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Environmental risk, Oxytocin Receptor Gene (*OXTR*) methylation and youth callous-unemotional traits: A 13-year longitudinal study

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Abstract

Youth with high callous-unemotional traits (CU) are at risk for early-onset and persistent conduct problems. Research suggests that there may be different developmental pathways to CU (genetic/constitutional vs environmental), and that the absence or presence of co-occurring internalizing problems is a key marker. However, it is unclear whether such a distinction is valid. Intermediate phenotypes such as DNA methylation, an epigenetic modification regulating gene expression, may help to clarify aetiological pathways. This is the first study to examine prospective inter-relationships between environmental risk (prenatal/postnatal) and DNA methylation (birth, age 7, age 9) in the prediction of CU (age 13), for youth low vs. high in internalizing problems. We focused on DNA methylation in the vicinity of the oxytocin receptor (*OXTR*) gene as it has been previously implicated in CU. Participants were 84 youth with early-onset and persistent conduct problems drawn from the Avon Longitudinal Study of Parents and Children. For youth with *low* internalizing problems (46%), we found that: (i) *OXTR* methylation at birth associated with higher CU (age 13) as well as decreased experience of victimization during childhood (birth – age 9), (ii) higher prenatal parental risks (maternal psychopathology, criminal behaviors, substance use) associated with higher *OXTR* methylation at birth, and (iii) *OXTR* methylation levels were more stable across time (birth – age 9). In contrast, for youth with *high* internalizing problems, CU was associated with prenatal risks of an interpersonal nature (i.e., intimate partner violence, family

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conflict) but not *OXTR* methylation. Findings support the existence of distinct developmental pathways to CU.

Keywords

DNA Methylation; Oxytocin Receptor gene; callous-unemotional traits; environmental risk; internalizing problems; ALSPAC

Introduction

In DSM 5, low prosocial emotions (i.e., callous-unemotional traits [CU] – lack of guilt, empathy), designate youth at risk for early-onset, persistent conduct problems (1, 2), and adult psychopathy (3). Yet, little is currently known about how CU traits develop. Research suggests that similar levels of CU may arise from distinct developmental circumstances (4, 5), and that the presence of co-occurring internalizing problems (anxiety/depression) is a key marker. More specifically, CU youth with low internalizing problems have been shown to experience less environmental risk (e.g. stressful life events) during childhood than those with high internalizing problems, despite showing similar levels of CU. This has led to speculations that CU may arise primarily from heritable/constitutional influences in the former group vs environmental influences in the latter group (6, 7). However, to date, few published biologically-informed longitudinal studies have tested whether such a distinction is valid.

Intermediate phenotypes, such as DNA methylation, may help clarify aetiological pathways to CU, for youth with low vs. high internalizing problems. DNA methylation is an epigenetic mechanism involved in transcriptional regulation (8) that can be influenced by the social environment (9). Recently, Dadds et al (10) reported that elevated DNA methylation in the vicinity of the oxytocin receptor gene (*OXTR*) is associated with (i) lower levels of circulating oxytocin and (ii) higher levels of CU. This is noteworthy, given that oxytocin (a hormone and neuropeptide) is known to modulate prosocial and affiliative behaviours that are impaired in CU youth, including empathy, emotional recognition, attachment and bonding (11–13). Also of interest, Dadds et al reported no association between levels of *OXTR* methylation and environmental risk exposure (measured as quality of family environment). The study, however, did not assess levels of co-occurring internalizing problems. As a result, it is not known whether *OXTR* methylation associates with CU and/or is influenced by environmental risks similarly for youth with low vs. high internalizing problems. Moreover, because the study was cross-sectional, it was not possible to pinpoint when in development environmental risks and/or alterations in *OXTR* DNA methylation may contribute to CU.

The present study is the first, to our knowledge, to make use of an integrative developmental model to examine, for youth low vs high in internalizing problems: (i) prospective interrelationships between environmental risk exposure (prenatal, postnatal) and *OXTR* methylation (birth, age 7, age 9); and (ii) the unique contribution of these factors to CU (age 13). Such a model not only has the capacity to further our understanding of how CU develop, but is also important for identifying the timing and targets of intervention to

prevent the emergence of CU. We focussed specifically on youth following an early-onset, persistent trajectory of conduct problems, as these typically present with the highest CU levels (14, 15). Based on previous literature, we expected that youth with low vs high internalizing problems would show similar levels of CU, but that youth with low internalizing problems would experience less environmental risk. In order to clarify aetiological pathways to CU, we then tested whether associations between *OXTR* methylation, environmental risk and CU differed for youth with low vs high internalizing problems.

Materials and Methods

Participants

The *Avon Longitudinal Study of Parents and Children* (ALSPAC) is an ongoing epidemiological study of children born from 14,541 pregnant women residing in Avon, UK, with an expected delivery date between April 1991 and December 1992 (85% of eligible population;16). Ethical approval was obtained from the ALSPAC Law and Ethics Committee as well as Local Research Committees. The sample is representative of the general population (17). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary: <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>.

The *Epigenetic Pathways to Conduct Problems Study* consists of a subsample of youth ($n = 339$, 50% female) nested within a larger study of DNA methylation in ALSPAC (www.ariesepigenomics.org) who follow previously established conduct problem trajectories and have epigenetic data at two or more time points (birth, age 7, age 9). The trajectories have been identified and validated using General Mixture Model based on data drawn from the Strengths and Difficulties Questionnaire 'Conduct Problem' subscale (4–13 years; 18). The conduct problem trajectories are: (i) Low (25.4%), Childhood-limited (24.8%), (iii) Adolescent-onset (20.4%), and (iv) Early-onset persistent (29.5%). This subsample is comparable to the full trajectory sample ($n = 7,218$) in terms of environmental risk and psychiatric comorbidity (14). DNA methylation was available for 326 youth at birth, 332 at age 7, and 339 at age 9. Except for factor analyses, in which we used data from all youth, the present study only included youth following the early-onset, persistent conduct problem trajectory, who had complete data for CU and internalizing problems (total $n = 84$). Consistent with prior research (15), these youth showed the highest CU levels ($M = 2.52$, $SD = .53$) compared to youth in other trajectories (see Supplementary Information, S11).

Measures

DNA methylation data (birth, age 7, age 9)—500ng genomic DNA from cord blood (birth) or peripheral blood (age 7 and 9) was bisulfite-converted using the EZ-DNA methylation kit (Zymo Research, Orange, CA, USA). The protocol followed manufacturer instructions using the recommended alternative incubation conditions for use with Illumina Infinium arrays. Illumina HumanMethylation450 BeadChips (Illumina, USA) were run following the manufacturer's protocol with no modifications and arrays were scanned using an Illumina iScan (software version 3.3.28). Initial quality control of data generated was

conducted using GenomeStudio (version 2011.1) to determine the status of staining, extension, hybridization, target removal, bisulfite conversion, specificity, non-polymorphic and negative controls. DNA methylation data was only available on samples that passed this stage. Samples were quantile normalised using the *dasen* function within the *wateRmelon* package (*wateRmelon_1.0.3*; 19) in R and batch corrected using the ComBat package (20).

We extracted probes located within the *OXTR* CpG island ($n = 12$), as this area has been previously investigated by Dadds et al (10; see Figure 1, Panel A) and others (13, 21, 22), and shown to play a key role in modulating the transcriptional activity of *OXTR* (23). For each probe, methylation levels were indexed by beta values (corresponding to the ratio of methylated signal divided by the sum of the methylated and unmethylated signal). Factor analysis was used to reduce the 12 *OXTR* probes into a smaller set of factors, which accounted for shared variance between them (24). A 3-factor solution (see Figure 1A) showed the best fit to the data as well as good temporal stability. Full details of the factor analysis procedure and results are provided as an online supplement (SI 2–5). We present findings relating specifically to Factor 2 (3 probes located on Exon 2), because (i) Factor 1 did not associate with CU at any time point in either youth with low or high internalizing problems, and (ii) Factor 3 variance was not significant at any time point, thereby precluding the examination of associations with environmental risk and CU traits.

Environmental risk (prenatal – age 9)—Cumulative environmental risk scores were created based on maternal reports. Risk items were organized into one of three developmental eras so as to coincide with the *OXTR* methylation data: (i) prenatal risks, (ii) early childhood risks (birth – age 7), and (iii) mid-childhood risks (age 8–9). For each developmental period, items were summed to create five conceptually distinct but related risk domains: (i) *Life events* (e.g. death in family, accident, illness), (ii) *Contextual risks* (e.g. poor housing conditions, financial problems), (iii) *Parental risks* (e.g. parental psychopathology, criminal involvement and substance use), (iv) *Interpersonal risks* (e.g. intimate partner violence, family conflict), and (v) *Direct victimization* (e.g. child bullied by peers or physically hurt ; available postnatally). Risk domains were positively and significantly correlated, both within and between developmental periods. We used confirmatory factor analyses (CFAs) to assess the internal reliability of the risk domains and to extract one global cumulative risk score for each developmental period, showing good model fit. Higher scores indicate greater environmental risk exposure. See SI 6–9 for full item descriptions, details of inter-correlations between risk domains and factor analysis fit indices.

Internalizing Problems (age 13)—Internalizing problems were assessed via maternal ratings using the well-validated Development and Well-Being Assessment (DAWBA). Computer-generated diagnostic ‘probability bands’ for anxiety and depression (six-level ordered-categorical variables ranging from <0.1% to >70% probability of DSM-IV psychiatric diagnosis) were averaged to create an interval level composite score. Description and validation of DAWBA bands are available elsewhere (25).

CU traits (age 13)—CU traits were measured using a 6-item questionnaire completed by mothers (26). Items were rated on a 3-point scale ranging from ‘not true’ to ‘certainly true’

($\alpha = .79$). These included: (i) Makes a good impression at first but people tend to see through him/her after they get to know him/her, (ii) Shallow or fast-changing emotions; (iii) Is usually genuinely sorry if s/he has hurt someone or acted badly (*R*); (iv) Can seem cold-blooded or callous; (v) Keeps promises (*R*); and (vi) Genuine in his/her expression of emotions (*R*). This measure has been shown to correlate highly with the CU scale of the Antisocial Process Screening Device (27).

Data Analysis

Youth were separated into two groups based on a median split on internalizing problems (median value = 1.00, range = 0 – 5), resulting in a low internalizing (INT–; $n = 39$) and a high internalizing (INT+; $n = 45$) group.

Step 1: Group characteristics—We compared INT– and INT+ on CU levels to ascertain that, consistent with previous research, they would show similar levels of CU even though different in levels of internalizing problems. We also compared the groups on environmental risk exposure (prenatal, early and mid-childhood), to establish whether INT– experience less environmental risk than INT+. We then assessed partial correlations (controlling for sex) between *OXTR* methylation, risk exposure and CU levels separately for each group, to assess whether associations between these variables differ for INT– vs INT+.

Step 2: Integrative developmental model—We estimated a path analytic model that incorporated environmental risk exposure, *OXTR* methylation and CU. This analytic strategy enabled us to establish for each group:

1. Longitudinal inter-relationships between environmental risk exposure and *OXTR* methylation (controlling for previous and subsequent measurements of each);
2. The unique timing of environmental risk and *OXTR* methylation effects on CU.

Sex was included as a covariate.

Analyses were performed in Mplus version 6.1.1 (28) using maximum likelihood estimation and bootstrapping. Bootstrapping is advantageous with small samples as it derives an approximation of the sampling distribution via repeated resampling of the available data to yield bias-corrected 95% confidence intervals. Significant associations were only presented if they survived bootstrapped confidence intervals. Model fit was first established using the chi-square statistic, which tests the difference between observed and expected covariance matrices, producing a non-significant value if this difference is close to zero (29). In the event of a significant chi-square value, we further examined relative fit indices that also test the discrepancy between the estimated model and the data, including the mean square error of approximation (RMSEA; acceptable fit $\leq .08$), the Comparative Fit Index and Tucker-Lewis Index (CFI & TLI; acceptable fit $\geq .90$) (30). Nested model comparisons – using the Satorra-Bentler Scaled Chi-Square test (31) – were used to assess differences between the INT– and INT+.

Youth with scores greater than 3 standard deviations from the mean on any study variable were treated as outliers ($n = 2$) and their scores winsorized (i.e. transformed to match next

highest value). This method uses censoring rather than exclusion, which is preferable with small sample size (32).

Results

Step 1: Group characteristics

Three results are highlighted. First, as seen in Figure 2A, INT- and INT+ did not differ in CU. Second, the INT- group (vs INT+) experienced significantly lower levels of cumulative environmental risk (Figure 2B) during early childhood (birth – age 7; $p = .008$). Third, as seen in Table 1, correlations between environmental risk, CU and *OXTR* methylation showed that (a) *Parental risks* were positively correlated with DNA methylation across both INT- (at birth) and INT+ (at age 7) youth; and (b) *OXTR* methylation at birth was significantly correlated with higher CU, but only for INT-. This result is visually presented in Figure 1B, where it can be seen that, for INT- youth, *OXTR* methylation levels increased as CU traits became more severe (6% beta change). Post-hoc analysis confirmed that the association between *OXTR* methylation at birth and CU differed for the INT- vs INT+ group (i.e. significant interaction effect; $p = .034$). Interactions were not significant at age 7 and 9.

Step 2: Integrative developmental model

Figure 3 illustrates the integrative developmental model for INT- vs INT+. Model fit was good: $X^2(12) = 20.78, p = .06$.

For the INT- (Figure 3A), three results are highlighted. First, higher *OXTR* methylation at birth was prospectively associated with higher CU at age 13, and this association was stronger for INT- vs INT+ ($\chi^2[1] = 4.78, p = .03$). Higher *OXTR* methylation at birth also associated with lower risk exposure during early childhood (birth – age 7) – specifically *direct victimization* (e.g., bullying by peers, physical harm by adults) – and this association was stronger for INT- vs INT+ ($\chi^2[1] = 7.11, p = .01$). In other words, for INT-, higher *OXTR* methylation at birth associated with both (i) higher CU and (ii) less subsequent victimization, suggestive of what we refer to as an ‘*evocative epigenetic-environment correlation*’. Second, although no effect of overall prenatal environmental risk on *OXTR* methylation at birth was observed, one specific risk domain, prenatal *parental risks*, was found to be significantly associated with *OXTR* methylation levels at birth. This association was stronger for INT- vs INT+ ($\chi^2[1] = 4.07, p = .04$). Third, temporal stability between birth and age 9 was greater in magnitude for the INT- vs. INT+ ($\chi^2[2] = 12.00, p = .001$).

For the INT+ (Figure 3B), three results are highlighted. First, *OXTR* methylation did not significantly associate with CU (see above difference test). Second, higher prenatal risks associated with higher CU. This association was specific to *interpersonal risks* (e.g., intimate partner violence, family conflict), and was stronger for the INT+ vs. INT- ($\chi^2[1] = 7.89, p = .005$). Third, postnatal risks – specifically *life events* (e.g., death of relative, accidents, illness) – associated with lower CU, and this association was stronger for INT+ vs. INT- ($\chi^2[1] = 1.48, p = .001$).

Follow up analyses

We conducted two follow-up analyses in light of the findings above. First, we unpacked the Factor 2 methylation-CU association at birth in the INT- group. We examined the three probes included in Factor 2 individually. DNA methylation at birth prospectively associated with CU traits for probe cg04523291 (Std $B = .46$, $B = 4.61$; bootstrapped 95% CI = .32 – 8.52) and probe cg15317815 (Std $B = .46$, $B = 3.97$; bootstrapped 95% CI = .76 – 8.05), but not for probe cg02192228 (Std $B = .34$, $B = 4.10$; bootstrapped 95% CI = -2.60 – 10.46).

Second, we investigated the potential influence of genetic variation on DNA methylation and CU (33, 34). We selected 4 SNPs (rs2301261, rs237915, rs4564970, and rs4686302) that were (a) available in ALSPAC via GWAS (for details see 35), (ii) located within the CpG island examined in the present study, and (iii) have been examined in previous studies in relation to phenotypes relevant to CU (36–39). None of these SNPs were found to associate with DNA methylation levels, CU or the INT-/INT+ groups (full details provided in SI9–10).

Discussion

Our goal was to examine whether aetiological pathways to CU differed for INT- vs INT+ youth, using repeated measures of environmental risk exposure and *OXTR* methylation. Consistent with our hypothesis, INT- and INT+ did not differ in CU levels, but INT- experienced lower risk exposure than INT+. Our integrative developmental model showed that, for INT- youth: (i) *OXTR* methylation at birth associated with higher CU (age 13), as well as decreased experience of victimization during childhood (birth – age 7); (ii) higher prenatal parental risks (e.g. maternal psychopathology, criminal behavior, substance use) associated with higher *OXTR* methylation at birth; and (iii) temporal stability of *OXTR* methylation was greater (birth – age 9) than for INT+. In contrast, for INT+ youth, *OXTR* methylation did not associate with CU. Rather, prenatal risks of an interpersonal nature (e.g., intimate partner violence and family conflict) associated with higher CU levels. Findings support the existence of distinct pathways to CU.

For INT- youth, we highlight three main findings. First, we support Dadds et al's (10) study showing an association between higher *OXTR* methylation and higher CU. Of interest, we show that this association is specific to INT- youth, and occurred at birth, whereas Dadds et al found an association in older youth. Together, these findings may suggest that there are multiple developmental periods of vulnerability for CU via *OXTR* methylation. In addition, it is worth noting that our methylation probes were different from Dadds et al's, which raises the possibility that multiple sites across the CpG island may be associated with CU. We also found that, in INT- youth, higher *OXTR* methylation at birth was associated with lower levels of direct victimization during childhood, suggestive of an 'evocative epigenetic-environment correlation'. More specifically, this finding parallels evocative gene-environment correlation studies showing that a child's genetic characteristics can influence his or her environment (40–43). Importantly, this finding may lend insight into how INT- youth experience less victimization than INT+ youth (6, 7). In light of prior evidence showing that (i) higher *OXTR* methylation is associated with lower circulating levels of

oxytocin (10) and (ii) lower levels of oxytocin are associated with deficits in prosocial and affiliative behaviours (12, 13), it is possible that INT– youth develop socio-emotional characteristics that actively discourage victimizing behaviour from others (e.g. showing lower empathy and trust), and potentially fit more of a ‘bullying-only’ profile (44, 45). Moreover, it is possible that higher *OXTR* methylation ‘protects’ INT– youth from developing internalizing problems, which act as both an antecedent and maintaining factor for victimization (46). More generally, this effect may lend support to the notion that epigenetic mechanisms can prepare children to cope with forthcoming environmental challenges (47). The second finding is that one specific domain of environmental risk, prenatal *parental risks*, are associated with higher *OXTR* methylation at birth. It is unclear whether this association is causal (e.g., a direct impact of parental risks on fetal development) or correlational (e.g., reflecting genetic confounding; 48, 49). Third, *OXTR* methylation in this group was found to have greater temporal stability (vs. INT+) from birth to age 9. The finding that *OXTR* methylation is more stable and associated with CU exclusively in INT– raises the question of whether this group may respond differently to interventions, such as intranasal oxytocin administration, compared to the INT+.

A different pattern of results emerged for INT+ youth. First and foremost, *OXTR* methylation did not associate with CU (at any time point). In addition, consistent with previous findings (6, 7, 50), this group experienced higher levels of environmental risk exposure than the INT–. Of interest, prenatal *interpersonal risks* (e.g. intimate partner violence, family conflict) prospectively associated with higher CU. Although speculative, this effect may be mediated by maternal stress, which has been associated with both internalizing problems (51) and CU (15) within ALSPAC. A counter-intuitive finding was that postnatal risks (i.e., adverse life events) associated with lower CU. As with the above results, this finding will need replication, particularly within high-risk samples.

The present findings should be interpreted in light of a number of limitations. First, the study focussed specifically on DNA methylation of annotated probes located within the CpG island of *OXTR* and it is likely that differences across groups may be found in other genes (e.g. glucocorticoid or serotonergic pathways; 52). While an epigenome-wide approach would have enabled us to examine group differences in DNA methylation across the genome (53), at present it is not plausible to build integrative developmental models, such as the one used here (i.e., with repeated methylation data included both as an independent variable and as a dependent variable), using a genome-wide approach, due to the computational burden of applying this method to hundreds of thousands of variables. Second, findings are based on a relatively small sample of youth with limited statistical power in view of the complex longitudinal models tested. Consequently, the present findings should be interpreted as well-grounded hypotheses for further examination in larger longitudinal studies. The use of larger studies may help to clarify the present findings, including (i) which aspects of prenatal parental risks associate with *OXTR* methylation at birth (e.g. parental criminality vs substance use) in INT– youth; (ii) what biological mechanisms mediate the effect of prenatal environmental risk exposure on CU for INT+ youth; and (iii) why we find a negative association between postnatal environmental risks and CU traits in the INT+ group. Third, the current study was based on a community sample of youth with relatively low rates of

internalizing problems. This resulted in the classification of groups based on a median split. In future, it will be important to replicate developmental pathways to CU in high-risk youth who show more severe internalizing problems (e.g. young offenders, psychiatric inpatients). Finally, although the current study did not find that DNA sequence-based variation in OXTR influenced DNA methylation or CU levels, analyses were limited to four SNPs. In future, it will be necessary to examine additional local (cis) and distant (trans) SNPs to better establish the relationship between genetic variation across the genome and methylation at the OXTR locus. More generally, the inclusion of genetic information may help further elucidate aetiological pathways to CU, for INT- vs. INT+ youth.

In summary, this is the first longitudinal study to examine the role of environmental risk exposure and *OXTR* methylation in the development of CU for INT- vs INT+ youth. Our findings show that: (i) *OXTR* methylation (at birth) prospectively associated with CU only for INT- youth; (ii) for this group, *OXTR* methylation (at birth) also associated with reduced experience of direct victimization (by peers and adults), which, to our knowledge, provides the first example (in humans) of what we refer to as an ‘evocative epigenetic-environment association’; (iii) *OXTR* methylation had greater temporal stability for the INT- vs. INT+ youth; and (iv) environmental risk (prenatal and postnatal) associated with CU only for the INT+ youth. As a result, the present study supports the existence of distinct developmental pathways to CU. Findings also identify targets and windows of opportunity for prevention as well as highlighting the salience of the prenatal period, both for INT- and INT+. More generally, the present study illustrates an innovative way to integrate longitudinal environmental and epigenetic information in the study of psychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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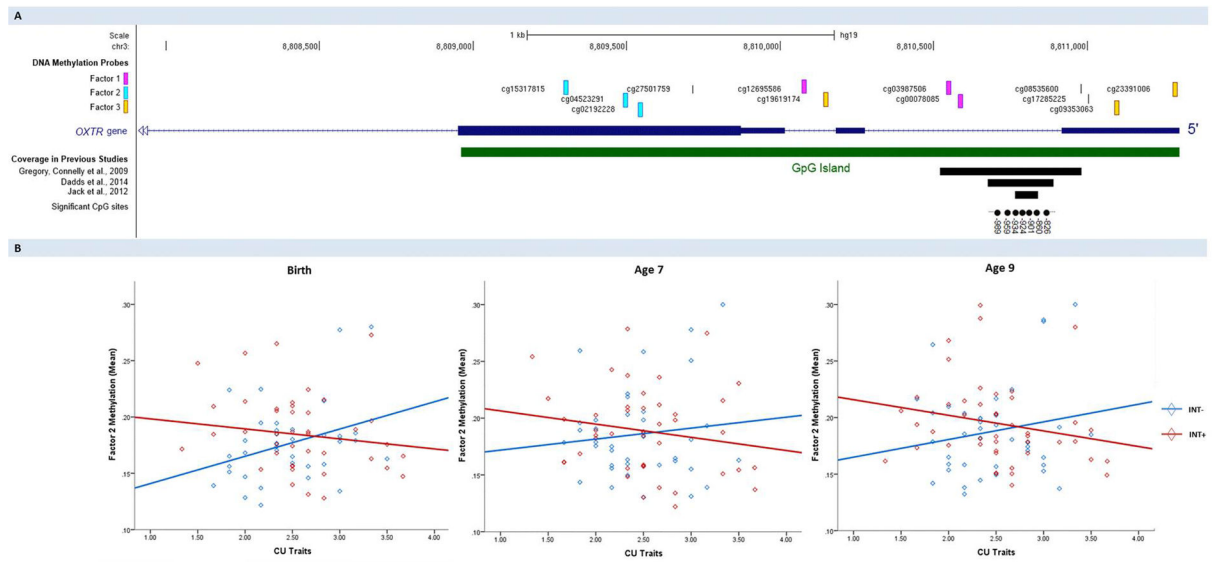


Figure 1. Location of *OXTR* methylation probes and associations with CU traits. *Panel A:* Location of methylation probes within the CpG island (hg19; chr3:8808962–8811280) included in the study, and how these are grouped into factors (i.e. Factor 1: purple; Factor 2: blue; Factor 3: yellow). **Black rectangles indicate the area of the *OXTR* CpG island investigated by previous research on DNA methylation. Significant CpG sites identified by these studies are shown as black circles. Numbering is relative to the translation start site (+1).** *Panel B:* Association between Factor 2 methylation and CU traits for youth with low (INT–) vs high (INT+) co-occurring levels of internalizing problems, across time points.

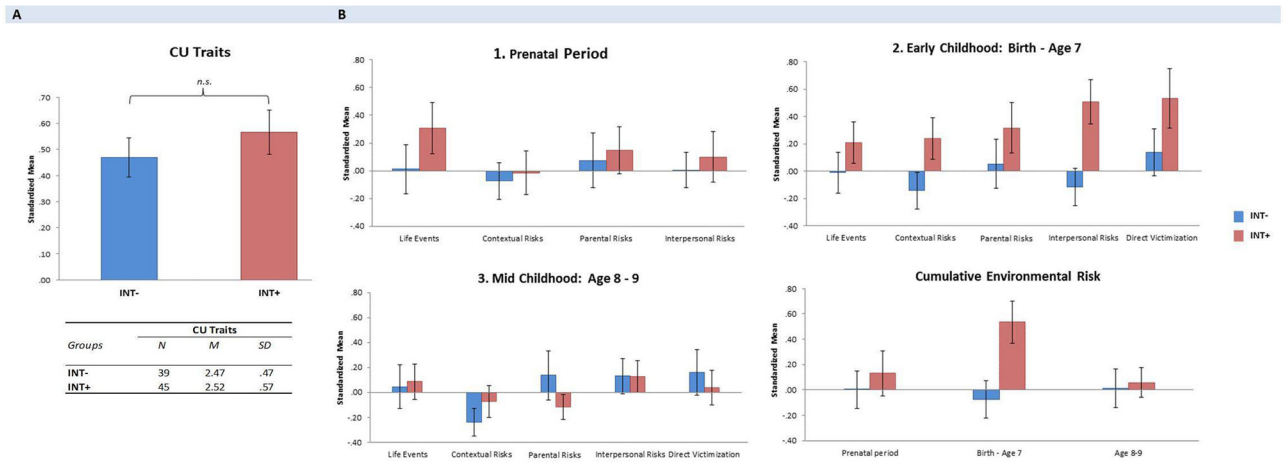


Figure 2. Levels of CU traits and environmental risk exposure across groups. *Panel A:* Standardized mean levels of CU and descriptives for INT– vs INT+. *Panel B:* Standardized mean levels of environmental risk exposure across individual domains and developmental eras for INT– vs INT+.

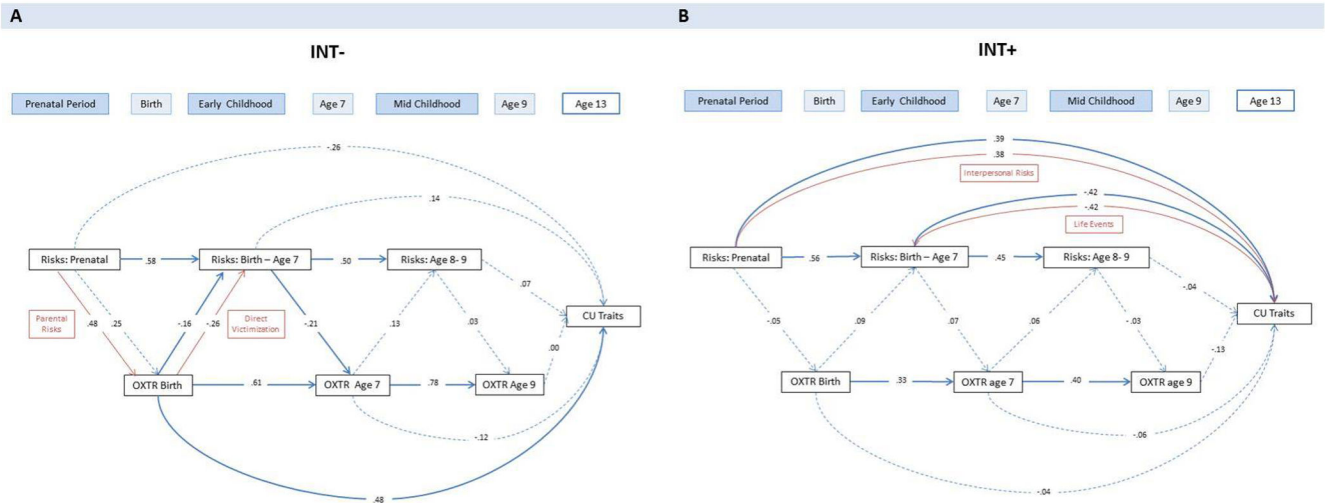


Figure 3. Integrative developmental model. *Panel A:* INT– group. *Panel B:* INT+ group. Single arrowed lines indicate standardized path coefficients that survived bootstrap-corrected confidence intervals (i.e. significant path). Red arrows show significant individual risk domains based on post-hoc analyses. Dotted arrowed lines indicate non-significant paths. Population effect sizes are interpreted using the standardized estimates (Std. B) following Cohen’s guidelines: an effect of .10 is small effect, an effect of .24 is a medium effect, and an effect of .37 is a large effect.

Table 1
Associations between environmental risk exposure, CU traits and *OXTR* methylation across groups

Environmental risk exposure	<i>OXTR</i> Methylation					
	INT-			INT+		
	Birth	Age 7	Age 9	Birth	Age 7	Age 9
Individual Risk Domains						
<i>Prenatal period</i>						
Life Events	-.01	-.14	-.09	-.13	-.06	.13
Contextual Risks	.14	.06	.18	-.03	-.08	.20
Parental Risks	.40*	.00	.24	.19	.32*	.25
Interpersonal Risks	.05	-.15	-.18	-.13	-.13	-.01
<i>Early childhood: Birth - Age 7</i>						
Life Events	---	-.13	-.24	---	-.03	.08
Contextual Risks	---	-.30	-.09	---	-.04	.01
Parental Risks	---	.04	.17	---	.25	.29
Interpersonal Risks	---	-.18	-.11	---	.04	.02
Direct Victimization	---	-.18	-.24	---	.06	.02
<i>Mid childhood: Age 8 - 9</i>						
Life Events	---	---	-.14	---	---	.09
Contextual Risks	---	---	.15	---	---	-.15
Parental Risks	---	---	.19	---	---	.45**
Interpersonal Risks	---	---	.11	---	---	-.45
Direct Victimization	---	---	.11	---	---	-.08
Cumulative Risk Composites						
Prenatal period	.23	-.07	.07	-.02	-.08	.04
Early childhood: Birth - Age 7	---	-.21	-.14	---	.07	.09
Mid childhood: Age 8 - 9	---	---	-.02	---	---	.01

N.b.

p < .001;

**
p < .01;

* $p < .05$. All associations control for sex.

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