference in the left anterior insula, but a trend ($p<0.009$, uncorrected) was also observed in the more ventral region. An additional focus of correlation between empathy levels and grey matter volume in the patient group was detected at an uncorrected statistical threshold ($p<0.001$) in the anterior part of the ACC bilaterally (Table 2). No significant correlation was observed between empathy scores and grey matter volume in the amygdala.

Discussion

To our knowledge, this is the first study to show structural brain abnormalities associated with aggressive behaviour as early as in adolescence. Reduced grey matter volume in CD patients compared to controls was detected in the left amygdala and the anterior insula bilaterally. Importantly, the group differences in bilateral anterior insula cortex could be related to aggressive behaviour. Moreover, empathy levels in the patient group correlated with anterior insular grey matter volume but not that of amygdala or any other of the regions assessed. Remarkably, these findings reached statistical significance despite a relatively small sample size. On the other hand, this also precludes strong conclusions about the absence of morphological differences in other brain regions.

The finding of reduced amygdala volume is in line with evidence from functional imaging studies showing dysfunction of this structure in adult psychopaths (Birbaumer et al., 2005; Kiehl et al., 2001) and adolescents with CD (Sterzer et al., 2005). Amygdala volume is also decreased in individuals with a genetic predisposition towards violent behaviour (Meyer-Lindenberg et al., 2006). The amygdala plays a central role in regulating social interactions as it mediates the processing of emotional stimuli. Amygdala function is thus a key determinant of behavioural responses to emotional information (e.g., distress cues) and a reduction of amygdala volume is in keeping with current models regarding the mechanisms that underlie aggressive behaviour (Blair, 2005; Davidson et al., 2000; Dolan, 2002). The observed group difference could not be attributed unequivocally to aggressive behaviour in our study population. In fact, the grey matter deficit in the left amygdala also correlated with aggression scores but was most strongly predicted by attention problems. Previous behavioural work has shown that patients with ADHD are impaired at recognizing emotional expressions (Cadesky et al., 2000; Pelc et al., 2006; Singh et al., 1998), which could originate from a failure to attend to the appropriate cues of affect. Recent evidence suggests an important role for the amygdala in allocating attention to features of a face that are critical for emotion recognition (Adolphs et al., 2005). Deficient amygdala function may thus underlie impaired emotion recognition related to attention problems, which is supported by a recent observation pointing towards reduced amygdala volume in patients with ADHD (Plessen et al., 2006). However, the relationship between attention problems and amygdala volume in our study should be interpreted with caution because attention problems were not the primary focus of our study and ADHD was diagnosed only in a subgroup of individuals in our patient group as a co-morbid condition along with conduct disorder.

The group differences in the bilateral anterior insula could be clearly attributed to aggressive behaviour rather than to other relevant co-morbid symptoms. Moreover, the negative correlation of anterior insular grey matter volume with empathy levels in CD patients further supports the functional significance of this finding. One might be concerned that the validity of the psychometric data could be hampered by verbal difficulties (Luengo et al., 1994; Miller and Eisenberg, 1988) or lack of insight in patients with CD. It should be noted, however, that the IVE questionnaire was developed especially for children and great care was taken to keep the language and content of the questions simple and appropriate for children (see examples in Materials and methods). Moreover, the observed group differences regarding both impulsivity and empathy are in accord with previous findings in antisocial individuals (Luengo et al., 1994; Miller and Eisenberg, 1988). Finally, differences in the ability to respond to the questions would have been unlikely to cause the specific differential effects for the three IVE subscales that we observed (see Table 1).

Anterior insular cortex plays a key role in emotion by providing an interface between the mapping of bodily reactions to emotional stimuli and subjective feeling states (Craig, 2002; Critchley, 2005; Paulus and Stein, 2006). Recent findings have highlighted that the right anterior insula contributes to emotional feeling states originating in representations of visceral arousal (Critchley et al., 2004). In this study, activity in the right anterior insula cortex correlated with interoceptive awareness and predicted general visceral sensitivity and subjective emotional experience (as did right anterior insular grey matter volume, in a parallel structural

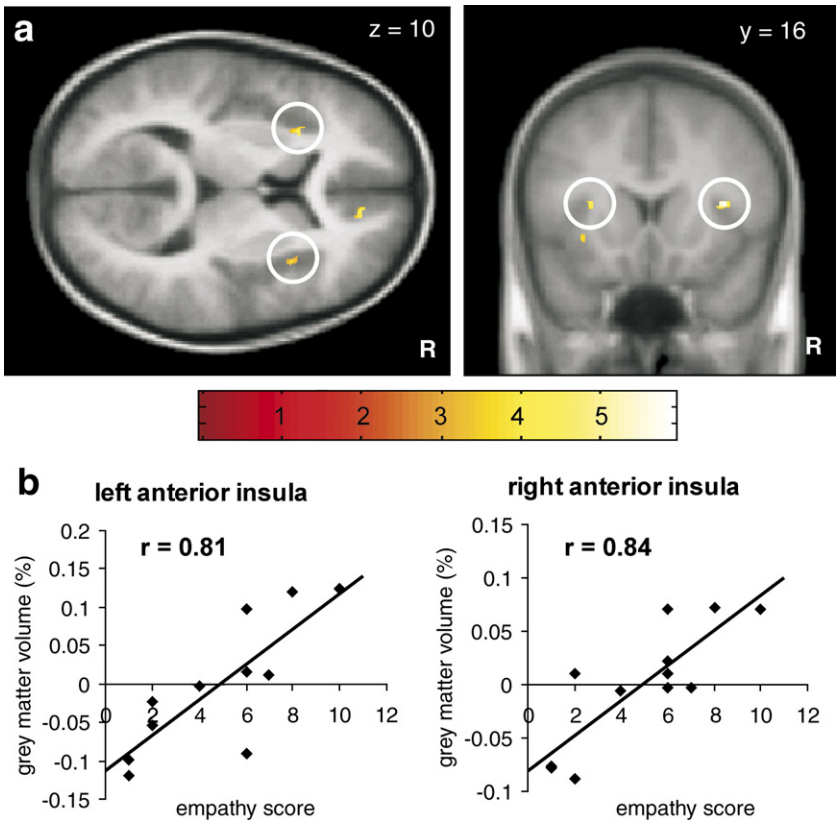

Fig. 2. (a) Areas where grey matter volume correlates with individual empathy scores as measured by the Impulsiveness–Venturesomeness–Empathy Questionnaire (Eysenck and Eysenck, 1991) in adolescents with conduct disorder ($n=12$) are rendered onto transversal and coronal sections of the mean structural scan of all participants (see Table 2). White circles indicate areas of significant correlation in bilateral anterior insular cortex. The colour scale represents t scores. (b) Scatter plots showing the correlation between grey matter volume and empathy scores at the peak voxels in left and right anterior insula as shown in panel a. The lines represent the linear best fit and r refers to the correlation coefficient.

study). An important role for right anterior insula for the representation of autonomic states is also supported by the finding that its volume is reduced in patients with an acquired failure of the peripheral autonomic nervous system (Critchley et al., 2003). This latter result is particularly interesting in the context of our present study, given the well-established finding of reduced autonomic responsiveness in antisocial individuals and those with psychopathic tendencies (Blair, 1999; Blair et al., 1997; Herpertz et al., 2003, 2005; Loney et al., 2003; Raine, 2002). In our study, insular grey matter in aggressive adolescents was reduced and correlated with empathy levels in both hemispheres, as opposed to a strong lateralization to the right hemisphere in studies investigating the central representations of autonomic states. It was recently proposed that this asymmetry may be related to differential roles of right and left anterior insula in representing sympathetic and parasympathetic nervous system activity, respectively (Craig, 2005). The bilateral anterior insular finding in our study may thus reflect an involvement of both sympathetic and parasympathetic representations in the experience of empathy.

While a more detailed characterization of the relationship between autonomic responses, aggression, and anterior insular cortex remains a topic for future research, our current data point at anterior insular cortex as a joint neuroanatomical substrate underpinning impaired capacity of empathy and aggressive behaviour. There is increasing evidence for a crucial involvement of anterior insula in the experience of empathy (Carr et al., 2003; Jackson et al., 2005, 2006; Singer et al., 2004, 2006; Wicker et al., 2003), but little is known about the role of this structure in aggressive behaviour. One indication for an insular deficit in relation to pathological aggression has come from a recent combined VBM and positron emission tomography study demonstrating bilateral anterior insular grey matter reduction and hypoperfusion in children with Smith Magenis syndrome, a genetic condition characterized by aggressive behaviour among other behavioural abnormalities such as mental retardation, speech delay, and attention deficits (Boddaert et al., 2004). Our finding that an abnormality in anterior insular cortex is linked with pathological social behaviour is consistent with the proposal that the same neural structures that serve the processing of one's own feeling states are also required for empathizing with others' feelings (Critchley, 2005; de Vignemont and Singer, 2006; Singer et al., 2004). Here, we provide empirical support for such a model by showing that a structural deficit in a region involved in mediating emotional experience is associated with a lack of empathy. Crucially, however, our findings go one step further by demonstrating a joint structural neural correlate of impaired empathy and aberrant social behaviour. This observation should serve as a starting point for future research explicitly addressing the question how anterior insular function, e.g., in tasks involving empathy, is related to aggressive behaviour. Moreover, it should be interesting to learn more about the role of anterior insular cortex for the relationship between autonomic functioning and empathy in

normal and aggressive individuals. One might hypothesize that the anterior insula could serve as a hub for the integration of autonomic responses, subjective feeling states, and social perception.

In addition to anterior insula, we also found correlations between empathy and grey matter volume in ACC bilaterally, while no significant group difference was found in this region. Previous studies investigating the neural correlates of empathy for pain have found strong effects in the ACC in addition to the anterior insula, albeit in a more dorsal and posterior ACC subregion (Jackson et al., 2005, 2006; Singer et al., 2004, 2006). These earlier findings may thus be specifically related to the subjective experience of (and empathy for) pain rather than reflecting a more general mechanism related to empathy. Remarkably, however, altered anterior cingulate function and structure has repeatedly been found in association with alexithymia, which refers to an impaired ability to identify and express one's own emotional states (Berthoz et al., 2002; Frewen et al., 2006; Gundel et al., 2004; Kano et al., 2003; Moriguchi et al., 2006). We did not assess alexithymia in our patients and cannot therefore make any strong conclusions about its role for the observed correlation between empathy and grey matter in ACC. However, it is tempting to speculate that this finding may hint at a common neural substrate of impaired access to one's own feeling states and empathy with the feelings of others.

Conclusion

We demonstrate a morphological neural correlate of pathological aggressive behaviour as early as in adolescence. Moreover, our results extend the relation between empathy and the brain both to the structural neural and the pathological behavioural level and hence provide a putative neurobiological substrate for the long-standing proposal that a lack of empathy might predispose towards violent social behaviour (Blair, 2005).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2007.04.043.

References

Achenbach, T.M., 1991. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Department of Psychiatry, Univ. of Vermont, Burlington, VT.

Adolphs, R., 2003. Cognitive neuroscience of human social behaviour. Nat. Rev., Neurosci. 4, 165–178.

Adolphs, R., Gosselin, F., Buchanan, T.W., Tranel, D., Schyns, P., Damasio, A.R., 2005. A mechanism for impaired fear recognition after amygdala damage. Nature 433, 68–72.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. DSM-IV, 4th ed. American Psychiatric Association, Washington (DC).

Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., Damasio, A.R., 1999. Impairment of social and moral behavior related to early damage in human prefrontal cortex. Nat. Neurosci. 2, 1032–1037.

Berthoz, S., Artiges, E., Van De Moortele, P.F., Poline, J.B., Rouquette, S., Consoli, S.M., Martinot, J.L., 2002. Effect of impaired recognition and expression of emotions on frontocingulate cortices: an fMRI study of men with alexithymia. Am. J. Psychiatry 159, 961–967.

Birbaumer, N., Veit, R., Lotze, M., Erb, M., Hermann, C., Grodd, W., Flor, H., 2005. Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study. Arch. Gen. Psychiatry 62, 799–805.

Blair, R.J., 1999. Responsiveness to distress cues in the child with psychopathic tendencies. Pers. Individ. Differ. 27, 135–145.

Blair, R.J., 2001. Neurocognitive models of aggression, the antisocial personality disorders, and psychopathy. J. Neurol. Neurosurg. Psychiatry 71, 727–731.

Blair, R.J., 2005. Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. Conscious. Cogn. 14 (4), 698–718.

Blair, R.J., Jones, L., Clark, F., Smith, M., 1997. The psychopathic individual: a lack of responsiveness to distress cues? Psychophysiology 34, 192–198.

Boddaert, N., De Leersnyder, H., Bourgeois, M., Munnich, A., Brunelle, F., Zilbovicius, M., 2004. Anatomical and functional brain imaging evidence of lenticulo-insular anomalies in Smith Magenis syndrome. NeuroImage 21, 1021–1025.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. 4, 215–222.

Cadesky, E.B., Mota, V.L., Schachar, R.J., 2000. Beyond words: how do children with ADHD and/or conduct problems process nonverbal information about affect? J. Am. Acad. Child Adolesc. Psych. 39, 1160–1167.

Carr, L., Iacoboni, M., Dubeau, M.C., Mazziotta, J.C., Lenzi, G.L., 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc. Natl. Acad. Sci. U. S. A. 100, 5497–5502.

Cattel, R.B., Catell, H.E.P., 1973. Measuring Intelligence with the Culture Fair Tests. Institute for Personality and Ability Testing, Champaign, IL, USA.

Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev., Neurosci. 3, 655–666.

Craig, A.D., 2005. Forebrain emotional asymmetry: a neuroanatomical basis? Trends Cogn. Sci. 9, 566–571.

Critchley, H.D., 2005. Neural mechanisms of autonomic, affective, and cognitive integration. J. Comp. Neurol. 493, 154–166.

Critchley, H.D., Good, C.D., Ashburner, J., Frackowiak, R.S., Mathias, C.J., Dolan, R.J., 2003. Changes in cerebral morphology consequent to peripheral autonomic denervation. NeuroImage 18, 908–916.

Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nat. Neurosci. 7, 189–195.

Damasio, A.R., 2003. Looking for Spinoza: Joy, Sorrow, and the Feeling Brain. Hartcourt, Orlando, FL.

Davidson, R.J., Putnam, K.M., Larson, C.L., 2000. Dysfunction in the neural circuitry of emotion regulation—A possible prelude to violence. Science 289, 591–594.

Decety, J., Lamm, C., 2006. Human empathy through the lens of social neuroscience. Sci. World J. 6, 1146–1163.

de Vignemont, F., Singer, T., 2006. The empathic brain: how, when and why? Trends Cogn. Sci. 10, 435–441.

Dolan, R.J., 2002. Emotion, cognition, and behavior. Science 298, 1191–1194.

Dopfner, M., Lehmkuhl, G., 2000. Diagnostik-System für Psychische Störungen im Kindes-und Jugendalter nach ICD-10 und DSM-IV (DISYPS-KJ). Huber, Bern, Switzerland.

Eysenck, H.J., Eysenck, S.B., 1991. The impulsiveness, venturesomeness and empathy scale. Eysenck Personality Scales. Hodder and Stoughton, London.

Eysenck, S.B., Daum, I., Schugens, M.M., Diehl, J.M., 1990. A cross-cultural study of impulsiveness, venturesomeness, and empathy: Germany and England. Z. Differ. Diagn. Psychol. 4, 209–213.

Frewen, P.A., Pain, C., Dozois, D.J., Lanius, R.A., 2006. Alexithymia in PTSD: psychometric and FMRI studies. Ann. N. Y. Acad. Sci. 1071, 397–400.

Frick, P.J., O'Brien, B.S., Wootton, J.M., McBurnett, K., 1994. Psychopathy and conduct problems in children. J. Abnorm. Psychol. 103, 700–707.

Gallese, V., Keysers, C., Rizzolatti, G., 2004. A unifying view of the basis of social cognition. Trends Cogn. Sci. 8, 396–403.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N., Friston, K.J., Frackowiak, R.S., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage 14, 21–36.

Gundel, H., Lopez-Sala, A., Ceballos-Baumann, A.O., Deus, J., Cardoner, N., Marten-Mittag, B., Soriano-Mas, C., Pujol, J., 2004. Alexithymia correlates with the size of the right anterior cingulate. Psychosom. Med. 66, 132–140.

Herpertz, S.C., Mueller, B., Wenning, B., Qunaibi, M., Lichterfeld, C., Herpertz-Dahlmann, B., 2003. Autonomic responses in boys with externalizing disorders. J. Neural Transm. 110, 1181–1195.

Herpertz, S.C., Mueller, B., Qunaibi, M., Lichterfeld, C., Konrad, K., Herpertz-Dahlmann, B., 2005. Response to emotional stimuli in boys with conduct disorder. Am. J. Psychiatry 162, 1100–1107.

Jackson, P.L., Meltzoff, A.N., Decety, J., 2005. How do we perceive the pain of others? A window into the neural processes involved in empathy. NeuroImage 24, 771–779.

Jackson, P.L., Brunet, E., Meltzoff, A.N., Decety, J., 2006. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 24 (5), 752–761.

Kano, M., Fukudo, S., Gyoba, J., Kamachi, M., Tagawa, M., Mochizuki, H., Itoh, M., Hongo, M., Yanai, K., 2003. Specific brain processing of facial expressions in people with alexithymia: an H2 15O-PET study. Brain 126, 1474–1484.

Kiehl, K.A., Smith, A.M., Hare, R.D., Mendrek, A., Forster, B.B., Brink, J., Liddle, P.F., 2001. Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. Biol. Psychiatry 50, 677–684.

Loeber, R., Burke, J.D., Lahey, B.B., Winters, A., Zera, M., 2000. Oppositional defiant and conduct disorder: a review of the past 10 years, part I. J. Am. Acad. Child Adolesc. Psych. 39, 1468–1484.

Loney, B.R., Frick, P.J., Clements, C.B., Ellis, M.L., Kerlin, K., 2003. Callous-unemotional traits, impulsivity, and emotional processing in adolescents with antisocial behavior problems. J. Clin. Child Adolesc. Psychol. 32, 66–80.

Luengo, M.A., Carrillo-de-la-Pena, M.T., Otero, J.M., Romero, E., 1994. A short-term longitudinal study of impulsivity and antisocial behavior. J. Pers. Soc. Psychol. 66, 542–548.

Lynam, D., Moffitt, T., Stouthamer-Loeber, M., 1993. Explaining the relation between IQ and delinquency: class, race, test motivation, school failure, or self-control? J. Abnorm. Psychology 102, 187–196.

Meyer-Lindenberg, A., Buckholtz, J.W., Kolachana, B., Hariri, A.R., Pezawas, L., Blasi, G., Wabnitz, A., Honea, R., Verchinski, B., Callicott, J.H., Egan, M., Mattay, V., Weinberger, D.R., 2006. Neural mechanisms of genetic risk for impulsivity and violence in humans. Proc. Natl. Acad. Sci. U. S. A. 103, 6269–6274.

Miller, P.A., Eisenberg, N., 1988. The relation of empathy to aggressive and externalizing/antisocial behavior. Psychol. Bull. 103, 324–344.

Moriguchi, Y., Decety, J., Ohnishi, T., Maeda, M., Mori, T., Nemoto, K., Matsuda, H., Komaki, G., 2006. Empathy and judging other's pain: an fMRI study of alexithymia. Cereb. Cortex [Electronic publication ahead of print].

Pardini, D.A., Lochman, J.E., Frick, P.J., 2003. Callous/unemotional traits and social-cognitive processes in adjudicated youths. J. Am. Acad. Child Adolesc. Psych. 42, 364–371.

Paulus, M.P., Stein, M.B., 2006. An insular view of anxiety. Biol. Psychiatry 60, 383–387.

Pelc, K., Kornreich, C., Foisy, M.L., Dan, B., 2006. Recognition of emotional facial expressions in attention-deficit hyperactivity disorder. Pediatr. Neurol. 35, 93–97.

Plessen, K.J., Bansal, R., Zhu, H., Whiteman, R., Amat, J., Quackenbush, G.A., Martin, L., Durkin, K., Blair, C., Royal, J., Hugdahl, K., Peterson, B.S., 2006. Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. Arch. Gen. Psychiatry 63, 795–807.

Raine, A., 2002. Annotation: the role of prefrontal deficits, low autonomic arousal, and early health factors in the development of antisocial and aggressive behavior in children. J. Child Psychol. Psychiatry 43, 417–434.

Raine, A., Meloy, J.R., Bihrle, S., Stoddard, J., LaCasse, L., Buchsbaum, M.S., 1998. Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behav. Sci. Law 16, 319–332.

Raine, A., Lencz, T., Bihrle, S., LaCasse, L., Colletti, P., 2000. Reduced prefrontal gray matter volume and reduced autonomic activity in anti-social personality disorder. Arch. Gen. Psychiatry 57, 119–127 (discussion 128-119).

Schmeck, K., Poustka, F., Dopfner, M., Pluck, J., Berner, W., Lehmkuhl, G., Fegert, J.M., Lenz, K., Huss, M., Lehmkuhl, U., 2001. Discriminant validity of the child behaviour checklist CBCL-4/18 in German samples. Eur. Child Adolesc. Psychiatry 10, 240–247.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157–1162.

Singer, T., Seymour, B., O'Doherty, J.P., Stephan, K.E., Dolan, R.J., Frith, C.D., 2006. Empathic neural responses are modulated by the perceived fairness of others. Nature 439, 466–469.

Singh, S.D., Ellis, C.R., Winton, A.S., Singh, N.N., Leung, J.P., Oswald, D.P., 1998. Recognition of facial expressions of emotion by children with attention-deficit hyperactivity disorder. Behav. Modif. 22, 128–142.

Soderstrom, H., 2003. Psychopathy as a disorder of empathy. Eur. Child Adolesc. Psychiatry 12, 249–252.

Stadler, C., Janke, W., Schmeck, K., 2004. Inventar zur Erfassung von Impulsivität, Risikoverhalten und Empathie bei 9 bis 14jährigen Kindern. Hogrefe, Göttingen, Germany.

Sterzer, P., Stadler, C., Krebs, A., Kleinschmidt, A., Poustka, F., 2005. Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. Biol. Psychiatry 57, 7–15.

Veit, R., Flor, H., Erb, M., Hermann, C., Lotze, M., Grodd, W., Birbaumer, N., 2002. Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. Neurosci. Lett. 328, 233–236.

Weiss, R.H., 1987. Grundintelligenztest Skala 2 (CFT 20). Hogrefe, Göttingen, Germany.

Wicker, B., Keysers, C., Plailly, J., Royet, J.P., Gallese, V., Rizzolatti, G., 2003. Both of us disgusted in my insula: the common neural basis of seeing and feeling disgust. Neuron 40, 655–664.