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Neural Profile of Callous Traits in Children: A Population-Based Neuroimaging Study

Koen Bolhuis, Essi Viding, Ryan L. Muetzel, Hanan El Marroun, Desana Kocevska, Tonya White, Henning Tiemeier, and Charlotte A.M. Cecil

ABSTRACT

BACKGROUND: Callous traits during childhood, e.g., lack of remorse and shallow affect, are a key risk marker for antisocial behavior. Although callous traits have been found to be associated with structural and functional brain alterations, evidence to date has been almost exclusively limited to small, high-risk samples of boys. We characterized gray and white matter brain correlates of callous traits in over 2000 children from the general population.

METHODS: Data on mother-reported callous traits and brain imaging were collected at age 10 years from participants of the Generation R Study. Structural magnetic resonance imaging was used to investigate brain morphology using volumetric indices and whole-brain analyses (n = 2146); diffusion tensor imaging was used to assess global and specific white matter microstructure (n = 2059).

RESULTS: Callous traits were associated with lower global brain (e.g., total brain) volumes as well as decreased cortical surface area in frontal and temporal regions. Global mean diffusivity was negatively associated with callous traits, suggesting higher white matter microstructural integrity in children with elevated callous traits. Multiple individual tracts, including the uncinate and cingulum, contributed to this global association. Whereas no gender differences were observed for global volumetric indices, white matter associations were present only in girls.

CONCLUSIONS: This is the first study to provide a systematic characterization of the structural neural profile of callous traits in the general pediatric population. These findings extend previous work based on selected samples by demonstrating that childhood callous traits in the general population are characterized by widespread macrostructural and microstructural differences across the brain.

Keywords: Callous-unemotional, Child psychiatry, Diffusion tensor imaging, Epidemiology, Gender differences, Structural neuroimaging

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Callous traits, including shallow affect, remorselessness, and a callous lack of empathy, are a key risk marker for antisocial behavior (1). In childhood, callous traits are part of a broader set of callous-unemotional/psychopathic traits used to identify a particularly problematic subgroup of children with conduct problems, as operationalized by the DSM-5 specifier of low prosocial emotions (2), distinguished by more severe and chronic antisocial behavior and at least partially distinct etiology of their presentation (3). Effects extend well beyond childhood, as callous traits independently predict a wide range of negative outcomes across the life span, including adult psychopathy, antisocial personality disorder, criminality, and substance abuse (4). Consequently, youth callous traits are an important target for etiologic research, prevention, and intervention (5).

A growing number of studies have been conducted to characterize the neurodevelopment of callous and related traits. Several different measures, varying in their coverage of specific behaviors, have been used to study callous-unemotional traits (5,6), and this needs to be considered when interpreting the existing literature and, in particular, findings that have not been replicated across studies. The majority of these studies have employed task-based functional magnetic resonance imaging (fMRI) in clinical and/or high-risk samples of male subjects (7,8). Based on a recent meta-analysis of fMRI studies, which included 108 cases and 115 controls from nine studies, youths with elevated psychopathic traits demonstrated decreased activity in ventromedial prefrontal cortex and the limbic system and increased activation in frontostriatal regions (8). These regions are known to be involved in reward processing and affect regulation (9), and these findings partly converge with findings from structural MRI (sMRI) studies. Indeed, a recent meta-analysis including 188 cases and 122 controls pooled from five studies reported gray matter volume reductions of the putamen in youths with elevated callous-unemotional traits (10). However, findings from structural studies regarding other brain regions have been inconsistent, likely owing to heterogeneity in samples, analytic methods, and participant age (7,11). Finally, very few studies

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have employed diffusion tensor imaging (DTI) to characterize the microstructural properties of white matter associated with youth callous traits. Several studies have been published on externalizing behavior more broadly (11), and we have recently demonstrated that lower whole-brain white matter connectivity was associated with more delinquent behavior in children (12). Publications on callous traits specifically are more sparse with small samples, and these have reported mixed findings, with both increased and decreased white matter integrity observed in various tracts (11). Most of these studies have uniquely focused on the uncinate fasciculus, a fiber bundle that connects prefrontal and subcortical structures, although recent work supports the involvement of a wider set of tracts (13).

Overall, the above evidence points to neurobiological alterations associated with callous traits (and related phenotypes). However, knowledge on the neurodevelopmental underpinnings of callous traits is limited in four key ways. First, findings have been primarily based on small, selected samples, so that it remains unclear to what extent structural brain differences are associated with callous traits in the general pediatric population. This is a notable gap, given compelling evidence that callous traits exist along a continuum in the general population (14). Second, no neuroimaging study has examined both sMRI and DTI data to assess both gray and white brain structural correlates of youth callous traits—an important step toward integrating mixed findings in the literature. Third, existing studies have focused primarily on male subjects owing to the higher prevalence of conduct problems. As such, little is known about neuroanatomical correlates of callous traits in girls and whether these differ from boys. Fourth, whereas previous imaging studies have largely focused on specific brain regions, it is important to employ a whole-brain approach to study callous traits, as it is well known from the wider neuroimaging literature that the brain functions in networks (15).

In the present study, we examined the relationship between brain structure and callous traits in over 2000 children, the largest neuroimaging study on pediatric callous traits to date, using data from a population-based cohort. Our aims were to assess both 1) structural brain morphology and 2) white matter microstructure in relation to child callous traits. Both aims were addressed following a hierarchical approach—i.e., global metrics were analyzed first, followed by more detailed regional analysis if an association with global measures was observed. Based on existing literature, we expected global gray matter reductions as well as regional reductions in subcortical structure volumes. Regarding DTI analyses, we had no specific hypotheses, given the mixed findings in the literature. Potential gender differences were also explored. However, because most prior neuroimaging studies have been based on male subjects, we had no specific hypothesis.

METHODS AND MATERIALS

Study Population

This cross-sectional study was embedded in the Generation R Study, a prospective population-based cohort from Rotterdam, the Netherlands (16). Study protocols were approved by the local ethics committee, and written informed consent and assent was obtained from all parents and children, respectively. At mean age 10 years (range, 8–11 years) in children, mothers completed a questionnaire about callous traits in their children, and children were invited to participate in a neuroimaging assessment (17). For the current study, participants were included if they had data on callous traits and sMRI scan or DTI scan available (n = 2146, and n = 2059, respectively) (Supplemental Figure S1).

Measures

Callous Traits. Callous traits were assessed through maternal report when the child was on average 10 years old, using a brief validated questionnaire adapted from the Youth Self-Report and the Inventory for Callous-Unemotional Traits (18). The questionnaire comprises seven items on mainly interpersonal callous traits, which were scored on a 4-point scale (range, 0–21) (Supplemental Figure S2), including "Does not find other people's feelings important," and "Is cold and indifferent." Although this measure does not comprehensively capture the full spectrum of unemotional or psychopathic traits, it has been shown to adequately capture childhood callous traits on a dimensional scale (18), correlates strongly with other measures of youth psychopathy, and is predictive of adult antisocial traits (19). Endorsement of the seven items is shown in Supplemental Table S1. Cronbach's α in the current sample was .73.

Other Behavioral Data. At age 10 years, co-occurring emotional and behavioral problems were assessed through mother report and child report using the well-validated Child Behavior Checklist and Brief Problem Monitor, respectively (20,21); mothers and children also completed the Strengths and Difficulties Questionnaire Prosocial scale (22). Concurrently, maternal psychopathology was assessed through four subscales of the self-reported Brief Symptom Inventory (23). Child intelligence (IQ) was measured at age 6 years with the Snijders-Oomen nonverbal intelligence test (24). See Supplement for more detailed information.

Brain Imaging

An overview of the imaging procedure, sequences, and quality assessment has been described previously (17) and can be found in the Supplement. Every child was invited to participate in a mock scanning session before the MRI scan to familiarize them with the procedure. If at any point the child was too anxious about the procedure, he or she did not progress to the MRI scan. All images were acquired on a 3T Discovery MR750W scanner (GE Healthcare, Chicago, IL) using an eight-channel head coil.

Covariates

All analyses were adjusted for the following covariates. Child gender and date of birth were retrieved from birth records. Child ethnicity was defined according to the classification of Statistics Netherlands, i.e., Dutch, other Western, and other non-Western. Maternal educational level was categorized into primary (no or primary education), secondary (lower and

Table 1. Sample Characteristics

	n (% Missing Data)	Descriptive Statistics	Correlation With Callous Traits, *r*
Child Characteristics			
Age at MRI scan, years, mean (SD)	2146 (0% missing)	10.10 (0.58)	—
Gender, girls, %	2146 (0% missing)	49.9	—
Ethnicity, %	2132 (0.7% missing)		
Dutch		68.9	—
Other, Western		8.3	—
Other, non-Western		22.8	—
Callous traits, median (IQR)	2146 (0% missing)	2.00 (3.00)	—
Nonverbal IQ at age 6 years, mean (SD)	1904 (11.3% missing)	104.4 (14.64)	−.08[a]
Mother-Reported CBCL, Median (IQR)			
Affective problems	2078 (3.3% missing)	1.00 (2.00)	.23[a]
Anxiety problems	2074 (3.5% missing)	0.00 (2.00)	.15[a]
Somatic complaints	2062 (3.9% missing)	0.00 (2.00)	.09[a]
ADHD problems	2073 (3.4% missing)	2.00 (4.00)	.36[a]
ODD problems	2071 (3.6% missing)	1.00 (2.00)	.39[a]
CD problems	2078 (3.3% missing)	0.00 (1.00)	.47[a]
Child-Reported BPM, Median (IQR)			
Internalizing problems	2044 (4.8% missing)	2.00 (3.00)	.07[a]
Externalizing problems	2042 (4.8% missing)	2.00 (3.00)	.22[a]
Attention problems	2042 (4.8% missing)	3.00 (3.00)	.20[a]
SDQ—Prosocial Scale, Median (IQR)			
Mother-reported	2098 (2.2% missing)	9.00 (2.00)	−.22[a]
Child-reported	2056 (4.2% missing)	9.00 (2.00)	−.12[a]
Maternal Characteristics			
Educational level, %	2020 (6.0% missing)		
High		66.7	—
Medium		31.7	—
Low		1.6	—

ADHD, attention-deficit/hyperactivity disorder; BPM, Brief Problem Monitor; CBCL, Child Behavior Checklist; CD, conduct disorder; IQR, interquartile range; MRI, magnetic resonance imaging; ODD, oppositional defiant disorder; SDQ, Strengths and Difficulties Questionnaire.

[a]$p < .01$.

intermediate vocational training), and higher (higher vocational training and university) educational attainment.

Statistical Analyses

Before the main analyses, we validated our measure of callous traits by examining whether correlations with mother-reported and child-reported emotional and behavioral problems, prosocial behavior, and IQ were in line with the previous literature. We then proceeded to examine neural correlates of callous traits, specifically structural brain morphology and white matter microstructure, using separate linear regressions. All sMRI and DTI analyses were adjusted for covariates as described above. A hierarchical stepwise approach was used to limit the number of comparisons.

With respect to sMRI measures, total global and subcortical volumetric indices first were assessed in association with callous traits. Analyses pertaining to subcortical volumes were corrected for intracranial volume. A false discovery rate (FDR) correction was applied to these analyses to address multiple testing (25,26). If an association with any global measure was observed, subsequent vertexwise analyses were conducted to investigate local differences in cortical morphology associated with callous traits.

With respect to DTI, initial analyses were performed with global fractional anisotropy and mean diffusivity (MD) in association with callous traits. Next, if an association between global fractional anisotropy or MD and callous traits was observed, 1) subsequent analyses were conducted on individual white matter tracts, and 2) associations with axial diffusivity (AD) and radial diffusivity (RD) (which are composites of MD) (see Supplement) were explored. For these analyses, multiple testing was addressed using an FDR adjustment.

In sensitivity analyses, our models were additionally adjusted for co-occurring emotional and behavioral problems, nonverbal IQ, and maternal psychiatric problems, in line with recent recommendations based on developmental studies (3,27). In addition, gender differences of observed associations were explored using interaction analyses. Similarly, we investigated whether Child Behavior Checklist conduct problems moderated the association of callous traits with global volumetric and white matter outcomes. We also explored nonlinear relationships by adding quadratic terms.

Table 2. Association of Global Structural Volumetric and Global White Matter Microstructural Measures With Callous Traits

	Callous Traits		
	β (95% CI)	*p*	FDR-Adjusted *p*
Structural Volumetric Measures (*n* = 2146)			
Total brain volume	−.10 (−.15, −.05)	< .001	—
Cortical gray matter volume	−.10 (−.15, −.05)	< .001	< .001
White matter volume	−.08 (−.13, −.03)	.001	.003
Subcortical structures			
Left amygdala	−.03 (−.08, .02)	.194	.652
Right amygdala	−.06 (−.11, −.01)	.030	.420
Left hippocampus	−.03 (−.08, .02)	.233	.652
Right hippocampus	−.02 (−.07, .04)	.559	.862
Left thalamus	.00 (−.06, .06)	.950	.987
Right thalamus	−.03 (−.09, .03)	.361	.760
Left caudate	−.03 (−.08, .02)	.223	.652
Right caudate	−.04 (−.09, .01)	.132	.652
Left putamen	−.01 (−.06, .04)	.616	.862
Right putamen	.00 (−.05, .05)	.987	.987
Left globus pallidus	.00 (−.05, .05)	.956	.987
Right globus pallidus	−.01 (−.06, .03)	.562	.862
Left nucleus accumbens	.02 (−.03, .07)	.380	.760
Right nucleus accumbens	.01 (−.04, .05)	.751	.956
White Matter Microstructural Measures (*n* = 2059)			
Global fractional anisotropy	.01 (−.03, .06)	.633	—
Global mean diffusivity	−.06 (−.11, −.02)	.006	—

All analyses are corrected for child gender, child age at magnetic resonance imaging scan, child ethnicity, and maternal educational level. Subcortical volumes are additionally adjusted for intracranial volume. Estimates reflect standardized coefficients.

CI, confidence interval; FDR, false discovery rate.

Because of skewness (Supplemental Figure S2), callous traits sum scores were square root transformed to approach a normal distribution. Standardized coefficients are presented throughout. All analyses were conducted using R statistical software (28). Missing values on covariates were dealt with using multiple imputations in mice version 2.25 (29); estimates from analyses of 100 imputed datasets were pooled.

RESULTS

Behavioral Validation of Callous Traits

As expected, callous traits showed high positive correlations with mother-reported conduct problems, followed by oppositional defiant disorder and attention-deficit/hyperactivity disorder symptoms. In contrast, we observed significantly lower correlations for affective, anxiety, and somatic symptoms

Table 3. Vertexwise Analyses of Cortical Surface Area and Callous Traits (*n* = 2146)

Hemisphere and Region	Cluster Size (mm^2)	Talairach Coordinates (x, y, z)	Number of Vertices Within Cluster	β (Average Across Cluster)	Clusterwise *p* Values
Left					
1. Fusiform	1476.88	−41.8, −47.3, −14.0	2445	−.08	.0001
2. Superior temporal	918.28	−51.8, 8.0, −18.0	1718	−.07	.0001
3. Lingual	681.36	−20.7, −54.0, −2.9	1422	−.08	.0003
4. Superior frontal	522.48	−13.7, 45.9, 3.5	973	−.08	.0016
5. Postcentral	457.15	−51.7, −12.5, 15.9	1209	−.06	.0036
6. Lateral orbitofrontal	357.56	−32.2, 26.6, −10.3	727	−.07	.0127
Right					
7. Middle temporal	1446.11	49.3, 7.5, −32.9	2541	−.08	.0001
8. Fusiform	545.16	41.6, −46.3, −16.6	1066	−.06	.0012
9. Isthmus of the cingulate	411.04	6.0, −20.1, 20.9	1036	−.07	.0065
10. Postcentral	396.81	60.0, −8.2, 15.9	872	−.07	.0077

Analyses are corrected for age, gender, child ethnicity, and maternal educational level. Numbers of the clusters correspond to the numbers shown in Figure 1. Cluster-forming threshold of .001.

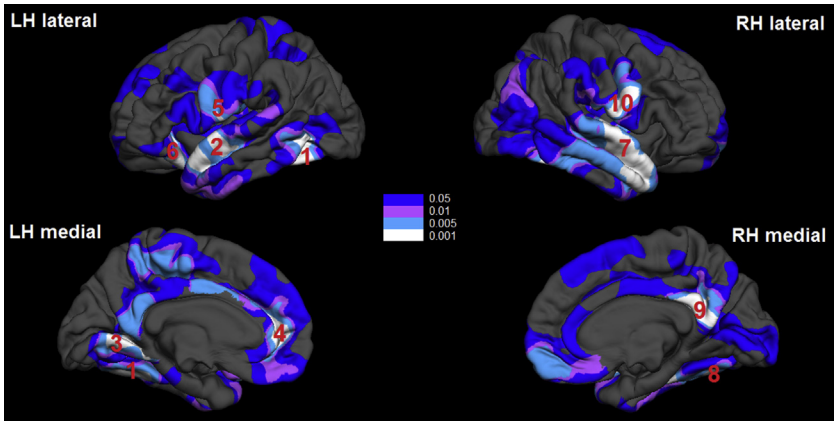

Figure 1. Negative associations between cortical surface area and callous traits (n = 2146). Note: Analyses are corrected for age, gender, child ethnicity, and maternal educational level. Colors represent the cluster-forming thresholds. Blue clusters represent a negative correlation between cortical surface area and callous traits at a clusterwise corrected p value threshold of $< .05$, with transition to light blue, purple, and white for clusters that are negatively correlated with callous traits at more stringent p value thresholds (i.e., .01, .005, .001; see legend on Figure). Numbers of the clusters correspond to the numbers shown in Table 3. LH, left hemisphere; RH, right hemisphere.

(difference in correlations, all z score > 4.9, $p < .001$) (Table 1). Similarly, child-reported externalizing and attention problems correlated more strongly with callous traits than did internalizing problems (all z score > 5.3, $p < .001$). Mother-reported and child-reported prosocial behavior were negatively correlated with callous traits.

Structural Brain Morphology

Total brain, cortical gray matter, and white matter volumes all were negatively associated with callous traits (Table 2). Right amygdala volume was negatively associated with callous traits, which did not survive FDR correction. No associations were found between subcortical volumes and callous traits. Similar results were observed in analyses with additional adjustment for co-occurring psychiatric problems, nonverbal IQ, and maternal psychopathology (Supplemental Tables S2–S4). In vertexwise analyses, 10 brain regions showed negative correlations between cortical surface area and callous traits (Table 3 and Figure 1), which were localized in the frontal and temporal lobes of both hemispheres. No vertexwise associations were found between cortical thickness and callous traits. Three gyrification clusters in the temporal lobe were negatively associated with callous traits (Supplemental Table S5). Additional adjustment for IQ and maternal psychopathology did not considerably alter these observations (Supplemental Tables S7 and S8), but after adjustment for co-occurring psychiatric problems, only the superior frontal gyrus was associated with callous traits (Supplemental Table S6).

White Matter Microstructure

Global MD, but not global fractional anisotropy, was negatively associated with callous traits (Table 2). Similarly, global AD and RD were negatively associated with callous traits (Supplemental Table S9). Several white matter tracts contributed to this global association (Table 4), including the superior longitudinal fasciculus, corticospinal tract, uncinate, and cingulum. These associations all survived FDR correction. Comparable results were observed in analyses with additional adjustment for co-occurring psychiatric problems, nonverbal IQ, and maternal psychopathology (Supplemental Tables S2–S4 and S10–S12). Callous traits were negatively associated with AD of the inferior and superior longitudinal fasciculi and corticospinal tract and with uncinate and cingulum RD (Supplemental Table S13). A visualization of the associated white matter tracts is presented in Supplemental Figure S2.

Gender Interaction Analyses

Callous traits were significantly higher in boys than in girls (2.33 vs. 1.85) ($t_{2116} = 5.1$, $p < .001$). Boys scored higher on almost all callousness items (Supplemental Tables S14 and S15); correlations between behavioral problems and callous traits were similar across genders. Nonverbal IQ negatively correlated with callous traits in boys but not in girls (Supplemental Table S16). No interaction was observed for structural volumetric measures (Supplemental Table S17). A significant gender-by-brain interaction was observed for the associations of MD with callous traits ($p = .005$). Stratified analyses demonstrated that our findings in the full sample were driven by the associations in girls, and these effects were observed in several tracts across the brain (Supplemental Tables S18 and S19). No such associations were found in boys.

Table 4. Associations Between Mean Diffusivity in Individual White Matter Tracts and Callous Traits

	β (95% CI)	p	FDR-Adjusted p
Inferior Longitudinal Fasciculus	−.04 (−.09, .00)	.072	.089
Superior Longitudinal Fasciculus	−.06 (−.11, −.01)	.010	.021
Forceps Minor	−.04 (−.08, .00)	.076	.089
Forceps Major	−.01 (−.06, .03)	.528	.528
Corticospinal Tract	−.15 (−.26, −.04)	.008	.021
Uncinate Fasciculus	−.06 (−.11, −.02)	.002	.014
Cingulum Bundle	−.06 (−.10, −.01)	.012	.021

Note: All analyses are corrected for child gender, child age at magnetic resonance imaging scan, child ethnicity, and maternal educational level. Microstructural properties of left and right tracts were combined and weighted for their respective volumes except for forceps minor and forceps major. Estimates reflect standardized coefficients.

CI, confidence interval; FDR, false discovery rate.

Sensitivity Analyses

Conduct problems did not moderate the associations of callous traits with global volumetric and white matter outcomes (Supplemental Table S20). Associations with quadratic terms were all nonsignificant (Supplemental Table S21).

DISCUSSION

This is the first study to characterize the structural neural profile of callous traits in the general pediatric population. Based on sMRI and DTI data from over 2000 children, we demonstrate that callous traits at age 10 are characterized by widespread macrostructural and microstructural differences across the brain. We highlight three key findings. First, childhood callous traits were associated with reduced global gray matter and decreases in cortical surface area and gyrification across several frontal and temporal areas. These observations are consistent with prior research using high-risk samples. Second, we observed increased global white matter microstructure in children with elevated callous traits, suggesting increased white matter integrity across various white matter tracts. Third, we found that white matter, but not gray matter, associations differed by gender, with associations observed only in girls. Together, the present findings contribute to a more complete understanding of the relationship between brain structure and callous traits and may be used as a guiding framework for future research to uncover causal neurodevelopmental pathways.

Findings from the sMRI analyses indicated that callous traits are associated with lower global brain volumes. More specifically, decreased cortical surface area and reduced gyrification were observed in various brain regions, including the temporal gyri and several (pre-)frontal gyri. These regions have previously been associated with behavioral inhibition, social cognition, and emotion regulation (30–33), which have been implicated in the development of callousness (3,6). Our findings corroborate studies that observed gray matter volume reductions in orbitofrontal, cingulate, and temporal cortices in older youths with callous traits in the clinical range (10) and support other studies that observed reduced cortical surface or gyrification across similar regions (34–37). We identified a nominally significant association between callous traits and lower right amygdala volume, which did not survive multiple-testing correction when accounting for other subcortical regions. Whereas aberrant amygdala function has been robustly associated with callous-unemotional traits (8), structural volumetric differences of the amygdala are rarely observed (10,38–41). This inconsistency between structural and functional neuroimaging findings could partly be explained by the use of different significance thresholds in studies taking a region-of-interest versus whole-brain approach. Our findings suggest the involvement of many regions with small effects. By extending these clinical MRI studies, our findings corroborate the notion that callous traits exist along a continuum in the general population, which has also been evidenced in genetic studies (3,5,14). Moreover, associations remained consistent after additional adjustment for co-occurring emotional, behavioral, and attention problems; IQ; and maternal psychopathology. In other words, whereas callous traits were significantly associated with other psychiatric symptoms (including conduct and attention-deficit/hyperactivity disorder problems) and IQ—consistent with the extant literature—these comorbid symptoms did not explain our global neuroimaging findings. Co-occurring emotional and behavioral problems did, however, account for a large portion of the explained variance in vertexwise cortical surface area analyses, supporting the presence of at least some shared neural alterations in callous traits and comorbid psychiatric problems (3,4). Of interest, unique variance for callous traits was observed in the superior frontal gyrus, which has been linked to callous traits in clinical cohorts (36,38).

Whereas structural brain connectivity has been examined in the context of externalizing problems more generally (11,12), few studies to date have examined the white matter microstructure profile of callous traits. This work has mainly focused on the uncinate fasciculus in older, selected samples and produced mixed results, reporting both lower and higher microstructure in adolescents with elevated callous traits (11,42). Two studies employing a whole-brain approach—both of which are based on data from adolescent (primarily boys) arrestee cohorts—reported that callous traits were associated with higher white matter integrity in many tracts across the brain, including the corticospinal tract, superior longitudinal fasciculus, and uncinate (13,43). These findings are consistent with the higher microstructural integrity in various tracts observed in the current study, e.g., uncinate and cingulum, which connect frontal with temporal/parietal brain regions (44–46). This is noteworthy considering the substantial differences in design and sample characteristics between these studies and ours, including the focus on different developmental periods, proportion of boys to girls, and the use of a high-risk versus general population sample. The decreases in MD identified across these studies suggest higher white matter microstructure, possibly indicating accelerated or precocious white matter development in children with elevated callous traits (15). Importantly, decreased integrity has also been observed within high-risk samples (44–46). The reason for such discrepancy is unclear; potential reasons include different sampling strategies, varying levels of exposure to adversities and comorbid psychiatric problems, case-control versus dimensional perspectives, and different definitions of the callousness phenotypes. Our current findings are in contrast with our previous publication where we showed lower white matter microstructure in preadolescent children with elevated levels of delinquent behavior (12), suggesting that callous traits and other externalizing behaviors are associated with differential neural correlates even though these behaviors are correlated. This is consistent with fMRI studies showing, for example, amygdala reactivity to fearful faces to be negatively associated with callous traits and positively associated with conduct problems across multiple independent samples, despite these psychiatric phenotypes' being positively correlated with one another (47–49). Findings from sMRI and DTI have been much less consistent (10,11), although differential amygdala volume reductions have been observed for callous-unemotional versus conduct problems (50,51). In this study, conduct problems were not found to moderate associations between callous traits and global brain measures. Importantly, in sensitivity analyses, we adjusted for all co-occurring problems, which left our sMRI and DTI findings unchanged even though callous traits were substantially correlated with

externalizing behaviors. This, together with our previous observations (12), suggests specific brain-callousness correlates independent of other types of psychopathology, indicating that there is added value in screening for callous traits in children at elevated risk for antisocial behavior.

This is the first study to examine neural correlates of callous traits using both sMRI and DTI. Overall, our findings corroborate 1) previous high-risk sMRI studies reporting associations between callous traits and lower brain volume across frontal and temporal regions and 2) previous high-risk DTI studies indicating higher microstructural integrity of the white matter tracts connecting these areas (13,35,36,38,42,43). As such, our findings support these seemingly discrepant associations and suggest that these are not simply the result of methodological differences between studies. The inverse relationship between the sMRI and DTI findings could potentially indicate decreased cortical functioning and consequently more dysregulated white matter connectivity, or vice versa (15). Multimodal neuroimaging approaches incorporating fMRI assessments are required to disentangle the origins of these observations.

Whereas boys and girls are known to differ considerably in prevalence of callous traits and trajectories of brain development (3,52), it is unclear whether there are gender differences in the neural profile of callous traits, as existing studies have primarily focused on male subjects. The equal distribution of boys and girls in our sample offered a unique opportunity to address this gap. We found no gender differences in global volumetric measures. However, we did find that the relationship of global white matter microstructure with callous traits was significant only in girls. Given that white matter has been shown to develop more quickly in girls compared with boys (52), it is possible that our findings reflect advanced white matter maturation in girls with elevated callous traits and thus potential residual (brain) age confounding. In post hoc analyses, we found that age did not moderate the association of global MD, AD, or RD with callous traits in girls (all $p > .100$). However, potentially, chronological age does not adequately capture differences in neurobiological maturation (53). Recent smaller studies have observed more pronounced cortical differences for callous traits in adolescent boys versus girls (54), which is not what we observed here. These findings could potentially signify that callous traits and their associated neural profile reflect differential development in girls compared with boys. Repeated neuroimaging assessments at later ages—in combination with pubertal development measures—will be particularly valuable for clarifying whether these gender differences persist across brain development or whether the developmental trajectories are similar for boys and girls, with possibly different onsets.

Our study had several strengths, including the use of a large sample of nonselected children from the community and the analysis of both sMRI and DTI data. Our hierarchical analytical approach allowed us to investigate both global and specific brain metrics without substantially increasing the risk of type II error. Stringent sensitivity analyses further enabled us to ascertain that our findings were robust to additional adjustment for co-occurring psychiatric problems, IQ, and maternal psychopathology. Finally, our study was the first to examine neuroanatomical correlates of callous traits in a sample with an equal distribution of boys and girls. Despite these strengths, several limitations should be noted. First, our measure of callous traits did not adequately cover unemotional/affective aspects, which are important features of callous-unemotional and broader psychopathic traits and which have been studied in the wider literature in clinical samples (5). Future work will need to take this limitation into account by exploring associations across a broader spectrum of traits (6) and, additionally, employ a multi-informant approach to childhood callous traits. Second, our findings were cross-sectional and hence should be interpreted as a neurobiological characterization of callous traits, rather than an underlying biological mechanism. Furthermore, we were unable to assess whether observed brain-behavior associations predicted functional outcomes, both concurrently and longitudinally, such as academic performance. Furthermore, the participants are still too young (i.e., do not have enough variability in behavior) for examining other relevant functional domains, such as substance use, risk-taking, and contact with law enforcement. In the future, it will be important to draw on longitudinal designs with repeated measures of neuroimaging and callous traits to trace neurodevelopmental trajectories of callous traits and their utility for predicting clinically relevant outcomes in later life. Third, a growing body of literature points to the existence of distinct developmental pathways to youth callous traits (3), with groups being differentially related to exposure to early adversity in childhood and accompanying anxiety symptoms versus development of similarly severe callous traits through inherited vulnerabilities (3). Our current population-based cross-sectional design did not allow us to study these differential developmental pathways. Repeated assessments of both neuroimaging and callous traits across childhood are needed, particularly with regard to differential developmental pathways (55,56). Nevertheless, we adjusted for behavioral as well as emotional problems in sensitivity analyses, which did not alter our main findings. Fourth, nonverbal IQ was assessed 4 years before callous traits and MRI assessments; it would have been better to have concurrent assessments of each. Despite this, intelligence is moderately stable during childhood (57), which supports the reliability of our analysis with adjustment for IQ at 6 years. Fifth, whereas our hierarchical analysis approach reduces the likelihood of false-positive results, it also increases chances of false-negative results—i.e., very focal findings might have been obscured if global associations were not found. Sixth, though the Generation R Study is an ethnically diverse study, most participants are of European descent. More research needs to be conducted in nonwhite populations, which is a considerable gap in the literature. Finally, more research should employ multimodal approaches, for example, integrating fMRI data to further characterize the neural profile of callous traits.

In conclusion, we found evidence for widespread macrostructural and microstructural brain alterations in callous traits based on a large community sample of children. These results underscore that youth callous traits are not uniquely associated with brain differences in frontolimbic or frontostriatal connections; rather, structural brain differences were observed in a wide range of areas across the brain. Our study provides further support for the value of conceptualizing pediatric callous traits as a neurodevelopmental condition. Priority should be given to prospective developmentally sensitive research, which will enable examination of early environmental

and neurobiological pathways to callous traits, potential gender differences, and their utility in predicting clinically relevant functional domains in later life. Finally, the current results may indicate that children with elevated callous traits show differences in brain development, which holds promise for etiologic research for a better understanding of the development of severe antisocial behavior later in life.

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ARTICLE INFORMATION

From the Departments of Child & Adolescent Psychiatry/Psychology (KB, RLM, HEM, DK, TW, HT, CAMC) and Pediatrics (HEM), Erasmus University Medical Center Rotterdam–Sophia Children's Hospital; Generation R Study Group (KB, DK) and Departments of Epidemiology (RLM) and Radiology (TW), Erasmus University Medical Center Rotterdam; Department of Psychology, Education & Child Studies (HEM), Erasmus University Rotterdam, Rotterdam, the Netherlands; Division of Psychology and Language Sciences (EV), University College London; Department of Psychology (CAMC), King's College London, London, United Kingdom; and Department of Social and Behavioral Sciences (HT), Harvard T.H. Chan School of Public Health, Boston, Massachusetts.

Address correspondence to Charlotte A.M. Cecil, Ph.D., Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Centre, Room NA-2815, P.O. Box 2060, 3000 CB Rotterdam, the Netherlands; E-mail: c.cecil@erasmusmc.nl or charlotte.cecil@kcl.ac.uk.

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