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Brain Age in Conduct Disorder:

A Mega-Analysis of the ENIGMA Antisocial Behavior Working Group

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Abstract

Conduct disorder (CD) is the leading global cause of mental health burden in children and adolescents and has recently been hypothesized to be a neurodevelopmental disorder. Although prior research has identified neuroanatomical differences associated with CD, it remains unclear whether these differences reflect atypical brain development. Here, we investigated the difference between an individual's brain age and chronological age as a proxy for variations in brain maturation. Using a pretrained model, we estimated brain age from structural neuroimaging data obtained from 1,119 youth with CD and 1,183 typically developing controls across 14 international cohorts participating in the ENIGMA-Antisocial Behavior Working Group. Youth with CD exhibited a statistically robust but small acceleration in brain age compared to typically developing youth (around 0.50 years), which was restricted to the adolescence-onset subtype of the disorder. Our large-scale, coordinated analysis provides the first evidence of accelerated neurodevelopment as a potential mechanism underlying CD.

Introduction

Conduct Disorder (CD) is characterized by a persistent pattern of behavior that violates societal norms and the rights and welfare of others¹. It is typically diagnosed in youth¹, defined here as a developmental stage extending through the mid-20s². Youth with CD represent a highly heterogeneous group, with substantial inter-individual variability in clinical presentation largely influenced by factors such as age of onset (i.e., childhood-onset [<10 years] vs. adolescent-onset [≥ 10 years]) and the presence of limited prosocial emotions (e.g., lack of remorse or guilt, callousness or lack of empathy)¹, often referred to as callous-unemotional traits³. Across the globe, CD associated with the highest burden of any mental disorder in children and adolescent aged 0–14 years⁴, and imposes significant economic and societal costs^{5,6}. Moreover, CD has been prospectively linked to many other mental illnesses, as well as poorer psychosocial adjustment and health outcomes in adulthood⁷. Given its widespread impact, research investigating putative developmental processes should be a priority.

Growing evidence suggests that CD may be a neurodevelopmental disorder⁷⁻⁹, especially in youth whose symptoms emerge during childhood¹⁰. For instance, it shares genetic influences¹¹ and neurobiological features^{12,13} with other neurodevelopmental disorders, particularly attention-deficit/hyperactivity disorder. Furthermore, prior meta-analyses have shown that youth with CD exhibit grey matter volume reductions in brain regions that undergo substantial development during childhood and adolescence (e.g., amygdala, anterior insula/ventrolateral prefrontal cortices)^{14,15}. Of note, the largest neuroimaging study to date on CD, a collaborative effort of the ENIGMA-Antisocial Behavior Working Group (ENIGMA-ASB), demonstrated that youth with CD exhibit robust and widespread reductions in cortical surface area and subcortical volumes (i.e.,

thalamus, amygdala, hippocampus, nucleus accumbens), but few differences in cortical thickness¹⁶. Despite considerable progress in characterizing structural brain alterations in youth with CD, the neurodevelopmental processes driving these differences remain poorly understood.

In the past decade, researchers have developed a new multivariate method to quantify whether an individual's structural brain metrics reflect accelerated or decelerated brain maturation¹⁷. This is typically achieved by predicting chronological age from neuroimaging brain metrics (e.g., surface area, cortical thickness, subcortical volume). The resulting difference between predicted and actual age -referred to as the brain predicted-age difference (brain-PAD) - is now widely used to capture deviations from normative brain maturation¹⁷. A brain-PAD significantly above zero would thus reflect accelerated brain age (brain age > chronological age), while a brain-PAD significantly below zero would indicate decelerated brain age (brain age < chronological age). This approach has opened promising avenues for understanding psychiatric disorders.

For instance, accelerated brain aging has been commonly observed in adults with psychiatric¹⁸⁻²⁴ and neurological disorders²⁵ compared to controls. In children, a preliminary study showed decelerated brain maturation in youth with attention-deficit/hyperactivity disorder²⁶, although a recent mega-analysis of multiple cohorts revealed no signs of such negative brain age gap in children with neurodevelopmental disorders (autism spectrum disorder and attention-deficit hyperactivity disorder)²⁷. Nevertheless, young adults with a history of conduct problems²⁸ have shown an average brain-PAD below zero, indicative of a potentially decelerated brain maturation in youth with externalizing problems²⁹. Another study found no significant group differences in brain-PAD between adult offenders with a history of violence and healthy controls, although brain-PAD and psychopathic traits were negatively correlated ($r=-.31$)³⁰. While these findings suggest

that CD and psychopathic traits may be associated with decelerated brain maturation, they are largely limited to adult males and thus may not be generalizable to youth. Indeed, the use of adult samples relying on retrospective accounts of conduct problems, in the absence of formal CD diagnoses, limits the relevance of prior findings for understanding CD in youth. Furthermore, the extent to which these findings generalize across the sexes remains unknown. As both the clinical features of CD and brain structures undergo marked developmental changes around puberty, examining brain age could provide key insights into its neurodevelopmental mechanisms.

In this preregistered and collaborative effort from the ENIGMA-ASB Working Group (<https://doi.org/10.17605/OSF.IO/U4D37>), we tested whether youth with CD show differences in brain-PAD compared to typically developing youth. First, based on the available evidence on the association between externalizing problems and brain aging^{26,28-30}, as well as recent longitudinal studies of brain development³¹⁻³³, we hypothesized that youth with CD would display decelerated brain age relative to their chronological age (brain-PAD significantly below zero). Second, we hypothesized that brain-PAD would negatively correlate with dimensionally assessed conduct problems in youth with CD. Third, we expected that decelerated brain age would be more pronounced in the childhood-onset CD subtype than in typically developing youth and adolescent-onset CD, consistent with neurodevelopmental impairments specific to the childhood-onset subgroup¹⁰. Moreover, because CD subgroups with high callous-unemotional traits often exhibit earlier onset and a more severe clinical presentation than those with low traits⁷, we hypothesized that the high-trait subgroup would show the greatest deceleration in brain age, relative to the low-trait subgroup and typically developing youth. We also examined whether sex moderated the association between CD and brain age. Although previous work has shown that the association between brain age and history of CP was limited to males²⁸, we did not formulate specific

hypotheses on this due to limited evidence in CD. Finally, we expected that decelerated brain age would generalize to non-overlapping participants with elevated conduct problems but without a formal diagnosis of CD derived from 10 ENIGMA-ASB cohorts (926 subthreshold CD youth vs. 922 controls).

- Insert Table 1 About Here -

Table 1. Demographic and clinical characteristics of the included cohorts in the main analysis on youth with Conduct Disorder

Cohorts	N	Age range, yrs	Typically developing youth				Youth with Conduct Disorder				Conduct disorder subgroups			
			n	F:M	Age, yrs	IQ	n	F:M	Age, yrs	IQ	CO-CD	AO-CD	CU-	CU+
ABCD (3.0, baseline)*†	572	9–10	286	81:205	9.5 (0.50)	94.9 (15.3)	286	85:201	9.5 (0.50)	94.6 (16.4)	256	30	-	-
BESD	86	14–19	36	0:36	16.7 (1.32)	97.3 (9.41)	50	0:50	16.4 (1.34)	95.9 (6.40)	-	-	38	12
Boys Town	349	10–19	169	62:107	13.7 (2.44)	108.8 (12.56)	180	62:118	15.3 (1.71)	99.3 (11.62)	-	-	64	112
Cambridge Female	46	14–19	23	23:0	17.0 (0.88)	105.7 (9.34)	23	23:0	16.7 (1.66)	99.5 (8.11)	5	17	11	8
Cambridge Male	88	16–21	25	0:25	18.0 (1.08)	101.6 (9.10)	63	0:63	17.2 (1.11)	98.8 (8.57)	26	37	24	26
CD-Zhou	27	16–18	13	0:13	16.9 (0.28)	-	14	0:14	17.0 (0.56)	-	-	-	-	-
CDKid	31	12–19	13	0:13	15.7 (2.02)	109.8 (11.06)	18	0:18	15.4 (1.54)	98.7 (7.14)	12	6	-	-
CSU-Yao	145	12–17	71	0:71	15.5 (0.56)	108.9 (9.03)	74	0:74	14.5 (1.14)	100.8 (12.96)	5	64	-	-
FemNAT-CD*	612	9–18	365	217:148	14.3 (2.53)	103.6 (11.56)	247	118:129	14.6 (2.16)	95.1 (12.48)	124	104	81	153
IMAGEN (baseline)*†	126	13–15	63	24:39	14.0 (0.46)	-	63	24:39	14.0 (0.46)	-	-	-	-	-
K23	34	12–18	24	14:10	14.8 (1.82)	-	10	4:6	15.9 (0.99)	-	-	-	5	1
MATRICS/Aggressotype*†	93	7–18	49	7:42	12.8 (2.63)	100.6 (10.91)	44	6:38	13.1 (2.82)	98.9 (10.93)	-	-	20	16
Southampton Family Study	71	13–18	35	6:29	16.0 (1.36)	104.2 (10.03)	36	4:32	16.1 (1.41)	93.6 (11.42)	20	16	18	18
Yale†	22	9–16	11	2:9	11.7 (1.62)	103.3 (14.40)	11	2:9	12.2 (2.27)	102.1 (12.98)	-	-	2	9
Total (14 samples)	2302	7–21	1183	436:747	13.3 (3.03)	102.2 (13.47)	1119	328:791	13.7 (3.04)	96.7 (13.13)	448	274	263	355

Note. The reported values reflect n or mean (SD), unless otherwise indicated. N refers to the total number of participants from a specific cohort that were included in the current study. Information on sex and age was available for all participants, whereas IQ, age-of-onset status, and CU traits data were not always available. F=Females. M=Males. IQ=intelligence quotient. CO-CD = Childhood-Onset Conduct Disorder; AO-CD = Adolescent-Onset Conduct Disorder; CU=callous-unemotional (- = Low; + = High).

* Multi-site or multi-scanner sample.

† Control group matched on age and sex (and IQ, if available) using propensity score matching;

Results

Sample Characteristics

In the current study, we included 1,119 youth with CD (328 females, 791 males; mean age of 13.7, SD = 3.04) and 1183 typically developing youth (436 females, 747 males; mean age of 13.3, SD=3.03) from the 14 participating cohorts of the ENIGMA-ASB Working Group. See Table 1 for demographic and clinical characteristics of the sample.

Brain Age in Conduct Disorder

The BrainAGE Global model showed adequate generalization in our sample, as demonstrated by a strong correlation ($r = 0.81$) between predicted age from neuroanatomical features and chronological age, and a relatively low mean absolute error (2.71 years). The model demonstrated similar performance for CD and typically developing youth, as well as for males and females (see Supplementary Fig. 1). Model performance was slightly lower for adolescent-onset CD subtype ($r = .61$, MAE = 3.60), compared to childhood-onset CD subtype ($r = .85$, MAE = 2.25) and typically developing ($r = .79$, MAE = 2.56). Similarly, CD subtype with high callous-unemotional traits showed slightly lower performance metrics ($r = .54$, MAE = 3.39) compared to those with low callous-unemotional traits ($r = .63$, MAE = 3.19) and typically developing groups ($r = .69$, MAE = 2.88).

Contrary to our predictions, youth with CD showed a significantly greater positive brain-PAD compared to typically developing youth ($p = 0.0002$, Cohen's $d = 0.14$, 95% CI: 0.05–0.22) after adjusting for sex, chronological age, and chronological age², with cohorts included as a random intercept to account for between-site variability. (Table 2, Fig. 1A). The mean brain-PAD was significantly above zero (+0.45 years), indicating greater brain age compared to chronological age. A jackknife resampling procedure, sequentially excluding each cohort, confirmed the stability

of the observed effect across cohorts (Mean estimate = 0.456, SE = 0.14, 95% CI: 0.18 - 0.73). All iterations were statistically significant (p -values ranging from 0.00003 to 0.0018), suggesting that the observed accelerated brain age was not driven by any specific cohort (see Supplementary Fig 2). The group difference in brain age was statistically robust after accounting for group differences in intelligence quotient (1016 CD vs. 1078 typically developing participants, $p = 0.00048$, $d = 0.14$), attention-deficit/hyperactivity disorder comorbidity (1102 CD vs. 1181 typically developing, $p = 0.0086$, $d = 0.09$), and medication status (1002 CD vs. 1051 typically developing, $p = 0.0014$, $d = 0.13$). No interactions with chronological age were found - there was no two-way (diagnosis-by-chronological age, $p = 0.992$) or three-way (diagnosis-by- chronological age-by-sex, $p = 0.745$) interaction with age. There was also no diagnosis-by-sex interaction ($p = 0.868$). Dimensionally assessed conduct problems were not associated with brain-PAD within the CD group ($n = 617$, $p = 0.348$, $r = 0.03$).

- Insert Table 2 About Here –
- Insert Fig. 1 About Here –

Table 2. Chronological Age, Brain Age, and Brain Predicted Age Differences per cohorts.

Cohorts	Typically Developing Youth				Youth with Conduct Disorder			
	n	Chronological age	Brain Age	Brain-PAD	n	Chronological age	Brain Age	Brain-PAD
ABCD (3.0, baseline)*†	286	9.5 (0.50)	8.6 (1.83)	-0.95 (1.78)	286	9.5 (0.50)	8.79 (2.16)	-0.66 (2.09)
BESD	36	16.7 (1.32)	17.8 (3.13)	1.12 (2.53)	50	16.4 (1.34)	19.2 (3.58)	2.75 (3.27)
Boys Town	169	13.7 (2.44)	15.2 (3.98)	1.45 (2.94)	180	15.3 (1.71)	17.7 (3.95)	2.43 (3.42)
Cambridge Female	23	17.0 (0.88)	19.0 (2.80)	1.94 (2.85)	23	16.7 (1.66)	18.5 (2.88)	1.72 (3.00)
Cambridge Male	25	18.0 (1.08)	19.3 (3.62)	1.28 (3.39)	63	17.2 (1.11)	18.7 (3.59)	1.45 (3.28)
CD-Zhou	13	16.9 (0.28)	22.6 (2.50)	5.69 (2.55)	14	17.0 (0.56)	23.6 (2.50)	6.61 (2.19)
CDKid	13	15.7 (2.02)	19.3 (3.87)	3.64 (2.78)	18	15.4 (1.54)	18.1 (3.24)	2.70 (3.33)
CSU-Yao	71	15.5 (0.56)	18.9 (2.15)	3.42 (2.22)	74	14.5 (1.14)	18.6 (2.81)	4.09 (2.88)
FemNAT-CD*	365	14.3 (2.53)	15.9 (4.36)	1.55 (3.25)	247	14.6 (2.16)	16.4 (4.03)	1.73 (3.34)
IMAGEN (baseline)*†	63	14.0 (0.46)	13.9 (1.33)	-0.07 (1.26)	63	14.0 (0.46)	14.1 (1.54)	0.10 (1.44)
K23	24	14.8 (1.82)	14.9 (5.68)	0.10 (4.45)	10	15.9 (0.99)	17.8 (3.87)	1.90 (3.43)
MATRICES/Aggressotype* †	49	12.8 (2.63)	13.5 (4.60)	0.77 (3.10)	44	13.1 (2.82)	15.4 (5.13)	2.37 (3.69)
Southampton Family Study	35	16.0 (1.36)	21.3 (3.77)	5.30 (3.44)	36	16.1 (1.41)	21.7 (3.50)	5.59 (2.71)
Yale†	11	11.7 (1.62)	12.9 (4.24)	1.14 (2.97)	11	12.2 (2.27)	13.0 (4.70)	0.81 (2.80)
Total (14 samples)	1183	13.3 (3.03)	14.4 (5.12)	1.06 (3.14)	1119	13.7 (3.04)	15.2 (5.30)	1.54 (3.37)

Note. Brain Age and Brain-PAD were computed using BrainAGE Global model of CentileBrain. Brain Age refers to Neuroimaging-Predicted Age. Brain-PAD = Brain-Predicted Age Difference (Δ brain age - chronological age)

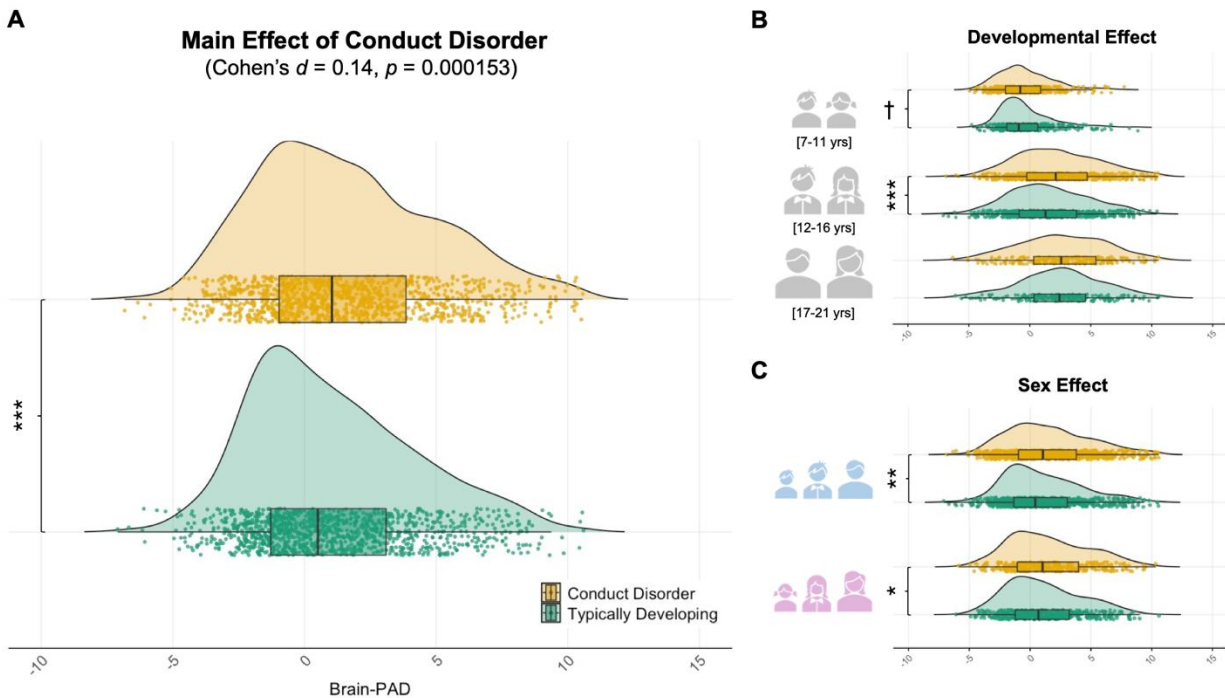


Fig. 1. Case-Control comparison of Brain-PAD between youth with CD and Typically Developing youth. **A.** A linear mixed effect model showed that youth with CD exhibited an accelerated brain age compared with typically developing youth ($b = 0.45$, $p = 0.000153$), representing a Cohen's d effect size of 0.14 after adjusting for chronological age, chronological age², sex, and cohort. **B.** Sensitivity analyses examined whether this effect was consistent across developmental periods approximating pubertal stages, which are childhood (7-11 years old, $n = 742$), adolescence (12-16 years old, $n = 1129$), and late adolescence/young adulthood (17-21, $n = 431$). Results showed strongest accelerated brain age in early to mid-adolescence ($d = 0.17$, $p = 0.001$), and weakest in young adulthood ($d = 0.04$, $p = 0.635$), with intermediate effect observed in childhood ($d = 0.12$, $p = 0.065$). **C.** Sensitivity analyses were also performed to assess this effect was consistent across sexes, and revealed that the accelerated brain age was observed across males ($n = 1,538$, $d = 0.13$, $p = 0.0019$), and females ($n = 764$, $d = 0.14$, $p = 0.04$). († $p = 0.065$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

Subsequent analyses explored whether the greater positive brain-PAD in CD compared to typically developing youth was consistent across developmental stages and/or across sexes. As shown in Fig. 1B, the CD group still showed greater positive brain-PAD when restricting the analyses to adolescents aged 12-16 years (568 CD *vs.* 561 typically developing; $p = 0.001$, $d = 0.17$). This effect was, however, not statistically significant among children aged 7 to 11 years (333 CD *vs.* 409 typically developing; $p = 0.065$, $d = 0.12$) or late adolescents/young adults aged 17 to 21 years old (218 CD *vs.* 213 typically developing; $p = 0.635$, $d = 0.04$), though the effects in these developmental stages were in the same direction and in close to significance levels. Moreover, accelerated brain age was also found when restricting the analyses to males ($n = 1,538$, $p = 0.0019$, $d = 0.13$), or females ($n = 764$, $p = 0.04$, $d = 0.14$), with very similar effect sizes in each sex (Fig. 1C).

Impact of Callous-Unemotional Traits and Age-of-Onset of CD

To better understand accelerated brain age, considering the substantial heterogeneity among youth with CD, we conducted sub-analyses to test the generalizability of this effect across subgroups. Table 1 outlines which cohorts contributed to these analyses, with further details provided in Supplementary Methods.

First, we examined the differences in brain-PAD across subgroups of CD by subdividing them based on whether they had elevated callous-unemotional traits, based on the normative cut-off for the ICU. Data on CU traits was available for 618 youth with CD (9 out of 14 cohorts). We observed greater brain-PAD in those with high levels of callous-unemotional traits compared to the other groups ($p = 0.008$, $d = 0.15$; Fig. 2). Pairwise comparisons revealed that this effect was mainly driven by differences between the high callous-unemotional traits subgroup and typically developing youth ($q = 0.024$, $d = .16$), but not those with low levels of callous-unemotional traits

($q = 0.474$, $d = 0.05$). Those with low levels of callous-unemotional traits did not significantly differ from typically developing youth ($q = 0.107$, $d = 0.12$), although the effect was in the direction of accelerated brain age. Using a dimensional approach, there was no association between callous-unemotional traits and brain-PAD, either focusing on youth with CD ($n = 618$, $r = 0.03$, $p = 0.416$) or across the full sample ($n = 1,342$, $r = 0.04$, $p = 0.088$).

Second, we investigated potential differences in brain-PAD across subgroups of youth with CD based on their age-of-onset (before [$n = 448$] or after 10 years of age [$n = 274$], with data available from 7 out of 14 cohorts). We observed a greater brain-PAD in adolescent-onset CD compared to the other groups ($p = 0.0076$, $d = 0.15$; Fig. 2). Pairwise comparisons revealed that this effect was mainly driven by differences between the adolescent-onset CD and typically developing groups ($q = 0.024$, $d = 0.15$), but not between the adolescent-onset and childhood-onset CD subgroups ($q = 0.139$, $d = 0.11$). The childhood-onset CD subgroup did not significantly differ from the typically developing group in brain-PAD ($q = 0.529$, $d = 0.03$).

- Insert Fig. 2 About Here -

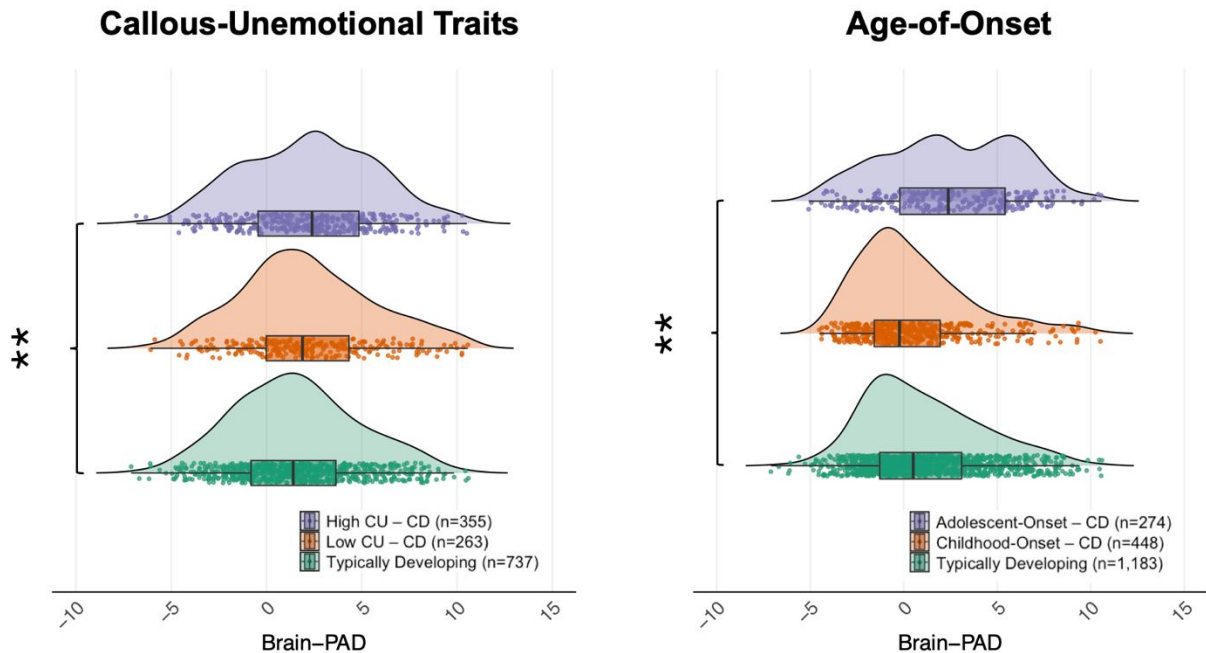


Fig. 2. Sub-analyses investigating the impact of Callous-Unemotional (CU) Traits and CD Age-Of-Onset on Brain-Predicted Age Difference (Brain-PAD) differences between the CD and typically developing groups. Brain-PAD refers to the difference between predicted age from neuroanatomical measures and chronological age. Ridge plot on the left panel represents the distributions of Brain-PAD among CD youth with clinical/high (n=355) and low (n=263) levels of CU traits, and typically developing youth (n=737). Ridge plot on the right panel denotes the distributions of Brain-PAD across CD youth with a childhood-onset (n=448) and adolescent-onset (n=274), and the typically developing group (n=1,183). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ without FDR adjustments).

Brain Age in youth with elevated Conduct Problems

In line with our previous study¹⁶, we further aimed to examine whether the brain-PAD difference observed in youth with CD would extend to those with elevated conduct problems, which represents a mix of sub-threshold and undiagnosed cases. A total of 926 youth with elevated conduct problems but without a formal diagnosis of CD (405 females, 521 males; mean chronological age of 11.7 years, SD=2.38) and 922 controls (435 females, 487 males; mean chronological age of 11.6 years, SD=2.34) from 10 cohorts of ENIGMA-ASB were pooled. None of the participants included in this analysis overlapped with those from the main analysis. Of note, this sample was younger ($M = 11.7$) than the sample from the main CD analysis ($M = 13.4$).

Both youth with elevated conduct problems (-0.50 years, $SD = 1.67$) and controls (-0.59 years, $SD = 1.58$) displayed a mean brain-PAD below zero, suggesting decelerated brain age (Supplementary Table 2, Supplementary Fig. 2). However, no significant difference was found between the groups ($b = 0.076$, $SE = .073$, $p = 0.299$, $d = .05$).

Discussion

To our knowledge, this study is the first to investigate brain age in youth with CD in comparison with TD youth. Building on prior work conducted on relatively small samples, we leveraged data from 14 international cohorts, comprising an unprecedentedly large sample of 1,119 youth with CD and 1,183 typically developing youth. We first hypothesized that youth with CD would exhibit decelerated brain age compared to their typically developing counterparts. Contrary to our expectations, analyses revealed that youth with CD showed accelerated brain age relative to typically developing youth, which was not driven by any specific cohort. Furthermore, this effect

was similarly observed across sexes but appeared limited early- to mid-adolescence (ages 12-16). Again, in contrast to our hypothesis, both CD subtype with elevated callous-unemotional traits and adolescent-onset CD subtype showed accelerated brain age compared to typically developing youth, although they did not significantly differ from CD subtype with low callous-unemotional traits and childhood-onset CD subtype, respectively. Neither CD subtype with low callous-unemotional traits nor childhood-onset CD subtype significantly differed from typically developing youth. Finally, we found that this accelerated brain age did not generalize to an independent sample of youth with subthreshold CD symptoms, contrary to our expectations. Taken together, our study provides evidence that accelerated brain age may be a potential neurodevelopmental mechanism underpinning CD.

CD Diagnosis relates to Brain Age

We show for the first time that youth with CD are characterized by accelerated brain age (+0.45 years), with an effect size approximately twice as large as those reported in neurodevelopmental disorders which were unrelated to brain age gap²⁷. This accelerated brain age co-occurs with widespread reductions in cortical surface area and subcortical volume previously reported in the ENIGMA-ASB youth sample¹⁶, which provides further support for a neurodevelopmental conceptualization of CD^{8,9}. In contrast to our findings, two previous studies reported a negative association between brain age and externalizing symptoms. This apparent discrepancy is likely attributable to differences in sample size, developmental timing (youth vs. adulthood), and study settings (clinical vs. community). Although delayed brain maturation has been proposed as a characteristic of youth with externalizing problems in developmental models²⁹, some studies have failed to support this hypothesis in youth with CD³⁴, while others have found that the severity of

conduct problems was instead associated with accelerated cortical thinning, particularly during late adolescence³⁵.

Accelerated brain age in youth has been associated with many environmental factors, such as adverse childhood experiences and neighborhood disadvantage^{36,37}. As many youth with CD experience socioeconomic deprivation, community violence, maltreatment⁷ and lifestyle factors, it is conceivable that early environmental factors may alter the typical trajectory of brain maturation towards the end of childhood. Furthermore, we found that this accelerated brain age was most prominent when restricting the analysis to adolescents (ages 12–16) and, to a lesser extent, children (ages 6–11). These results highlight early- to mid- adolescence as a potential period during which brain aging appears most advanced in CD. Interestingly, this effect appears to be specific to those with a diagnosis of CD, as those with subthreshold CD failed to differ from controls. However, because the cohorts of youth with conduct problems without a formal CD diagnosis were younger ($M = 11.7$) than those in the main CD analysis ($M = 13.4$), this age difference may partly explain why the effect was not observed in this group. Nevertheless, these youth generally exhibit a less severe clinical profile, and deficits in cortical surface area and subcortical volume associated with CD did not generalize to this group in our previous study¹⁶.

Callous-Unemotional Traits in CD Youth relate to Brain Age

Among youth with CD, it is estimated that up to 50% display high levels of callous-unemotional traits³. Hence, the DSM-5 included these traits (termed limited prosocial emotions) as a specifier for CD¹. In the current study, we observed accelerated brain-PAD in youth with high callous-unemotional traits compared to TD youth, although they did not significantly differ from those with low CU traits. Prior work has demonstrated strong overlapping genetic influences between callous-unemotional traits and CD^{38,39} as well as more severe CD symptoms in youth with CD and

high callous-unemotional traits (versus low callous-unemotional traits)^{3,7}. Therefore, the stronger brain-PAD difference could reflect greater genetic loading. Yet, in youth with CD, brain-PAD did not correlated with severity of callous-unemotional traits and did not differ between CD subgroup with high and low callous-unemotional traits. One potential explanation is that callous-unemotional traits may interact with environmental factors in shaping maturational brain processes in youth with CD. While genetic factors explain most of the variance in the initial risk for early callous-unemotional traits, both genetic (distinct from initial risk) and non-shared environmental influences contribute significantly to the developmental course of callous-unemotional traits^{40,41}. That said, CD youth with high and low callous-unemotional traits showed widely overlapping distributions of brain-PAD. This may partially be explained by null differences in cortical thickness between the two groups¹⁶, which appears to be more influential in the prediction of brain age, compared to other morphometric measures (see Supplementary Fig 3, see also²²). Given the heterogeneous developmental trajectories of callous-unemotional traits^{42,43}, the high/low cut-offs used in the current study may have obscured meaningful differences. Taken together, longitudinal studies tracking the co-development of CU traits and brain-PAD across multiple developmental stages could clarify the accelerated brain age observed in this study.

Age-of-Onset of CD Youth relates to Brain Age

The DSM-5-TR (and earlier versions of the DSM) also accounts for the clinical heterogeneity of CD based on the age-of-onset of CD symptoms, i.e., whether they emerge before or after the age of 10¹. This specifier was introduced following the seminal developmental taxonomic theory of antisocial behaviors¹⁰. In this theory, Moffitt¹⁰ posited two subgroups of individuals exhibiting antisocial behaviors, namely *life-course-persistent* and *adolescent-limited*. While the first subgroup was hypothesized to show a continuous and stable pattern of severe antisocial behaviors

beginning before puberty (< 10 years old), the latter was hypothesized to show antisocial behaviors for a temporary period during adolescence. Despite showing superficially similar antisocial behaviors, Moffitt⁴⁴ also argued that the underlying mechanism for engaging in antisocial behaviors may vary between the subgroups. Specifically, deficits in verbal and executive functions are believed to underlie early-onset antisocial behaviors, as demonstrated by poorer performance on neuropsychological tasks¹⁰. In contrast, the adolescent-onset subgroup is thought to engage in antisocial behaviors as an adaptive response to being trapped in a maturity gap between their biological and social age, a feature not found in the childhood-onset subgroup⁴⁴. As such, we hypothesized that the childhood-onset CD subtype would exhibit decelerated brain age, reflecting its presumed neurodevelopmental origins, compared to the adolescent-onset CD subtype and typically developing youth. Instead, we found accelerated brain-PAD in youth with the adolescent-onset CD subtype compared to typically developing youth, although they did not significantly differ from those with childhood-onset CD. While no significant differences were observed between the two CD subgroups, the more pronounced difference in the adolescent-onset subgroup (relative to typically developing youth) is partially in line with Moffitt's hypothesis. Indeed, she argued that youth following the adolescent-onset trajectory may engage in antisocial behaviors as an adaptive response to being caught in a maturity gap between their biological and social age, often mirroring the behavior of older peers.

Early adolescence is a critical developmental period marked by significant variability in pubertal growth⁴⁵. Pubertal onset, rather than chronological age, may offer clearer insights into the different etiological pathways of CD. Indeed, the association between early pubertal timing and risk for disruptive behaviors⁴⁶, and delinquency^{47,48} is well-documented. Furthermore, externalizing problems are among the strongest mental health correlates of the *puberty age gap*:

the predicted pubertal age compared to chronological age⁴⁹. Intriguingly, pubertal timing appears to moderate the heritability of CD. Specifically, the heritability of CD has been shown to be strongest (67%) in youth with average pubertal timing (around 12 years old), compared to only 8% for those with precocious puberty, suggesting a significant contribution of environmental influences on CD in the latter group⁵⁰. These findings further support the idea that environmental factors -such as peer influences, parenting, and neighborhood factors -may ensnare those with early pubertal development into a persistent pattern of severe antisocial behaviors^{48,51}. As environmental factors (e.g., abuse, maltreatment, exposure to violence, and neighborhood disadvantage) have also been linked to accelerated brain aging^{36,37}, it could be argued that youth who engage in antisocial behaviors in adolescence may be particularly sensitive to socio-environmental influences during this critical developmental window, compared to those who start to engage in antisocial behaviors in childhood, who are presumably at greater genetic risk but do not show/experience such a maturity gap. While the current conceptualization defines CD subtypes based on chronological age (± 10 years old), biological age (i.e., brain age, pubertal age) may offer a more sensitive approach for identifying inter-individual variability in the etiological pathways to CD.

Strengths & Limitations

In this study, we report robust differences indicating accelerated brain age in youth with CD compared to typically developing peers. This effect was consistent across multiple international cohorts drawn from heterogeneous populations and across datasets with different acquisition protocols. Despite our rigorous analytic approach, several limitations must be acknowledged. First, the cross-sectional design prevented us from establishing whether accelerated brain age increases the risk for CD or, instead, the emergence of CD (and its related environmental features)

accelerates maturational brain processes. Of note, despite a stronger effect found during adolescence, the developmental trajectory of brain-PAD among youth with CD remains largely unknown. As CD is characterized by different developmental pathways (e.g., childhood-onset, adolescent-onset), using prospective longitudinal designs may help clarify how brain-PAD maps onto those pathways over time (and based on our findings, whether those with a more advanced brain age experience the ‘maturity gap’ more keenly). Second, the BrainAGE model used in the current study showed somewhat variable performance across CD subtypes (Age-of-Onset, CU traits), suggesting that the findings should be interpreted with caution. It remains unclear whether these differences reflect true biological variation or are partly due to lower model performance and smaller sample sizes, as performance metrics are inherently linked to brain age (e.g., correlation between predicted and chronological age, mean absolute brain age difference). Third, the lack of consistency in assessment measures across cohorts prevented us from examining whether, and to what extent, accelerated brain age in youth with CD is associated with variations in pubertal development and/or socio-environmental risk factors (e.g., childhood adversity), and/or substance misuse, and/or clusters of CD symptoms. For instance, aggression and rule-breaking are known to be characterized by distinct developmental trajectories⁵² and neurobiological correlates⁵³, leaving the possibility that these clusters of symptoms may be differentially associated with brain age. Because the brain-PAD difference between the CD and typically developing groups was most prominently found in adolescence, a period typically characterized by a sharp increase in rule-breaking behaviors (peak ≈ 15 years old)⁵², future studies should investigate the association between brain age and different CD symptom clusters. Fourth, while previous work has found that antisocial populations, including youth with CD, are characterized by greater variability in brain volume compared to controls⁵⁴, our analyses demonstrated that a homoscedastic model provided

a better fit to the data than a model with unequal residual variance ($\Delta\text{BIC} = 3.16$). This suggested the residual variance was comparable between groups and that our main results were not driven by variance differences. Fifth, we acknowledge that our approach, based on traditional specifiers (e.g., differentiating between childhood- and adolescent-onset forms of CD, and high versus low CU traits), does not fully account for the substantial clinical and neurobiological heterogeneity observed in youth with CD. Future work -particularly using approaches such as normative modeling may allow for a finer-grained characterization of this heterogeneity, even after accounting for these so-called “*specifiers*”.

Conclusion

This large collaborative effort, involving 14 international cohorts, identified a robust accelerated brain age of approximately five and a half months greater among youth with CD compared to typically developing youth. This effect appeared to be specific to early- to mid-adolescence and was stronger in those with high levels of callous-unemotional traits and those with adolescent-onset form of the disorder. Although these findings provide further support for conceptualizing CD as a neurodevelopmental disorder, prospective longitudinal studies are needed to better understand how this accelerated brain age unfolds over time and how it relates to variations in pubertal development and socio-environmental factors (e.g., childhood adversity and/or risky behaviors such as substance misuse).

Methods

Study samples

The current study pooled individual participant data from 14 (CD main analysis) and 10 (secondary analysis on elevated conduct problems) international cohorts within ENIGMA–ASB, comprising clinical, forensic, and community-based or population-based samples (for more details see¹⁶ and Supplementary Methods). Briefly, cohort eligibility criteria were a) a mean sample chronological age of 18 years or less, b) data available on sex, chronological age, and a diagnostic assessment of CD, and c) at least ten participants with CD or elevated conduct problems and 10 typically developing participants. More detailed information about inclusion criteria, subgrouping, and protocols can be found in Supplementary Methods and elsewhere¹⁶. Each contributing cohort had obtained ethical approval for their original study and for sharing de-identified data. This study was pre-registered (<https://osf.io/u4d37>) and the overall project received ethical approval from the University of Bath's Psychology Research Ethics Committee (19-297/22-148). In the current study, a final sample of 1,119 youth with CD and 1,183 typically developing youth were included (see Supplementary Methods for more detailed information). Additionally, a total of 926 youth with elevated conduct problems and 922 typically developing youth¹⁶ were included in the secondary analysis testing the generalizability of the effect to subthreshold CD youth. This sample did not overlap with the CD sample from the main analysis. Demographic and clinical characteristics of the cohorts are presented in Supplementary Table 1.

Image acquisition and pre-processing

Individual-level 3D T1-weighted volumetric brain magnetic resonance imaging data were pre-processed and quality controlled at the individual sites or project lead analysis sites (University of Birmingham and University of Bath) following standard ENIGMA imaging protocols¹⁶.

Neuroimaging data were pre-processed using FreeSurfer (version 5.3 or 6.0)⁵⁵ and regions were parcellated based on the Desikan-Killiany and Aseg atlases.

We extracted global measures (i.e., total intracranial volume, average cortical thickness, and total surface area), as well as regional outcomes (i.e., cortical thickness and surface area for 68 cortical regions, and volume for 14 subcortical regions). The data were subsequently visually inspected, statistically evaluated for outliers (greater than $2.69 \times \text{SD}$), and pooled at the lead sites. For the current study, poorly segmented regions were excluded and imputed using the missForest R Package⁵⁶, as used recently in the ENIGMA Consortium⁵⁷. Participants with greater than 20% of missing neuroanatomical data were excluded [73 participants].

Brain age prediction

The BrainAGE Global model of CentileBrain was used to predict brain age in the current mega-analysis (see <https://centilebrain.org/>)^{58,59}. Twenty-one machine learning algorithms were initially trained on 2,105 typically developing children and adolescents (5-22 years old) from 5 cohorts and tested on two independent holdout datasets (n=4078, and n=594). The best performing algorithm using the Desikan–Killiany parcellation scheme was the Support Vector Regression with a Radial Basis Function⁵⁸. The model was then re-trained 35,683 healthy individuals (aged 5–90 years) and tested on an independent sample of 2102 healthy individuals, to examine the impact of harmonization strategies, chronological age range, and sample size on discovery and independent samples⁵⁹. The best-performing model was retained, which included no cohort harmonization and two chronological age-bins (i.e., 5-40 and 40-90 years)⁵⁹. In line with the BrainAGE Global framework, participant-level morphometric features were entered into the model separately for males and females. Brain-PAD was computed by subtracting chronological age from predicted

neuroanatomical age. As in recent work^{18-20,22}, the model's generalization performance was assessed through Pearson's correlation and mean absolute error between predicted brain age and chronological age. A positive brain-PAD value indicates accelerated brain age compared to chronological age, while a negative value instead suggests a younger-appearing brain. Participants with brain-PAD beyond 1.5 times the interquartile range were considered outliers and excluded from further analyses [23 participants].

Statistical Analyses

Given that previous work identified that the model estimating brain age without harmonization across cohorts best fit the data (BrainAGE Global⁵⁹), we conducted linear mixed-effects models with random intercepts to estimate group differences in brain-PAD between children and adolescents with CD and typically developing, while accounting for the variability between cohorts. Chronological age and its quadratic term were included as covariates⁶⁰ to mitigate the known bias whereby predicted age tends to be overestimated in younger populations⁶¹. BrainPAD of the i -th individual at j -th cohort was modeled as follows:

$$\text{BrainPAD}_{ij} = \text{intercept} + \beta_1(\text{diagnosis}) + \beta_2(\text{sex}) + \beta_3(\text{chronological age}) + \beta_4(\text{chronological age}^2) + U_j + \varepsilon_{ij}$$

In the equation, intercept, diagnosis (CD), sex, chronological age, and chronological age² effects were fixed. The terms U_j and ε_{ij} represent the random intercept attributed to the cohorts and the residual error, respectively. Cohen's d was computed to enable comparisons with previous work that has examined brain age in other psychiatric disorders^{18-20,22}.

To assess the robustness of our findings across cohorts, we conducted jackknife resampling by systematically removing one cohort at a time and recalculating the beta estimate for each

iteration. To account for possible overlap with healthy subjects from the ABCD cohort used in the BrainAGE Global model training, this additional analysis evaluated their impact on our overall findings. We subsequently tested for two- (diagnosis-by-chronological age; diagnosis-by-sex) and three-way (diagnosis-by-chronological age-by-sex) interactions. The main analysis was then repeated while covarying separately for comorbid attention-deficit/hyperactivity disorder, intelligence quotient, and medication status. Finally, we also explored whether brain-PAD was linearly associated with severity of conduct problems among youth with CD (see Supplementary Methods for more details).

Furthermore, to examine whether differences in brain-PAD between CD and typically developing participants would be moderated by developmental stages and/or sex, analyses were repeated by stratifying the samples with three chronological age bins approximating to the three stages of pubertal development⁴⁵ (childhood [5-11 years old], adolescence [12-16 years old], late adolescence [17-21 years old]), and across sexes.

Subanalyses were conducted to identify sources of variation contributing to the brain-PAD difference. Specifically, we tested for potential differences between childhood-onset versus adolescent-onset CD subgroups (defined by symptom onset at age <10 years vs ≥ 10 years), and subgroups with low versus high callous-unemotional traits (defined by informant [self-reported or parent-reported], sex, and [for self-report] age-specific normative cutoffs on the Inventory of Callous-Unemotional traits (see Supplementary Methods for more details). We also tested whether callous-unemotional traits correlated with brain-PAD across the full sample, and specifically in youth with CD (see Supplementary Methods). Pairwise comparisons were adjusted for using the Benjamini-Hochberg false discovery rate method ($q < 0.05$)⁶².

Data Availability

The ENIGMA-Antisocial Behavior CD data used in the current study can be provided by the ENIGMA-Antisocial Behavior Working Group pending scientific review and a completed material transfer agreement. Request for the data should be submitted to: <https://enigma.ini.usc.edu/ongoing/enigma-antisocial-behavior/>.

Code Availability

The analyses were conducted using BrainAGE Global model available online (<https://centilebrain.org/>).

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Interpretation of the findings: AAM, AB, AB-S, BF, CAMC, CRKC, DM, DSP, DGS, EJSS-B, EV, GF, GK, JC-F, JKB, JRD, KJM, KI, LWH, MS, MJYK, MCS, MA, NJah, NMR, OFC, PMT, RJRB, SIT, SADB, SB, and YG.

Writing of the original draft: GF, JRD, MS, SADB, and YG.

Review and editing: AAM, AK-V, AIC, AD, AB, AB-S, AM, AHD, ASm, ASe, ALWB, BF, CA, CAMC, CPSB, CS, CMF, CDT, CRKC, CSM, CCH, CM, DD, DED, DB, DSP, DM, DGS, EJSS-B, EDB, EMC, EV, GF, GK, GS, HCo, HP, HBW, HCh, IS-O, JC-F, CR, JKB, J-LM, JCG, JianZ, JZha, JN, JRD, KJM, KG-M, KI, KS, KB, KK, KL, LEM, LP, LWH, MO, MJPA, MS, MJYK, MCS, MC, MR-J, MA, MLP, NEH, NJah, NJAvdW, NT, NJab, NMR, OFC, P-MA, PMT, PJH, QM, QW, RLJ, RM, RJRB, RV, RP, RR, SAB, SB, SCC, SM, SIT, SADB, SD, TB, UMES, XC, XW, XS, YJ, and YG.

*Due to data sharing and privacy regulations, not all authors had access to the full dataset but have granted full consent to the corresponding author to submit the current study for publication. GF, JRD, MS, SADB, and YG have accessed and verified the data. Authors are listed alphabetically by first name.

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Ethics declarations

Competing Interests

AAM is the cofounder of the 501(c)(3) non-profit organization Psychopathy Is.

ALWB received honorarium from Elsevier Inc for work as Associate Editor in Neuroimage.

BF received educational speaking fees and travel support from Medice.

CA has been a consultant to or has received honoraria or grants from Abbot, Acadia, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion, Takeda, and Teva.

CMF receives royalties for books on ADHD, autism spectrum disorder, and depression. She received speaker's fees for talks on mental disorders by clinical, public and teaching organisations in 2023 and 2024. She worked as consultant for the German Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) in 2023.

CS receives royalties for a book on aggression.

DGS receives royalties from Guilford Press for a treatment manual on cognitive behavioral therapy for anger and aggression in children; the present work is unrelated to this relationship.

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LP is currently an employee of Biogen (Cambridge, MA, USA) but the work and the data presented in this manuscript are not related to his current functions at Biogen. All other authors declare no competing interests.

NMR received honoraria and speaker fees for public talks on brain development, learning, and wellbeing and serves on the board of the Citizen Science Center Zurich and the FENS Kavli Network of Excellence.

SADB has received speaker fees from the Child Mental Health Centre and the Centre for Integrated Molecular Brain Imaging.

TB served in an advisory or consultancy role for eye level, Infectopharm, Medice, Neurim Pharmaceuticals, Oberberg GmbH and Takeda; received conference support or speakers' fees from Janssen-Cilag, Medice, and Takeda; and received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press; the present work is unrelated to these relationships.

The other authors report no potential conflicts of interest.