

Ventral striatum and amygdala activity as convergence sites for early adversity and conduct disorder

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Abstract

Childhood family adversity (CFA) increases the risk for conduct disorder (CD) and has been associated with alterations in regions of affective processing like ventral striatum (VS) and amygdala. However, no study so far has demonstrated neural converging effects of CFA and CD in the same sample. At age 25 years, functional MRI data during two affective tasks, i.e. a reward ($N = 171$) and a face-matching paradigm ($N = 181$) and anatomical scans ($N = 181$) were acquired in right-handed currently healthy participants of an epidemiological study followed since birth. CFA during childhood was determined using a standardized parent interview. Disruptive behaviors and CD diagnoses during childhood and adolescence were obtained by diagnostic interview (2–19 years), temperamental reward dependence was assessed by questionnaire (15 and 19 years). CFA predicted increased CD and amygdala volume. Both exposure to CFA and CD were associated with a decreased VS response during reward anticipation and blunted amygdala activity during face-matching. CD mediated the effect of CFA on brain activity. Temperamental reward dependence was negatively correlated with CFA and CD and positively with VS

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activity. These findings underline the detrimental effects of CFA on the offspring's affective processing and support the importance of early postnatal intervention programs aiming to reduce childhood adversity factors.

Key words: childhood adversity; conduct disorder; amygdala; ventral striatum; fMRI

Introduction

Conduct disorder (CD) is one of the most prevalent psychiatric disorders during childhood and adolescence (around 2%, Sterzer and Stadler, 2009), with less than a quarter of CD patients receiving effective help (Coghill, 2013). Individuals with CD show aggressive, deceptive, rule-violating, and destructive behaviors (American Psychiatric Association, 1994, 2013). Recently, there has been growing interest in different subtypes of antisocial behavior (AB), which pertains to identifying individuals exhibiting the more severe callous-unemotional (CU) behavior, i.e. lack of remorse or guilt, lack of empathy, indifference about performance and shallow or deficient affect (American Psychiatric Association, 2013). Moreover, the psychobiological model of personality as proposed by Cloninger (2000, 2003) provided comprehensive temperamental characteristics of AB, including low reward dependence, i.e. an intrinsically lower sensitivity to social rewards, such as praise (Cloninger et al., 1994; Lahey et al., 2003). Several studies in juvenile offenders (Atarhouch et al., 2004) and incarcerated girls (Sevecke et al., 2010) with CD confirmed this relationship. Evidence from twin and adoption studies has indicated that CD (without CU) is moderately heritable, with about half of the variance being explained by genetic make-up (for review see Glenn et al., 2013) and a substantial environmental contribution (Viding and McCrory, 2012). In this context, the heritability of antisocial behavior with high CU traits was reported to be considerably greater than for those low on CU traits (Viding and McCrory, 2012). However, this does not imply that environmental adversity plays a negligible role regarding CU traits. Actually, recent work suggested that CU traits may be shaped by parenting across all developmental stages and that CU individuals are responsive to parenting-focused interventions (Waller et al., 2013; Hyde et al., 2016). Further evidence in support for a role of environmental adversity in CU traits has been provided by Kimonis et al. (2011, 2012). According to these authors, two distinct CU subgroups are designated (primary and secondary CU), with the secondary variant being specifically characterized by a maltreatment history (and high anxiety) when compared to the primary variant (Kimonis et al., 2011, 2012). This underlines the importance of probing for environmental factors to explain the variance, which cannot be attributed to genetic influence. Among these, childhood family adversity (CFA) has a prominent role, including poverty, poor parental monitoring and harsh and coercive discipline (Jaffee et al., 2012; Blair et al., 2014; Humphreys and Zeanah, 2015). Neuropsychological studies have suggested that CD patients exhibit deficits in tasks involving motivation and affect. For example, impaired reversal learning of stimulus-response contingencies during reward processing, probably due to decreased sensitivity to punishment and incentives, has been demonstrated in CD (Budhani and Blair, 2005; Rubia, 2011). Moreover, antisocial individuals were found to be impaired in facial emotion recognition, including anger and disgust (Fairchild et al., 2010), especially in early onset CD (Fairchild et al., 2009), as well as fear, reflecting a reduced level of empathy, particularly as a function of CU traits (Blair et al., 2001; Fairchild et al., 2009; Blair et al., 2014).

Consistent with these deficits, deviant functioning of the ventral striatum (VS), in particular of the caudate, and the amygdala has been implicated as neural underpinnings of AB. For example, CD patients with comorbid substance use disorder displayed hypoactivity in the striatum during a risky incentive decision-making task (Crowley et al., 2010). Finger et al. (2011) confirmed the finding of blunted caudate activation in CD during a passive avoidance learning task, suggestive of disrupted prediction error signaling in the caudate during reward processing (White et al., 2013). A subsequent study (White et al., 2014) extended these findings to a comparable environmental reinforcement paradigm, indicating that in CD patients, caudate activity decreased during the presentation of rewarding cues. Regarding the amygdala, differential neural activation has been found depending on the subtypes of CD. While blunted amygdala activity during emotion processing has been associated with CD during the perception of negative pictures (Sterzer and Stadler, 2009) and angry faces (Passamonti et al., 2010), also as a function of CU traits during fearful face processing (Viding et al., 2012; Blair et al., 2014), heightened amygdala activity to angry faces has been linked to impulsive aggression (Coccaro et al., 2007).

Recently, the study of long-term consequences of early adversity on brain structure and function has garnered increasing interest, with evidence of the VS and the amygdala being particularly sensitive to stress. Various studies demonstrated reduced activation in the basal ganglia in response to reward-predicting cues following early adversity, including CFA (Boecker et al., 2014), stressful life events (Hanson et al., 2016), childhood maltreatment (Dillon et al., 2009) and global early deprivation in Romanian adoptees (Mehta et al., 2010). Notably, differential changes in amygdala activity depending on the type of early adversity have been observed. While major parts of the literature point to heightened amygdala activation during emotion processing following severe forms of emotional stress, i.e. as a function of maltreatment (McCrory et al., 2011, 2013; Dannlowski et al., 2012; van Harmelen et al., 2013), institutionalization in children (Tottenham et al., 2011) or history of caregiver deprivation and emotional neglect in youth (Maheu et al., 2010), there is also evidence that an adverse family environment is related to blunted amygdala activity during emotion processing (Taylor et al., 2006). Such diverse patterns of deviance have also been demonstrated for amygdala structure, with both volume increases (Mehta et al., 2009; Tottenham et al., 2010) and reductions (Ganzel et al., 2008; Lui et al., 2013; Hanson et al., 2015) after the experience of various stressors.

Using longitudinal data from an epidemiological cohort study of young adults followed since birth (Laucht et al., 2000), the present investigation aimed to (i) replicate the well-established link between CFA and CD and (ii) examine the neural convergence of CFA and CD in the same sample in two different affective paradigms. Specifically, in line with previous literature examining the impact of environmental adversity and CD on affective processing, VS response during reward processing is expected to be blunted during anticipation. Regarding amygdala activity, previous heterogeneous results on the effect of adversity and CD allow to make alternative predictions: (1)

Table 1. Sample characteristics

CD diagnoses, No.	None	1CD	2CD	3CD	4CD	Test statistics	P-value
No. (%)	145 (80.1)	20 (11.0)	8 (4.4)	4 (2.2)	1 (0.6)		
Males, No. (%)	54 (37.2)	10 (50.0)	7 (87.5)	2 (50.0)	1	$\beta = -0.60$	0.01 ^a
CFA, mean (SD)	3.11 (2.22)	4.25 (2.20)	6.75 (1.67)	8.00 (1.63)	5.00	$\beta = 0.12$	<0.001 ^{b,c}
ADHD diagnoses, mean (SD)	0.26 (.56)	0.90 (1.02)	1.50 (1.31)	2.00 (1.41)	6.00	$\beta = 2.07$	<0.001 ^{b,c}
Lifetime nicotine dependence, mean (SD)	-0.32 (3.30)	0.92 (4.23)	1.67 (5.02)	1.69 (2.67)	12.72	$\beta = 1.27$	0.001 ^b
Lifetime impulsivity, mean (SD)	0.38 (.69)	1.20 (1.36)	2.25 (1.17)	2.00 (.00)	4.00	$\beta = 0.73$	<0.001 ^{b,c}
PSD CU traits, mean (SD)	1.61 (1.48)	1.63 (1.54)	2.73 (1.60)	4.75 (2.06)	2.00	$\beta = 0.41$	0.02 ^{b,c}
Current YASR aggression, mean (SD)	1.18 (1.47)	1.80 (2.12)	0.88 (1.36)	3.75 (2.63)	1.00	$\beta = 0.63$	0.02 ^{b,c}
RT monetary (ms), mean (SD)	194.84 (25.44)	200.41 (31.01)	206.66 (35.18)	223.77 (29.63)	228.74	$\beta = 7.66$	0.008 ^b
RT verbal (ms), mean (SD)	224.22 (42.25)	233.54 (41.08)	251.22 (70.48)	237.68 (33.32)	251.58	$\beta = 8.42$	0.07 ^b

Note: CD = conduct disorder, CFA = childhood family adversity, SD = standard deviation, ADHD = attention deficit/hyperactivity disorder, RT = reaction time, PSD = Psychopathy Screening Device, YASR = Young Adult Self-Report.

^aLogistic regression.

^bLinear regression.

^cAdjusted for parental antisocial disorder, sex, obstetric adversity, lifetime substance abuse. The regressions do not change when adjusted for sex only (CFA $\beta = 0.12$, $P < 0.001$; ADHD $\beta = 2.21$, $P < 0.001$; impulsivity $\beta = 0.75$, $P < 0.001$; YASR aggression $\beta = 0.56$, $P = 0.03$; CU traits $\beta = 0.53$, $P = 0.002$).

amygdala activity could be heightened in case of impulsive CD (Coccaro et al., 2007) and after exposure to adversity, in line with McCrory et al. (2011, 2013), (2) amygdala activity could be blunted as a function of CD with CU traits (Viding and McCrory, 2012) and following adversity (Taylor et al., 2006). A further aim is (3) to test whether the effect of CFA on activity in the VS and the amygdala is mediated by CD and (4) relate CFA, CD and neural activity to social reward dependence (Cloninger et al., 1994), assumed to be a stable temperamental trait (Cloninger, 1987).

Materials and methods

Sample

This investigation was conducted in the framework of the Mannheim Study of Children at Risk, an ongoing epidemiological cohort study of the long-term outcome of early risk factors (for full details c.f. Laucht et al., 2000, Supplementary Methods). CD and exclusion criteria at age 25 were assessed by a Structured Clinical Interview (American Psychiatric Association, 1994; German version, Wittchen et al., 1997) (see Supplementary Methods). Only currently healthy participants free of medication were included (reward: $N = 171$; face: $N = 181$; Table 1). Previous publications from our group with a largely overlapping sample (Boecker et al., 2014; Holz et al., 2016) already provided evidence for the susceptibility of VS and amygdala activity on environmental adversity. In this paper, however, a novel focus on previous psychopathology is reported (details depicted in the Supplementary Methods). The study was approved by the ethics committee of the University of Heidelberg and written informed consent was obtained from all participants.

Assessments

CFA until 11 years of age was determined using a standardized parent interview conducted at each of the five assessments during childhood by informed trained psychologists, yielding an 'enriched' family adversity index as proposed by Rutter and Quinton (1977) which covered difficulties of the parents, their partnership and the family environment including socio-economic disadvantages during a period of 1 year prior to the assessment (Laucht et al., 2000) (11 items, range 0–10, detailed

description is provided in Supplementary Table S1). A total CFA score was formed by counting the number of psychosocial risks present in the period until 11 years of age (without repeating items which only apply to the first assessment wave, e.g. unwanted pregnancy; faces sample: $M = 3.5$, $SD = 2.40$; reward sample: $M = 3.6$, $SD = 2.41$).

Given the heterogeneity of the CFA items, we additionally confirmed our results by extracting one factor as identified by principal component analysis, which correlated highly with CFA ($r = 0.99$, $P < 0.001$). Using this factor as a main predictor (instead of CFA) did not change the results (Supplementary Methods and Supplementary Table S7 depicted in the supplement).

Disruptive symptoms, such as aggression (at the age of 2) and CD diagnoses (4–19 years of age) during childhood and adolescence according to DSM IV (American Psychiatric Association, 1994) were assessed using diagnostic interviews with the parents (Mannheim Parent Interview; MPI; Esser et al., 1989) until the age of 11 years and with the children at ages 8 and 11 years. The MPI is a highly structured interview adapted from Rutter's parent interviews (Cox and Rutter, 1985) and modified to include all symptoms related to major DSM-IV diagnoses, such as ADHD, ODD, CD, anxiety and mood disorders. CD diagnoses were based on both parent and self-reports. We examined inter-rater reliability in 8-year-olds. On single behavior problems, mean inter-rater reliability was kappa = 0.77 (range 0.71–1.00), indicating a high level of agreement. At age 15 years, the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL; Kaufman et al., 1996; German version by Delmo et al., 2000) was conducted independently with parents and adolescents. A diagnosis was defined as present when criteria were met in either the parent or adolescent interview. At the age of 19 years, the Structured Clinical Interview for DSM-IV (SCID; American Psychiatric Association, 1994; German version, Wittchen et al., 1997) was performed with the offspring to assess current diagnoses. The presence of a CD diagnosis in each of the six assessments was rated as 0 = not present, 1 = present (Figure 1). A sum score was computed by adding up these values, which yielded a continuous score with a maximum of four diagnoses (range 0–4). In case of self- and parent report of a CD diagnosis, the presence of a diagnosis was counted only once. To further specify the results for impulsive

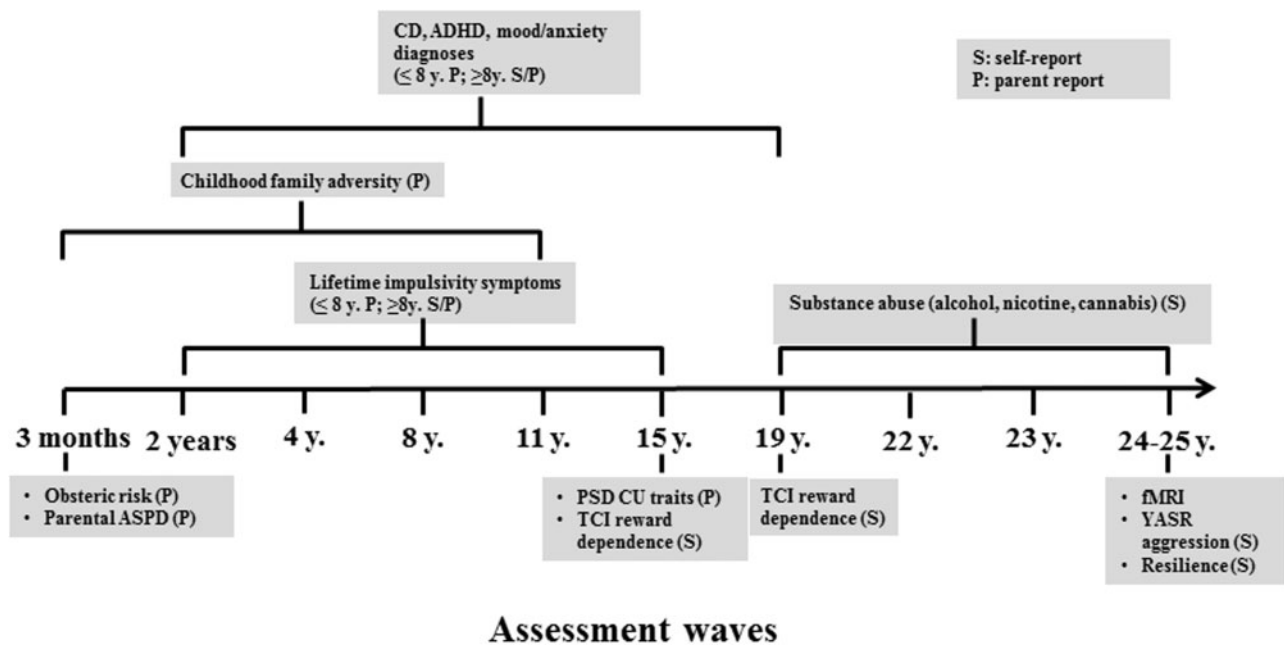


Fig. 1. Assessment waves through lifespan. S = self-report, P = parent report.

and callous-unemotional CD dimensions (Buitelaar et al., 2013), additional measures were obtained (1) lifetime impulsivity symptoms assessed at the ages of 2–15 years (using the MPI and the ADHD supplement of the K-SADS-PL) and (2) parent-reported CU traits using the Psychopathy Screening Device (PSD; Frick and Hare, 1998) at the offspring's age of 15. Moreover, due to the high comorbidity between CD and ADHD as well as mood and anxiety disorders, lifetime diagnoses of these disorders have been assessed in analogy to CD and were controlled for in further analyses.

To further clarify the association with social functioning, information on *reward dependence* (RD) was acquired at ages 15 and 19 years with the (Junior) Temperament and Character Inventory (Cloninger et al., 1994). RD reflects the tendency to react strongly to reinforcements and maintain behavior previously associated with rewards. Individuals low on RD are socially detached, practical, tough minded, emotionally cool and independent. Thus, low RD may predispose individuals to show decreased activity in the VS during reward processing.

To evaluate *current aggressive behaviors*, the Young Adult Self-Report (YASR, Achenbach, 1991) was administered to the participants at the age of 25.

Further details of assessments are provided in the Supplementary Methods.

Covariates and confounders

All results presented (except for task main effects) were adjusted for confounders including sex, obstetric adversity, and lifetime substance abuse, including lifetime nicotine dependence [Fagerström Test for Nicotine Dependence (FTND, Heatherton et al., 1991)], lifetime alcohol abuse [Alcohol Use Disorders Identification Test (AUDIT, Babor et al., 2001)], and lifetime cannabis abuse (12-month prevalence). In addition, results were controlled for parental antisocial personality disorder diagnosis [ASPD; assessed using the SCID (German version, Wittchen et al., 1997)] to rule out that the observed brain patterns merely reflect familial risk (the results, however,

remained unchanged when this covariate was not additionally controlled for). Moreover, to evaluate the specificity of the effects, lifetime ADHD as well as mood and anxiety disorder (assessed in analogy to CD diagnoses) were controlled for in further analyses. Finally, since we included currently healthy participants who previously have had CD, brain activity was correlated with self-reported resilience to ensure that the observed brain patterns reflect vulnerability markers rather than resilience. Resilience was assessed using the resilience scale (Schumacher et al., 2005). To warrant that the results are not due to adjustment for confounders, analyses controlled for sex only as well as details for all measures are provided in the Supplementary Methods.

Reward task

The reward paradigm used yields reliable and robust activation of the VS (Boecker et al., 2014), which requires a fast button-press directly after a flash target in order to gain reward. An anticipation cue is presented followed by the flash target which is followed by feedback about their current balance. The cues consistently signaled different types of reward anticipation: either a smiley signaling that responding sufficiently fast after the flash target would yield monetary feedback ('0.50Euro' or '0.00Euro'), or a scrambled smiley indicating only verbal feedback ('Fast reaction!' or 'Not fast enough!'). Boost trials with a monetary reward of 2Euro instead of 0.50Euro occurred after approximately every eighth win trial in order to improve the participants' level of motivation. In total, 50 monetary and 50 verbal feedback trials were presented in a pseudo-randomized order. The reaction time (RT) window (common to both reward conditions, with a maximum of 1s) was adaptively tailored to the individual RTs to yield comparable winnings across participants (~60%). After every trial, the participants were informed about their current account balance. The time window between the beginning of cue presentation and feedback was jittered mainly by varying cue duration (3–5 s). For further details see Supplementary Methods.

Face-matching task

To assess emotion processing, 12 blocks of sequences of fearful/angry faces alternated with sequences of shapes (Hariri et al., 2002). In the face blocks, participants were instructed to indicate which of the two faces at the bottom was identical to the target face (at the top) and to press the button on the respective side. In the sensorimotor control task, participants had to compare circles and ellipses according to the same criterion. Both stimulus sets consisted of six different trios of faces, one trio consisting of both fearful and angry faces, or shapes, each presented every 2.5 s on average. The total task time was 409 s, and reaction time was measured. One subject was excluded due to left amygdala activation > 3 SD from the mean.

fMRI parameters and data analysis

Functional magnetic resonance imaging was performed using a 3 Tesla scanner (Magnetom TRIO, Siemens, Erlangen, Germany) with a standard 12-channel head coil at the age of 25 years. The functional images were analyzed using Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab 7.12. (Mathworks Inc., Natick, MA, USA) with standard preprocessing steps (as also described in Boecker et al., 2014; Holz et al., 2016). More details in Supplementary Methods.

The first four fMRI volumes were discarded to allow longitudinal magnetization to reach equilibrium. Preprocessing included slice time correction of the volumes to the first slice, realignment to correct for movement artifacts, co-registration of functional and anatomical data, spatial normalization to standard MNI (Montreal Neurological Institute) space and smoothing with a Gaussian kernel of 8 mm full-width-at-half-maximum (FWHM). For the reward task, eight regressors of interest (laughing and scrambled smiley, flash, response, monetary and verbal, win and no-win trials, respectively) were created and convolved with the SPM hemodynamic response function (HRF). For the face-matching task, two vectors comprising onsets and durations of either shapes or faces were convolved with the SPM8 canonical hemodynamic response function in the context of a General Linear Model in order to model the BOLD time course. A further six movement parameters were included as regressors of no interest in both models. First-level contrast images reflecting activation (1) to the anticipation of monetary vs. verbal trials (i.e. cue onset), (2) to the delivery contrast of win vs no-win trials pooled over the monetary and verbal condition (i.e. trials with positive monetary and verbal feedback versus trials with negative monetary and verbal feedback) during reward and (3) to faces vs shapes during emotion processing were used. These contrasts were entered into separate second-level group analyses, with CFA and CD diagnoses during childhood and adolescence, respectively, as the main predictor while controlling for all covariates previously mentioned (see 'covariates and confounders'). The results remained significant when adjusted for sex only, which is specified in the supplement. The caudate head, the putamen and the amygdala were defined as regions of interest (ROIs), using anatomical masks implemented in the Wake Forest University (WFU) PickAtlas v2.4 (Maldjian et al., 2003), where a $P < 0.05$ FWE correction (minimum of five adjacent voxels) was applied. For display reasons, the statistical threshold was set at $P = 0.005$ uncorrected. For exploratory whole brain analyses, a $P < 0.001$ uncorrected threshold and a criterion of 10 adjacent voxels was set. Mediation analysis using the Sobel Test (Baron and Kenny, 1986) was applied and CD diagnoses were treated as a mediator. This model assumes that a CD related lifestyle may have led to

the observed brain changes. Mediation was tested using the overlap of the FWE significant clusters ($k = 5$) controlling for all covariates previously mentioned. Further details can be found in the Supplementary Methods.

Voxel-based morphometry

We acquired $1 \times 1 \times 1$ mm T1-weighted anatomical images with 192 slices covering the whole brain (matrix 256×256 , repetition time = 2300 ms, echo time = 3.03 ms, 50% distance factor, field of view $256 \times 256 \times 192$ mm, flip angle 9°). Images were bias-corrected and classified into gray matter, white matter, cerebrospinal fluid and non-brain tissue using Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) registration toolbox (Ashburner, 2007). Data were segmented based on tissue probability maps, indexing the prior probability of any voxel in a registered image being grey or white matter or cerebrospinal fluid. An average template from the data was created, to which the images were registered. Additionally, the images were affine-transformed to MNI space and smoothed with a 6-mm FWHM kernel. Total intracranial volume was calculated by adding the tissue probabilities of gray matter, white matter and cerebrospinal fluid and used as a covariate. For group statistics of gray matter images, the same analysis as with the functional images was performed while additionally controlling for total intracranial volume. In order to control for the influence of gray matter differences, brain volume was extracted using anatomical masks comprising the caudate, the putamen and the amygdala derived from the WFU PickAtlas v2.4 (Maldjian et al., 2003) and separately added as an additional covariate.

Results

Sample characteristics

As hypothesized, CFA increased the level of CD and ADHD diagnoses during childhood and adolescence, lifetime impulsivity and CU traits. Concerning task performance, the participants with CFA displayed slower reaction times for monetary trials. More males than females had previous CD diagnoses. In addition, CD diagnoses during childhood and adolescence were related to higher lifetime impulsivity, more CU traits, more ADHD diagnoses, a higher level of nicotine dependence and slower reaction times for monetary trials. Further, CD diagnoses were associated with increased current YASR aggression scores (Supplemental Figure S1).

More details are provided in Table 1 and in the Supplementary Results and Supplemental Table S2.

VBM results

CD and CFA neither affected caudate nor putamen structure (all $p_{FWE} > 0.08$). While CFA was associated with increased left amygdala volume, no relationship emerged with CD ($p_{uncorrected} > 0.05$, Table 2).

Task effects

Robust caudate and putamen activation emerged during the anticipation of reward [caudate right: $t(170) = 18.37$, $p_{FWE} < 0.001$, peak: 12 12 -2; left: $t(170) = 16.71$, $p_{FWE} < 0.001$, peak: -10 10 -2; putamen right: $t(170) = 18.85$, $p_{FWE} < 0.001$, peak: 16 8 -6; left: $t(170) = 18.35$, $p_{FWE} < 0.001$, peak: -16 6 -6] as well as during the delivery [caudate right: $t(170) = 11.62$, $p_{FWE} < 0.001$, peak: 12 12

Table 2. Functional magnetic resonance imaging and voxel-based morphometry results

	fMRI results				VBM results			
	Reward anticipation (N = 171)		Emotion processing (N = 181)		N = 181			
	Caudate		Putamen		Caudate		Putamen	
Hemisphere	L	L	R	L	L	L	R	L
CD	t(161) = 3.62, p _{FWE} = 0.005	t(161) = 3.87, p _{FWE} = 0.007	t(161) = 3.42, p _{FWE} = 0.04	t(169) = 3.04, p _{FWE} = 0.03	n.s.	n.s.	n.s.	n.s.
CFA	t(163) = 3.95, p _{FWE} = 0.002	t(163) = 3.67, p _{FWE} = 0.01	t(163) = 4.09, p _{FWE} = 0.003	t(172) = 3.25, p _{FWE} = 0.01	n.s.	n.s.	n.s.	t(173) = 3.06, p _{FWE} = 0.047

Note: CD = conduct disorder, CFA = childhood family adversity; n.s. = not significant, L = left, R = right.

–4; left: $t(170) = 11.80$, $p_{FWE} < 0.001$, peak: $-20 -12 24$; putamen right: $t(170) = 12.23$, $p_{FWE} < 0.001$, peak: $30 -14 8$; left: $t(170) = 12.47$, $p_{FWE} < 0.001$, peak: $-16 6 -6$. Emotion processing during the faces task elicited significant amygdala activation [right: $t(180) = 22.79$; $p_{FWE} < 0.001$; left: $t(180) = 20.25$; $p_{FWE} < 0.001$].

Reward processing and brain structure in the ventral striatum

During the anticipation of reward, operationalized by the contrast monetary versus verbal trials, CD diagnoses during childhood and adolescence were associated with decreased VS activity and CFA was related to reduced VS activity (Table 2 and Figure 2A and B) extending to the dorsal striatum when adjusted for covariates. Whole brain results are depicted in Supplementary Tables S3 and S4. Critically, no such effect of CD or CFA was observed during reward delivery.

Likewise, the fMRI results for reward anticipation remained significant when gray matter differences in the left caudate and the putamen were accounted for [CD: caudate left: $t(160) = 3.60$, $p_{FWE} = 0.005$; putamen left: $t(160) = 3.89$, $p_{FWE} = 0.006$; right $t(160) = 3.25$, $p_{FWE} = 0.04$; CFA: caudate left: $t(162) = 4.08$, $p_{FWE} = 0.001$; putamen left: $t(162) = 3.76$, $p_{FWE} = 0.009$; right $t(162) = 4.24$, $p_{FWE} = 0.002$]. In addition, all results remained significant when adjusted for the reaction time difference between monetary and verbal trials.

Emotion processing and amygdala volume

CD diagnoses during childhood and adolescence were related to decreased left amygdala activity (Table 2 and Figure 2C) when controlled for covariates. Similarly, there was an inverse correlation between CFA and activity in the left amygdala (Table 2 and Figure 2C). Whole brain results are depicted in Supplementary Tables S5 and 6.

The effects of CFA and CD during childhood and adolescence on amygdala activity during emotion processing remained significant when controlled for left amygdala volume [CD: $t(168) = 3.03$, $p_{FWE} = 0.03$; CFA: $t(171) = 3.26$, $p_{FWE} = 0.01$]. In addition, the results did not change when the reaction time difference between faces and shapes was used as an additional covariate.

Specificity of the effects

After adjustment for previous ADHD or mood and anxiety disorder, all results remained significant (details depicted in the Supplementary Results). This also applied to VS activity when adjusting for CU traits but not for amygdala activity, where the

voxel criterion was no longer reached. In line with this, CU traits as a main predictor were associated with decreased amygdala activity during emotion processing [$t(168) = 3.19$, $p_{FWE} = 0.02$] but were not significantly related to VS activity during reward anticipation (all p 's > 0.008 uncorrected). When using lifetime impulsivity as a covariate of interest, results were similar to those found for CD during reward anticipation, with negative relationships obtained with caudate [$t(162) = 3.42$, $p_{FWE} = 0.02$] and putamen activity [$t(159) = 3.22$, $p_{FWE} = 0.047$]. Impulsivity was, however, not significantly related to amygdala activity [$p_{uncorrected} = 0.006$]. Details of the analyses conducted are depicted in Supplementary Results.

When controlled for CFA, the association between CD and VS activity failed to reach significance [$t(160) = 2.40$, $p_{uncorr} = 0.009$]. Regarding amygdala activity, the association with CD remained significant [$t(168) = 3.07$, $p_{FWE} = 0.03$] but failed to reach the minimum voxel criterion.

Mediation

Given that the effects of CFA and lifetime CD diagnoses converged in reduced caudate, putamen and amygdala activity, we tested for a mediating effect of CD on the relationship between CFA and neural activity. Including CD diagnosis as a mediator revealed a significant indirect effect ($t = -2.23$, $P = 0.026$; Figure 3A), with a significant path between CFA and lifetime CD, and between CD and caudate activity. Moreover, the direct path between CFA and caudate activity remained significant, albeit at a lower threshold, suggesting partial mediation. A similar partial mediation emerged when including CD as a mediator between the relationship of CFA and putamen activity ($t = -2.11$, $P = 0.03$, Figure 3B). In addition, CD mediated the relationship between CFA and amygdala ($t = -1.96$, $P = 0.049$; Figure 3C) with significant paths between CFA and CD and between CD and amygdala activity. The effect of CFA on amygdala activity was no longer significant, indicating full mediation.

Association with temperamental reward dependence and resilience

Both CD diagnoses during childhood and adolescence and CFA were associated with a lower level of reward dependence irrespective of the inclusion of confounders (CD: $r = -0.17$, $P = 0.03$; CFA: $r = -0.22$, $P = 0.005$). Likewise, caudate and putamen response to reward anticipation correlated with temperamental reward dependence ($r = 0.17$, $P = 0.03$; $r = 0.18$, $P = 0.02$, respectively). While resilience was inversely related to CFA ($r = -0.15$,

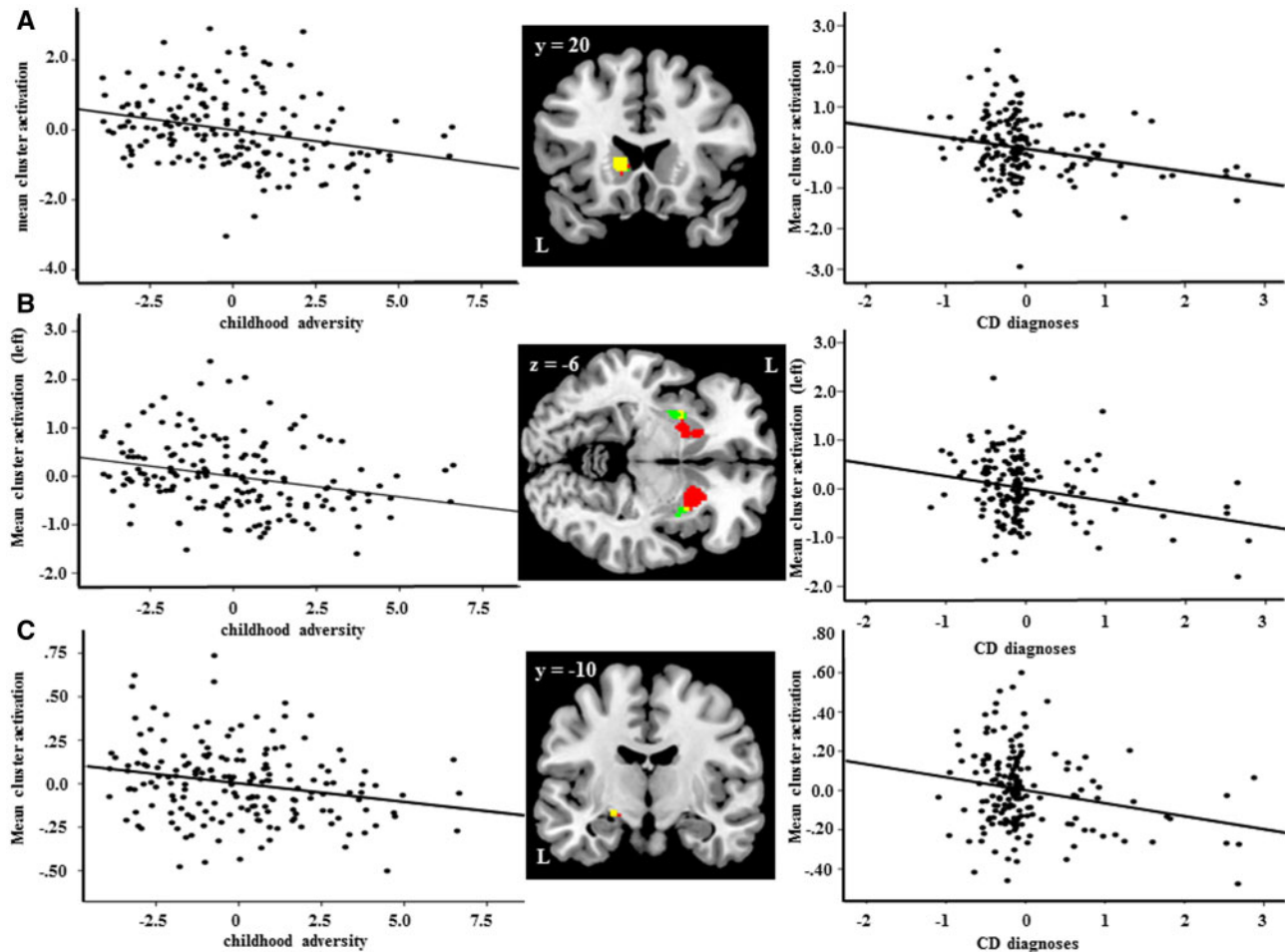


Fig. 2. Effect of exposure to childhood family adversity (CFA) and conduct disorder (CD) diagnoses during childhood and adolescence on VS activity during reward processing (panels A and B) and amygdala activity emotion processing (panel C) (activity averaged over cluster). (A) left caudate reward processing: Left: activity decreased with increasing CFA (157 voxel, peaks -4.64 ; -14.18 6). Right: activity decreased with increasing CD during childhood and adolescence (40 voxel, peak -14.20 6). B. left putamen. Left: activity decreased with increasing CFA (31 voxel, peak -20.16 8). Right: activity decreased with increasing CD during childhood and adolescence (16 voxel, peak -32.4 -6). C. left amygdala. Left: activity decreased with increasing CFA (10 voxel, peak -22 -10 -12). Right: activity decreased with increasing CD during childhood and adolescence in green, with their overlap in yellow. Note that the scatter plot is a partial regression plot depicting the relationship of CFA and CD with brain activity when corrected for all confounders previously mentioned (such as sex, lifetime substance abuse etc.). Thus, negative CFA and CD levels may emerge.

$P = 0.047$), no significant association with CD or brain activity in the ROIs (all p s > 0.28) was found.

Discussion

The novel aspect of the present investigation is the focus on functional characteristics of reward and emotion processing as convergence sites of persistent CD and CFA in one and the same sample. Specifically, our results from a prospective study over 25 years replicated previous evidence of higher levels of CD following CFA. Increased amygdala volume emerged following CFA. Moreover, individuals previously diagnosed with CD or from adverse backgrounds exhibited a reduced response in the VS extending to the dorsal striatum including the caudate head and the putamen during reward anticipation and blunted amygdala activity when confronted with angry and fearful faces with all effects being independent from gray matter differences. Moreover, the impact of CFA on brain activity in the VS and the amygdala was (partially) mediated by CD. In addition, there was a negative relationship between temperamental reward

dependence (reflecting decreased social reward dependence) and both CFA and CD, and a positive association with the VS response.

Blunted VS activity during reward anticipation might be indicative of deficits in approach behavior to biologically salient goals. This may result in less effort to obtain rewards, which is a crucial precondition for adequate social functioning. Interestingly, our results demonstrated that deficient motivational processing, indexed by decreased VS activity and linked with CD and exposure to CFA, was associated with lower levels of temperamental reward dependence, suggesting reduced social cognition, such as sentimentality, openness to emotional communication, attachment and dependence on others' approval. Dysfunction in the VS might further disrupt the development of stimulus-reward contingencies and poor decision-making, which, in turn, might lead to frustration and aggression. Likewise, the poor ability to learn from reinforcement information, as an evident VS function, may contribute to dysfunctional reinforcement exchanges between parents and children, i.e. might provoke harsh and inconsistent parenting

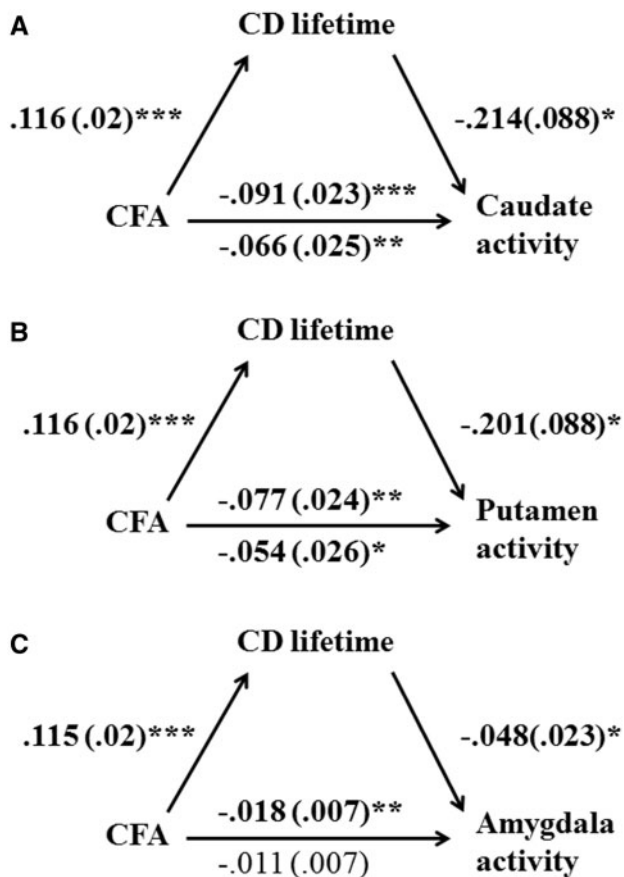


Fig. 3. Mediation analysis. Path model showing that CD (partially) mediated the association between CFA and caudate (A), putamen (B) and amygdala activity (C). *** $P < .001$; ** $P < .01$; * $P < .05$

(Viding and McCrory, 2012). Therefore, the findings presented here may be relevant for future targets regarding parenting based interventions, which could be tailored towards enhancing positive parenting. Moreover, understimulation of the reward circuit might increase reward-seeking behavior, such as drug abuse or rule-breaking behavior, in order to minimize stimulus hyporeactivity, often seen in CD (Carpentier et al., 2012) and in individuals from adverse backgrounds (Mersky et al., 2013).

The amygdala is activated during the perception of salient stimuli such as negative emotional faces. Here, we demonstrated blunted amygdala activity in individuals with child and adolescent CD and from CFA backgrounds. This might be indicative of reduced sensitivity to negative emotions, potentially implying less attribution of significance to these stimuli. In analogy to decreased reward sensitivity in these individuals, this might lead to impaired emotion processing and further contribute to inappropriate social functioning. Whereas less VS activity (Dillon et al., 2009; Mehta et al., 2010; Boecker et al., 2014) following exposure to early life stress echoes previous reports, evidence has been conflicting and task-dependent with regard to amygdala activity. Importantly, Taylor et al. (2006) also demonstrated less amygdala activity during the observation of emotional faces as a function of CFA including abuse and neglect but with opposite results during more active emotion-labeling, which is in accordance with the majority of studies investigating the effects of various measures of childhood maltreatment (Maheu et al., 2010; McCrory et al., 2011; Tottenham et al., 2011; Dannlowksi et al., 2012; McCrory et al., 2013; van Harmelen et al.,

2013; Teicher and Samson, 2016). Our results mimic the observation results by Taylor et al. (2006), in line with our face matching task which can be performed as a simple physical match requiring no emotion labeling. However, further evidence also indicates decreased amygdala activity following unresolved trauma (Kim et al., 2014). Due to results suggesting both hypo- and hyperactivity following adversity, it is intriguing to speculate that amygdala activity in the midrange might be optimal. Some experience of emotional arousal may be adaptive and beneficial (Reynaud et al., 2013), while excessive arousal may be deleterious. An alternative explanation of the discrepant findings regarding increased and decreased amygdala activity might relate to the type of the stressor. In contrast to severe forms of maltreatment, CFA covers more normative types of family adversity including 'objective' measures of adversity, such as socioeconomic disadvantage. Studies using similar adversity types have also reported opposite results when examining the effect of global family functioning as compared to severe childhood adversities on brain volume (Walsh et al., 2014) or reported null findings of poverty (Kim et al., 2013) or of moderate CA (Schweizer et al., 2016) on amygdala activity (but see Gianaros et al., 2008). Hence, while maltreatment may specifically involve a lower level of parental care, this does not necessarily apply to participants from high CFA backgrounds, where a warm parent-child relationship can still be fostered, and, thus, could have a different effect on emotion-related regions. Moreover, secure attachment and positive parenting have been linked to an increased efficiency in upregulating positive emotions (Moutsiana et al., 2014) and to decreased amygdala volume (Moutsiana et al., 2015) as well as to attenuated growth (Whittle et al., 2014). Likewise, maternal warmth has been shown to buffer the effects of low socioeconomic status in terms of pro-inflammatory signaling (Chen et al., 2011). Further, resilience, age, timing of the stressor and developmental trajectories (first hyperactivity followed by hypoactivity in adulthood) could not account for amygdala hypoactivity (compare to Dannlowksi et al., 2012; van Harmelen et al., 2013). Notably, such discrepant findings have also been found for the effect of maltreatment on amygdala volume (Teicher and Samson, 2016). In general, this might prove that there is no monocausal explanation for the differences found in the effects on amygdala activity, which corroborates the complexity of the neural scars of adversity. One might argue that these different forms of adversity might lead to different alterations in the development of emotional processing and regulation, which might represent alternative pathways of vulnerability to types of psychopathology. Whereas mood and anxiety disorders have been associated with heightened responding during emotion processing (Anand and Shekhar, 2003), CD with high CU traits has previously been linked to blunted amygdala activity (Sebastian et al., 2012; Viding and McCrory, 2012; Viding et al., 2012; Herpers et al., 2014), which is also echoed by the results presented. In contrast to other studies (e.g. Fairchild et al., 2011), no effect of CD on amygdala structure was found in this study. Rather than interpreting this as a non-replication, this could instead be attributed to the fact that all individuals included in our study have remitted from CD until age 25 years. Thus, altered amygdala volume may rather be a marker of current CD.

The present study concentrated on the persistence of CD during childhood and young adulthood in individuals who currently had no CD diagnosis. While this restricts the generalizability of the findings in light of evidence suggesting that half of ASPD patients had a history of CD, it is also notable that only 25–30% of CD patients later develop ASPD (for review see Vloet

et al., 2008). However, the absence of a current diagnosis does not necessarily imply that individuals in this study qualitatively differ from those who develop ASPD, as brain activity may be a state-independent vulnerability marker. Therefore, on a dimensional view, brain vulnerability markers such as decreased ventral striatum activity seem to persist even in the absence of a diagnosis on a phenotypic level. In further support of this, participants with previous CD were found to still exhibit increased (subclinical) levels of aggression and brain activity in the VS and amygdala was unrelated to resilience, although an inverse relationship of resilience with CFA emerged. Further, the investigation of healthy subjects, with established developmental risk factors for AB (previous CD and CFA) allows the examination of brain activity independent of non-specific disease load and medication, which might impact on motivation processing (Insel et al., 2014). Of note, in the remaining sample which did not participate in the fMRI session, only three individuals (2.4%) were diagnosed with ASPD, although one third of this sample previously had CD (see Supplementary Methods), indicating that our currently healthy fMRI sample is likely to be unbiased.

A unique feature of the present study was the possibility to control for previous diagnoses and substance abuse, which are highly comorbid with CD (Blair et al., 2014). Importantly, our results were independent of substance abuse, ADHD as well as mood and anxiety diagnoses with regard to VS and amygdala activity (details in the Supplementary Results). Likewise, the effects were disentangled with regard to specific effects of different CD dimensions. Notably, both impulsive and CU behavior is often present in the same individuals (Munoz et al., 2008) and may represent partly related behaviors rather than separable subtypes. The reward processing results presented here may be more driven by the impulsive facet of CD, given the similar impact of both CD during childhood and adolescence and lifetime impulsivity on VS activity and the unchanged results after adjustment for CU traits. Moreover, apparently CFA significantly contributes to the effect of CD on caudate head activity. In contrast, the emotion processing results suggested that blunted amygdala activity seems to be driven by CU traits, which is line with the affective pattern observed in these individuals (Viding and McCrory, 2012; Blair et al., 2014). Likewise, amygdala activity did not reach the voxel criterion after control for CFA, suggesting that the shared variance of CD and CFA may account for blunted amygdala activity.

When evaluating the results, several limitations have to be considered. While the possibility of creating a score of CD diagnoses during childhood and adolescence is a unique feature of this longitudinal study, measures of brain activity were not longitudinally assessed and our sample is currently healthy. Future longitudinal studies on patients are needed to disentangle cause and effect relationships between brain measures and psychopathology to clarify whether blunted activity in the ROIs examined here may be interpreted as a vulnerability factor or a long-term vestige of CD, i.e. an effect of the disease itself. However, given that the fMRI results largely overlap with emotion-related findings from CD patients, and, crucially, are also seen in individuals without a clinical diagnosis of CD (Sebastian et al., 2012; Viding and McCrory, 2012), the brain alterations reported may also be a vulnerability factor rather than a consequence of the disease. Moreover, only a small number of the participants in this study had received a CD diagnosis. However, 18% of the sample was diagnosed with CD, which is about twice the rate of lifetime CD prevalence in the general population (~10%, Vloet et al., 2008). This might result from the fact that the present sample is enriched with participants

characterized by psychosocial and obstetric risk factors. Likewise, our results on the effects of CD on brain activity should be interpreted with caution, as the majority of participants only received one diagnosis during childhood and adolescence. Given the low number of participants with CD diagnoses, we were unable to differentiate between individuals with child-(CO) and adolescent-onset (AO). However, as previous studies did not detect any difference regarding amygdala volume (Fairchild et al., 2011) or amygdala activity to angry faces (Passamonti et al., 2010) according to onset type, the effect on emotion processing should be minimal. Future studies should disentangle the effect of CO and AO on the VS response during reward processing. Further our effects were not whole-brain but only region of interest corrected, which is, however, a standard approach in neuroimaging for the examination of a priori hypotheses (Poldrack, 2007). Moreover, although the face matching paradigm is a very well-validated task, it comprises a pooled emotion contrast over angry and fearful faces. For future studies, it would be preferable to investigate fear and anger separately, especially, given the dissociation between reactivity to anger and fear in CD with and without CU traits (Blair et al., 2001; Fairchild et al., 2008; Marsh et al., 2008; Fairchild et al., 2009, 2010) and the specific hypervigilance in the amygdala to threat following exposure to early adversity (McCrory and Viding, 2015). Finally, this report focused on environmental effects, which are unlikely to exert their influence independent from the individuals genetic make-up, as has been emphasized by recent reports from our group (Nikitopoulos et al., 2014; Zohsel et al., 2014). In this context, it is necessary to consider the possible influence of gene-environment correlations (rGE), i.e. the degree of overlap between genetic and environmental factors implying that exposure to adverse environment may depend upon the genetic vulnerability within families. In this study, it may be conceivable that the parents themselves exhibited antisocial behavior and CU traits (passive rGE), which in turn might have led to CFA. However, by controlling for parental ASPD, we partly accounted for this influence.

Conclusion

In conclusion, blunted activity in the VS and the amygdala may present possible convergence sites of CD and CFA affecting motivation and emotion processing, respectively. Specifically, altered affective processing following CFA may impact on social functioning and may increase the risk for CD. Since environmental risk factors are modifiable in nature, this may offer an attractive opportunity for intervention.

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Supplementary data

Supplementary data are available at SCAN online.

Conflicts of interest

TB served in an advisory or consultancy role for Hexal Pharma, Lilly, Medice, Novartis, Otsuka, Oxford outcomes, PCM scientific, Shire and Viforpharma. He received conference attendance support and conference support or received speaker's fee by Lilly, Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Lilly, Shire & Viforpharma. AML received fees for consultancy Lundbeck International Neuroscience, Thieme Verlag Germany and Elsevier USA; for lectures, including travel fees from Aula Médica Congressos, Grupo Ferrer International, Janssen-Cilag, Lilly Deutschland, Roche Pharma AG; and also grants from the Federal Office for Radiation Protection Germany and the Prix Roger de Spoelberch. JKB has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Medice, Shire and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. All other authors declare that they have no biomedical financial interest or potential conflicts of interest. The present work is unrelated to the above grants and relationships.

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