

Normal variation in behavioral adjustment relates to regional differences in cortical thickness in children

Kristine B. Walhovd · Christian K. Tamnes ·
Ylva Østby · Paulina Due-Tønnessen ·
Anders M. Fjell

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Abstract Neuroanatomical correlates of developmental psychopathology such as attention deficit hyperactivity and conduct disorder have been identified. The majority of studies point to lesser gray matter in psychopathology, often involving prefrontal cortices. The goal of this study was to test whether similar neural correlates exist for behavioral variance in healthy children and adolescents. A large sample ($n = 106$) aged 8–19 years underwent MR scanning and their parents completed the Strength and Difficulties Questionnaire. The relationships between cortical thickness and conduct problems and hyperactivity/inattention scale scores were investigated throughout the cerebrum. No associations were found between normal variance in hyperactivity/inattention and cortical thickness. Normal variance in conduct problems was associated with thinner left hemisphere prefrontal and supramarginal cortices. Relationships between conduct problems and cortical thickness interacted with age, with the greatest differences in cortical thickness seen in the younger children. These interactions were observed in the anterior cingulate, orbitofrontal, middle and superior frontal, as well as lateral and medial temporal cortices. In conclusion, the results indicate neurobiological continuity between symptoms of

conduct problems within the normal range, and conduct disorder. Relationships of thinner cortices and conduct problems were primarily seen in younger children, and appeared to decrease with age, indicative of different maturational trajectories in the groups. The long-term consequences are unknown, and the results point to a need for longitudinal studies of developmental trajectories of neuroanatomical foundations of behavioral adjustment.

Keywords Cortical thickness · Orbitofrontal cortex · Cingulate cortex · Conduct problems · Maturation

Introduction

The psychological and behavioral adjustment of children is the result of a dynamic interaction between maturation and learning, and is profoundly linked to brain development. Recent reports indeed indicate that such adjustment problems in childhood psychopathology are related to structural brain characteristics, e.g. in attention deficit hyperactivity disorder (ADHD) [27, 33, 34], pediatric bipolar disorder (PBD) [27], and conduct disorder (CD) [6, 9, 21, 34]. Several brain areas have been implicated, and the exact neural foundations vary according to the nature of developmental pathology [43]. However, there also appear to be similarities across conditions, and differences between healthy and clinical groups, including ADHD, CD and prenatally substance-exposed children with increased regulatory problems, have repeatedly been identified in prefrontal areas, including, but not limited to, orbitofrontal and cingulate cortices [6, 21, 33, 34, 40, 41, 43]. These areas are central in regulatory processes which appear disturbed in a number of childhood psychiatric conditions. In addition, there may likely be cerebral cortical

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K. B. Walhovd (✉) · C. K. Tamnes · Y. Østby ·
P. Due-Tønnessen · A. M. Fjell
Department of Psychology, Center for the Study of Human
Cognition (CSHC), University of Oslo, PO Box 1094, Blindern,
0317 Oslo, Norway
e-mail: k.b.walhovd@psykologi.uio.no

P. Due-Tønnessen
Oslo University Hospital, Rikshospitalet, Oslo, Norway

differences specific to distinct types of behavioral problems. In CD, cortical differences relative to controls have also been observed in areas involved in processing socio-emotional stimuli, including temporal areas and the insula [9, 21], and in ADHD, cortical differences have been found in additional frontal areas, including, e.g. motor and premotor cortices as well as parieto-temporal areas [33, 34].

Many features contributing to developmental diagnoses are likely not unique to pathology, but rather represent quantitative differences along a continuum, elevations of characteristics also present in broader populations. Still, with very few exceptions [34], there is a lack of studies of the neuroanatomical foundations of the normal variance in psychological and behavioral adjustment in development. Shaw and colleagues [33, 34] found that children with ADHD attained peak cortical thickness later, with a subsequent slower cortical thinning, and a similar pattern of cortical development was linked to symptoms of hyperactivity and impulsivity also in typically developing children and adolescents. The present study is aimed at relating variance in psychobehavioral adjustment as measured by the conduct problems and hyperactivity/inattention scales of the well-validated and clinically broadly used Strength and Difficulties Questionnaire (SDQ) [17] to differences in cortical thickness as quantified from magnetic resonance imaging (MRI) scans in a large sample of healthy children and adolescents aged 8–19.

As reviewed above, a number of brain areas have been implicated in childhood psychopathology. These include also the hippocampus and amygdala, in CD and striatal and cerebellar areas in ADHD [43]. Cerebellar and subcortical areas are, however, beyond the scope of the present study, which focuses on cerebral cortical differences. The conduct problems and hyperactivity/inattention SDQ scales have never been investigated in relation to brain indices in a sample of healthy children, so the present study is exploratory and hypotheses can be tentative only. Therefore, relationships were investigated across the entire cortical mantle. In line with recent evidence supporting a dimensional view of childhood behavioral pathology [34], we expect that weaker, but similar relationships between behavioral and brain indices may be observed also in healthy children. The majority of findings point to lesser prefrontal gray matter in both CD and ADHD [43], with additional regions of thinner cortices specific to diseases. However, at least in ADHD, there also seems to be a delay of cortical development, rather than an entirely different course [33], suggesting that these differences may weaken with age. Hence, we tentatively hypothesize that (1) both conduct problems and hyperactivity/inattention symptoms will be negatively related to prefrontal cortical thickness, possibly with thickness differences specific to hyperactivity/inattention also in premotor and temporoparietal areas, and

differences specific to CD in temporal/insular areas. (2) If found, such cortical thickness relationships may interact with age and be stronger in younger than older children.

Materials and methods

Sample

The study was approved by the Regional Ethical Committee of South Norway and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants older than 12 years of age and from a parent of participants under 18 years of age. Oral informed consent was given by participants under 12 years of age. Volunteers were recruited through newspaper advertisements and schools. Standardized health screening interviews were conducted with participants aged 16–19 years and with a parent of all participants. All MR scans were examined by a neuroradiologist and required to be deemed free of significant anomalies. Further details regarding recruitment and enrolment are given elsewhere [26, 37]. For the included 106 participants (55 females), mean age was 13.9 years (total 8.3–19.7, SD = 3.4) and there was no significant age difference between females and males [$F = 14.1$ (3.5), $M = 13.7$ (3.4), $P = .512$]. IQ was estimated from the tests Vocabulary, Similarities, Matrix reasoning and Block design from the Wechsler Abbreviated Scale of Intelligence (WASI) [42]. Age, IQ and SDQ scores for the sample divided in three subgroups based on age for descriptive purposes are shown in Table 1. There were no significant differences between groups in terms of IQ or SDQ scores as determined by an analysis of variance ($P > .05$). There were significant ($P < .001$) intercorrelations among the SDQ scores, as expected (r for hyperactivity–conduct problems = 0.36, hyperactivity–total difficulties = 0.66, conduct problems–total difficulties = 0.59).

MRI acquisition

Imaging data were acquired using a 12 channel head coil on a 1.5 T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). The pulse sequences used for morphometry analysis were two repeated T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequences, with the following parameters: repetition time (TR)/echo time (TE)/time to inversion (TI)/flip angle (FA) = 2,400 ms/3.61 ms/1,000 ms/8°, matrix 192 × 192, field of view = 192. Each volume consisted of 160 sagittal slices with voxel size 1.25 × 1.25 × 1.20 mm. Acquisition time for each sequence was 7 min, 42 s. The two runs were averaged during post-processing in order to increase the

Table 1 Age, IQ and SDQ scores for the sample divided in three subgroups

	8–11 years 17 F/18 M			12–15 years 19 F/18 M			16–19 years 19 F/15 M		
	<i>M</i>	<i>SD</i>	Range	<i>M</i>	<i>SD</i>	Range	<i>M</i>	<i>SD</i>	Range
Age	10.0	1.1	8.3–11.8	13.9	1.2	12.0–15.9	18.0	1.0	16.2–19.7
IQ	106.8	11.0	82–127	108.1	10.7	91–141	112.3	10.6	91–132
Conduct problems	0.7	0.8	0–3	0.8	0.9	0–3	0.9	0.8	0–3
Hyperactivity/inattention	2.1	2.1	0–9	1.6	1.6	0–5	1.5	1.7	0–7
Total difficulties	4.1	3.4	0–15	4.8	3.9	0–13	4.1	3.3	0–12

signal-to-noise ratio. Primarily due to motion artifacts, only one usable MPRAGE was available for 25 of the participants (23.6%) [38]. The protocol also included a 176 slices sagittal 3D T2-weighted turbo spin-echo sequence (TR/TE = 3,390/388 ms), and a 25 slices coronal FLAIR sequence (TR/TE = 7,000 – 9,000/109 ms) used for clinical assessment.

MRI analyses

Cortical thickness was estimated using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>) by means of an automated surface reconstruction scheme described elsewhere [4, 5, 11, 12, 14, 31, 32]. In short, thickness measurements were obtained by reconstructing representations of the GM/WM boundary and the cortical surface and then calculating the distance between those surfaces at each point across the cortical mantle [4, 5, 11]. The technique has been validated via histological [28] and manual measurements [23]. The cortical thickness maps were mapped to a common surface, smoothed with a full width at half maximum of 15 mm [13], and fed to statistical analyses. The cortical surface is also parcellated [7, 15] as part of this processing, facilitating description of the anatomical localization of effects.

Strengths and Difficulties Questionnaire

The SDQ asks about 25 attributes, divided between five scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and pro-social behavior. The first four scales can be added to generate a total difficulties score. Recent studies indicate that SDQ is not only suitable for distinguishing clinical and healthy groups of children but also is a valid continuous measure of child mental health across the full range [18], making it suitable for the present purpose.

Statistical analyses

First, for descriptive purposes, a correlation analysis was run to test the relationships between age and SDQ scores,

and for the reconstructed brain surfaces, the relationship of age and cortical thickness was tested at each vertex with sex as a covariate. To test the hypothesis that behavioral problems would be negatively related to cortical thickness, the relationships between cortical thickness and behavioral symptoms—conduct problems and hyperactivity/inattention, respectively, were tested using general linear models at each vertex with age and sex as covariates. The data were tested against an empirical null distribution of maximum cluster size across 10,000 iterations using Z Monte Carlo simulations as implemented in FreeSurfer [19, 20] synthesized with a cluster-forming threshold of $P < .05$ (two-sided), yielding clusters corrected for multiple comparisons across the surface.

Analyses were repeated with the effects of IQ controlled for in addition to age and sex. To test the hypothesis that the relationship of cortical differences and behavioral symptoms would be stronger in younger than older children, general linear models also run including interaction terms of behavioral symptoms \times age (each standardized to the whole sample), controlling for age, sex, and symptom load per se. Also, these analyses were repeated with the effects of IQ controlled for in addition.

Results

None of the SDQ scales correlated significantly with age. The relationships between age and cortical thickness are shown in Online Figure 1. As expected, significant negative age correlations were found for cortical thickness throughout most of the cortical mantle. The general linear models testing for relationships between cortical thickness and hyperactive/inattention symptoms with age and sex as covariates showed no significant relationships in either hemisphere. There was no significant relationship between conduct problems and cortical thickness of the right hemisphere. For the left hemisphere, conduct problems were negatively related to thickness in two clusters, covering large parts of the lateral orbitofrontal cortex (889 mm², $P = .02730$) and supramarginal gyrus (913 mm², $P = .02340$), and these effects are

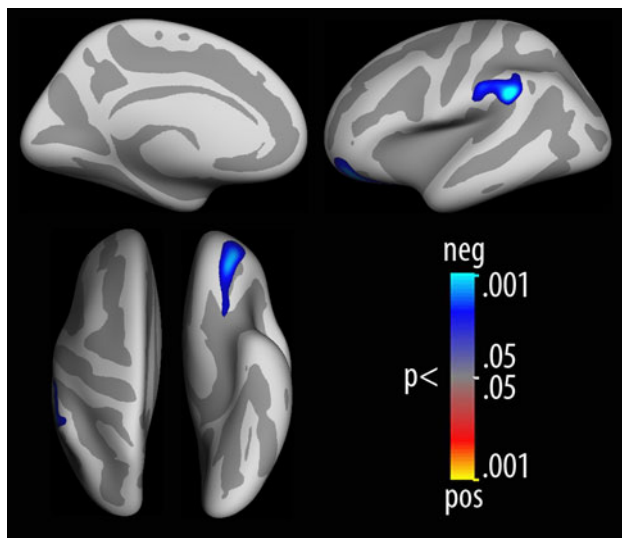


Fig. 1 Cortical thickness and conduct problems. Conduct problems was negatively related to cortical thickness in two clusters in the left hemisphere (cluster-wise $P < .05$, two-tailed, fully corrected for multiple comparisons across space). Sex and age were included as covariates. No relationships were seen in the opposite direction. The results are shown as color-coded overlays and projected onto an inflated template brain

shown in Fig. 1. These relationships were not influenced by differences in IQ. The results of a general linear model testing for the relationship between conduct problems and cortical thickness with IQ as an additional covariate are shown in Online Figure 2, and were largely similar, i.e. IQ did not influence the results.

The results of the interaction analyses with age and behavioral problems on cortical thickness showed no significant effects in either hemisphere for hyperactivity/inattention problems. For conduct problems, bilateral effects were observed, and these are shown in Fig. 2. All interactions were positive, meaning that thickness and conduct problems were more closely related in the younger than the older children. Effects were observed bilaterally in large prefrontal clusters (left hemisphere: $2,581 \text{ mm}^2$, $P = .00010$; right hemisphere: $3,429 \text{ mm}^2$, $P = .00010$). For both hemispheres, these clusters included parts of the superior frontal, medial orbitofrontal and rostral middle frontal gyri, and for the left hemisphere also most of the rostral anterior cingulum, whereas for the right hemisphere, this prefrontal cluster only bordered the rostral anterior cingulum. In the right hemisphere, an additional interaction effect was observed in and areas of the parahippocampal and lingual cortices ($1,050 \text{ mm}^2$, $P = .01080$). In the left hemisphere, two additional effects were observed, one covering parts of the middle and inferior temporal cortex (899 mm^2 , $P = .02550$), the other in the posterior part of the superior frontal gyrus likely part of the supplementary motor area (865 mm^2 , $P = .03230$). No relationships were

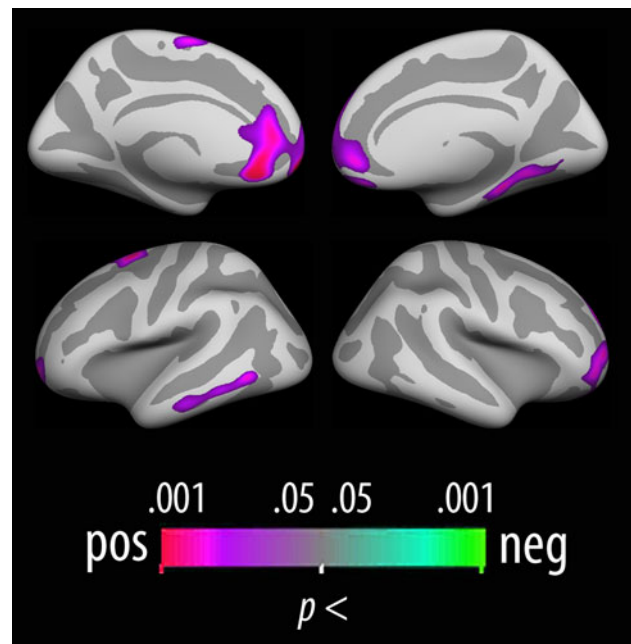


Fig. 2 Age–conduct problems interactions. Significant interactions between age and conduct problems were seen in three clusters in the left and two clusters in the right hemisphere (cluster-wise $P < .05$, two-tailed, fully corrected for multiple comparisons across space). All interactions were positive, meaning that thickness and conduct problems were more closely related in the younger than the older children. No relationships were seen in the opposite direction. The results are shown as color-coded overlays and projected onto an inflated template brain

seen in the opposite direction. The analyses were repeated with IQ as an additional covariate, with virtually identical results (see Online Figure 3).

Since significant interactions with age were observed for conduct problems, the relationships of conduct problems and cortical thickness in an ROI largely covered by these effects, namely the left rostral anterior cingulate cortex, were subjected to further analysis analyses with regard to age, for purpose of visualization of effects only. Correlations within each age group (8–11, 12–15, 16–19 years) between cortical thickness of left rostral anterior cingulate and conduct problems with the effects of age partialled out were $r = -.45$, $-.31$, and $.00$, respectively. That is, a weaker relationship was seen with age. Again, for purpose of visualization of the age interaction effects only, correlation coefficients for cortical thickness of left anterior cingulum and age for the sample split into two groups based on the amount of conduct problems reported (0–1 vs. 2–3) were calculated. Note that this group division is done without regard to any clinical subcategory, but purely to visualize the age trajectories within groups of children of the present sample with more and less symptoms, i.e., multiple conduct symptoms and not. The group with multiple conduct symptoms ($n = 18$) showed an absence

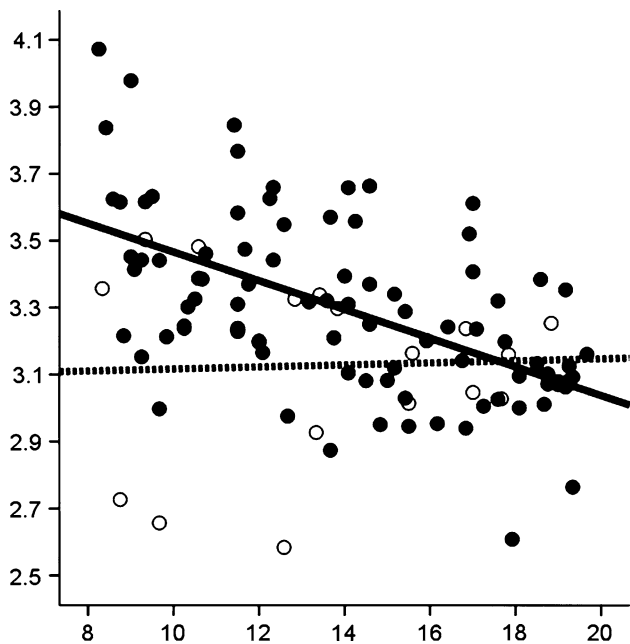


Fig. 3 Scatterplot showing the cortical thickness (mm, y-axis)–age (years, x-axis) relationships for the left rostral anterior cingulate cortex in children with more (2–3, dotted line, transparent circles) and less (0–1, solid line black dots) conduct symptoms

of age effect on cortical thickness ($r = .04$, $P = .881$), while the group with no or only one conduct symptom ($n = 88$) showed a strong negative age effect on cortical thickness ($r = -.56$, $P < .001$). For appreciation of the interaction effect, a scatterplot showing the cortical thickness–age relationships for the left anterior cingulate in the two conduct symptom groups is shown in Fig. 3. For this analysis, the automated parcellation of the left rostral anterior cingulate, which was nearly entirely covered by the effects, was used. In this parcellation the rostral boundary is the rostral extent of the cingulate sulcus (inferior to the superior frontal sulcus), and the caudal boundary is the genu of the corpus callosum. The medial boundary is the medial aspect of the cortex. The superolateral boundary is the superior frontal gyrus, and the inferolateral boundary is defined as the medial division of the orbitofrontal gyrus [30]. It is evident from this figure that there is a greater age effect on cortical thinning in children with fewer conduct problem symptoms.

Discussion

The present study indicates that conduct problem symptoms within the normal range, with only very light difficulties, is associated with regionally moderately thinner cortices. Relationships between conduct symptoms and cortical thickness controlling for age were observed in left

prefrontal and supramarginal areas. A follow-up analysis revealed that relationships were primarily found in the younger age groups. These interactions of age and conduct problems were reflected in regionally thinner frontal and temporal cortices bilaterally. Evidence of an association between total difficulties and hyperactivity symptoms and cortical characteristics in healthy children was not found in the present study, though the latter has recently been reported [34]. A reason for this discrepancy, besides the use of different rating scales (Conner’s Parent Rating Scale vs. SDQ), may likely be that the previous study employed rates of cortical thinning longitudinally, whereas such a measure is not yet available for the present sample (see further discussion below).

The present associations between symptoms of conduct problems and cortical thickness observed in healthy children fit with the majority of other studies showing evidence of lesser orbitofrontal, cingulate and temporal gray matter in groups with CD [21, 43], but have not previously been demonstrated in normally functioning children. What may be the neurobiological foundations of these relationships? First, the areas of regionally thinner cortices in healthy children with more conduct problems are found in areas implicated in a range of functions important in self-regulation, emotional processing and attention. Early acquired prefrontal developmental brain damage has in multiple cases been associated with the development of severe conduct problems [1, 2]. The orbitofrontal and anterior cingulate cortices are important in cognitive and emotional processing, serving important behavioral regulatory functions, e.g. in reward-guided decision making, response selection and inhibition [8–10]. The significance of the supramarginal effect in relation to conduct problems is less clear. This area is pivotal in language processing, and is also important for motor attention [29, 36]. The supplementary motor area is also central in the internal control of motor actions [24]. The parahippocampal gyrus is well known for its role in memory functioning, but temporal effects have also been previously observed in behavioral difficulties. For instance, Huebner et al. [21] identified reduced gray matter in the temporal lobes of boys with CD, including the amygdala and hippocampus, and the present temporal effect may be linked to these findings.

In order to appreciate the significance of the age interactions, one must take into regard the normal development of structural cortical characteristics. Cortical thickness is known to show an overall decrease with age in school years in MRI studies, including the present [16, 37]. This cortical thinning is seen as a form of cortical maturation, likely related to positive processes such as pruning and/or intracortical myelination. Some have focused on a late-onset protracted gray matter decrease of prefrontal relative to more posterior areas, indicating later maturation of prefrontal

areas governing higher-order cognitive processes [16]. However, prefrontal areas also showed thinning in development in the present sample. The interaction of age and conduct problems on cortical thickness in frontal as well as temporal areas indicated that the negative relationships between conduct problems and cortical thickness were stronger, and primarily found, in younger age. As visualized in Fig. 3, this age interaction may be caused by children with more conduct problems showing less developmental cortical thinning in this sample. In light of this, one may speculate that the present relationships of conduct problems and cortical thickness in young children may be due to a slightly lesser maximum gray matter growth to begin with in children showing light problems, with this pattern no longer being visible with further pruning or intracortical myelination in older age. Such an interpretation would be in line with findings of later attainment of peak cortical thickness in other childhood psychopathology: Shaw and colleagues [33] showed that the median age at which 50% of the cortical points reached peak thickness was 7.5 years in typically developing children, but 10.5 years in ADHD. However, it should be noted that while a different cortical developmental trajectory is established with these behavioral difficulties, a delay may not be the only feature distinguishing children with behavioral problems, and it is unknown.

The present results may indicate a neurobiological relationship between very light symptoms of conduct problems, within the normal range, and conduct disorder as studied in pathological samples, where lesser gray matter and smaller neuroanatomical volumes have repeatedly been found [3, 9, 21, 22]. There is one exception to these findings in the literature, where greater gray matter volumes were found in a subgroup of CD boys (aged 9–13 years) showing callous-unemotional traits thought to be antecedents of psychopathy [6]. De Brito and colleagues interpreted their findings as an indication of delayed maturation in the callous-unemotional conduct problem group. It is not clear, however, whether maturational delay in pruning could lead to later lesser prefrontal gray matter, as is a rather well-established finding in adult psychopathy [39]. A recent study including adolescents with various subtypes of CD, including callous-unemotional traits, did not replicate the finding of greater gray matter volumes in these children, but overall found reduced gray matter volume in prefrontal, insular as well as subcortical regions [9]. Regardless, it is not likely that all findings in a group selected based on traits seen as antecedents of psychopathy may be directly related to the present findings in children with conduct problems within the normal range. However, there has recently been an increased acknowledgement of the importance of maturational trajectories rather than the size of neuroanatomical structures at any given time, i.e. the neuroanatomical expression of traits is dynamic [35]. In their recent study of

hyperactivity symptoms in healthy children, Shaw and colleagues [34] also reported some evidence of differential cortical maturation trajectories in motor and middle frontal regions with symptoms of conduct problems in healthy children, although these differences were not marked and not the focus of their study.

The present study is cross-sectional, and inferences about brain maturation processes should be cautiously interpreted. Additional studies, preferably longitudinal and also including younger children are needed to further inform us on neuroanatomical developmental trajectories underlying the psychobehavioral adjustment of children and adolescents. The present study used a health screening interview to avoid the inclusion of children with a diagnosis of somatic or psychiatric disorders. However, a structured psychiatric interview was not employed to formally confirm that such disorders were not present, and this may be a limitation. The reported conduct problem symptoms were, however, within the normal range [25], indicating that the presence of clinical CD in this sample is unlikely. The present results suggest that also normal variance in conduct problems is related to regional differences in cortical thickness in childhood, including prefrontal and temporal areas. Hence, brain abnormalities that are related to child and adolescent psychopathology may be regarded as extremes on a continuum of variation, and there may be neurobiological continuity between normal symptoms of conduct problems and conduct disorder.

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Conflict of interest The authors declare that they have no conflicts of interest.

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