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Regular Article

Sensation-seeking-related DNA methylation and the development of delinquency: A longitudinal epigenome-wide study

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Abstract

Heightened sensation-seeking is related to the development of delinquency. Moreover, sensation-seeking, or biological correlates of sensation-seeking, are suggested as factors linking victimization to delinquency. Here, we focused on epigenetic correlates of sensation-seeking. First, we identified DNA methylation (DNAm) patterns related to sensation-seeking. Second, we investigated the association between sensation-seeking related DNAm and the development of delinquency. Third, we examined whether victimization was related to sensation-seeking related DNAm and the development of delinquency. Participants ($N = 905$; 49% boys) came from the Avon Longitudinal Study of Parents and Children. DNAm was assessed at birth, age 7 and age 15–17. Sensation-seeking (self-reports) was assessed at age 11 and 14. Delinquency (self-reports) was assessed at age 17–19. Sensation-seeking epigenome-wide association study revealed that no probes reached the critical significance level. However, 20 differential methylated probes reached marginal significance. With these 20 suggestive sites, a sensation-seeking cumulative DNAm risk score was created. Results showed that this DNAm risk score at age 15–17 was related to delinquency at age 17–19. Moreover, an indirect effect of victimization to delinquency via DNAm was found. Sensation-seeking related DNAm is a potential biological correlate that can help to understand the development of delinquency, including how victimization might be associated with adolescent delinquency.

Keywords: ALSPAC; childhood victimization; delinquency; DNA methylation; sensation-seeking

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Youth who show heightened sensation-seeking are at risk of developing delinquent behavior in adolescence (Harden et al., 2012; Mann et al., 2015). In addition, studies have indicated that heightened sensation-seeking is an important mediating factor in the link between environmental stressors, such as childhood victimization, and the development of delinquency (Choy et al., 2015; Fagan et al.; Van Goozen et al., 2007, 2008). It is suggested that (neuro)biological correlates of sensation-seeking, such as lowered autonomic arousal and disturbances in the dopaminergic system play a pivotal role in these associations (Van Goozen et al., 2007, 2008). In the last years, epigenetic processes that regulate gene expression have emerged as another potential biological correlate that may explain the link between childhood risks, and behavioral maladjustment (Barker et al., 2018; Cecil et al., 2020). In this study, we focused on epigenetic correlates of sensation-seeking in three ways. First, we investigated whether children who show heightened sensation-seeking behavior have different DNA methylation patterns. Second, we investigated whether these DNA methylation patterns are related to the development of delinquency. And third, we examined whether these DNA methylation patterns were associated with earlier adverse childhood experiences (i.e., childhood victimization) and thereby, possibly, act as an indirect factor between childhood victimization and delinquency.

Sensation-seeking is defined as "the need for varied, novel and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experiences" (Zuckerman, 1979). Previous studies have shown that individuals who show high levels of sensation-seeking during late childhood are at risk of developing delinquent behavior later in adolescence (Harden et al., 2012; Mann et al., 2015). It has been suggested that this sensation-seeking – delinquency association among adolescents might be due to biological correlates, such as lower resting state heart rate (Hammerton et al., 2018; Ortiz & Raine, 2004; Portnoy et al., 2014; Sijtsema et al., 2010), dysregulated dopaminergic activation (Chester et al., 2016), increased gonadal hormone secretion (Aluja & Torrubia, 2004; Campbell et al., 2010), altered reward-related brain activity (Gjedde et al., 2010), and shared genetic influences (Mann et al., 2016).

In the last years, epigenetic processes have emerged as another biological mechanism of interest in the development of mental health problems, including antisocial and delinquent behaviors (Barker et al., 2018; Tremblay, 2015). One of these epigenetic processes, DNA methylation (DNAm), has received increasing attention. In short, DNAm is the process where a methyl group binds to the DNA, which in turn causes changes in gene expression

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without changing the sequence of the bases in the DNA itself. It has been shown that DNA methylation patterns are related to individual variation in delinquency as well as to other measures of antisocial behavior (Cecil, Walton, Jaffee, et al., 2018; Cecil, Walton, Pingault, et al., 2018; Checknita et al., 2015; Guillemin et al., 2014; Provencal et al., 2013; Wang et al., 2012). However, behavioral phenotypes, such as delinquency are complex and multiply determined. Barker et al. (2018) therefore proposed that, to be able to identify biologically relevant biomarkers for behaviors such as delinquency, it may be fruitful to examine epigenetic correlates of antecedents of these phenotypes. To date, to our knowledge, there is no study into epigenetic correlates of sensation-seeking and its potential link with delinquency. However, given the clear sensation-seeking – delinquency link, this seems an important avenue to better understand this association. Therefore, in the present study we will investigate DNA methylation patterns that are related to heightened sensation-seeking behavior. Second, we will investigate whether these DNA methylation patterns are related to the development of delinquency.

Another important aspect of DNA methylation in relation to psychopathology is that DNA methylation is influenced both by genetic sequence variation (Gaunt et al., 2016) and environmental stressors, including childhood victimization (Cecil et al., 2020; Szyf et al., 2008). Previous studies have documented that childhood victimization is related to increases in sensation-seeking (Bornovalova et al., 2008), and to biological correlates of sensation-seeking such as lower heart rate (Miskovic et al., 2009), reduced cortisol (Lovallo, 2013) and dopamine reward responses (Oswald et al., 2014). However, it is not known whether childhood victimization is related to changes in DNAm correlates of sensation-seeking. Given the pivotal role of sensation-seeking in the link between childhood adversity and adolescent delinquency, our third goal is to investigate whether DNAm correlates of sensation-seeking are related to earlier adverse childhood experiences and whether this in turn is related to the development of delinquent behavior in late adolescence.

Thus, in this study we have three key research aims. First, we will investigate DNA methylation patterns of sensation-seeking. Second, we will examine whether there is an association between these DNA methylation patterns and delinquency in late adolescence. And our third research question is whether experiences of childhood victimization are related to sensation-seeking-related DNAm correlates and whether these adverse experiences via DNAm associate with the development of delinquent behavior later in adolescence.

Methods

Sample

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 1st, 1991 and December 31st, 1992 (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019). The current study focuses on the Accessible Resource for Integrated Epigenomics Study substudy (Relton et al., 2015), which consists of 1,018 mother-offspring pairs who provided DNA samples at multiple timepoints. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time and consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Children included in the present study had at least one available measure of victimization in early childhood (birth-age 7) or mid-childhood (age 8–9) (97% complete data), at least one available measure of DNAm at either birth, age 7 or age 15–17 (81% complete data), and at least one assessment of antisocial activities at age 8 or delinquency at age 17–19 (68% complete data). This resulted in a total sample of 905 children (49% boys, all Caucasian).

Measures

Sensation-seeking was assessed via self-reports using a modified version of the Arnett's Inventory for Sensation Seeking (Arnett, 1994) at age 11 and age 14 including 19 items. Example items are "I like the feeling of standing next to the edge/looking down" or "When I ride a bike I go as fast as I can whenever possible." Items were presented on a computer screen. Response categories were 0 = not at all like me, 1 = not much like me, 2 = quite like me, 3 = very like me. We performed an exploratory factor analysis (EFA) to reduce the items into smaller subsets of factors that showed shared variance. EFA on the modified version of the AISS revealed a three-factor structure which was used in the subsequent analyses to identify chronic high sensation-seekers and their associated DNAm patterns. See Table S1 for a description of the EFA.

Delinquent Behavior at 17–19 years of age was assessed with a variety score including 12 items regarding delinquent behavior that were taken from the Edinburgh Study of Youth Transition and Crime (Smith & McVie, 2003). Participants were asked to answer questions about delinquent behavior such as "During last year I stole something from a shop" or "During last year I started a fight" with responses classified into "yes" (= 1) or "no" (= 0). All items were summed into an overall delinquency variety score (range 0–12).

Childhood victimization was obtained two times via mother reports about the period between child's birth and age 7 and when the children were between the age of 8 and 9. Items about whether the child has been bullied ("child is bullied/picked on"), physically hurt by someone ("child has been physically hurt by someone") or has been sexually abused ("child has been sexually abused") were assessed plus two more specific items on peer victimization, namely, "child has been overtly victimized" and "child has been relationally victimized." The scale was derived from an overall adversity score that was previously estimated and validated by Cecil et al. (2014).

DNA methylation data were extracted from cord blood on delivery, and from peripheral blood samples in childhood (age 7) and in adolescence (age 15–17). DNA methylation of over 450,000 CpG sites was quantified using Illumina Infinium HumanMethykation450K BeadChip assay (HM450; Illumina Inc., CA). Arrays were scanned using the Illumina iScan. To extract signal intensities and to assess initial quality review GenomeStudio was used. For each sample, the estimated methylation level at each CpG site is expressed as a beta value (β), which is the ratio of the methylated probe intensity to the overall intensity and ranges from 0 (no cytosine methylation) to 1 (complete cytosine methylation). Background correction and functional normalization were performed using Meffil in R (Min et al., 2018). Samples with >10% of sites with a detection p value > .01 or a bead count < 3 in > 10%

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of probes were removed from further analysis. Nonspecific probes and probes on sex chromosomes were removed. Following QC procedures, data were available for 381,871 probes. Probes were annotated using information provided by Illumina (genome build: hg19). To account for potential differences in methylation arising from cell composition in whole-blood samples, cell counts were estimated using the Houseman algorithm and included as covariates. The cell counts in cord blood were estimated using the Gervin panel (Gervin et al., 2019). However, for longitudinal analyses including data from cord blood and whole-blood samples, analyses instead included the first 20 independent surrogate variable components to account for both heterogeneity between cord blood and peripheral blood samples as well as batch effects. Previous research has indicated that surrogate variables derived in this way account for cell count heterogeneity as well as estimated cell counts (Kaushal et al., 2017; McGregor et al., 2016).

Control variables

Substance use was assessed and included as a control variable to prevent potential confounding of the DNAm levels by participant's substance use (Dogan et al., 2016). Tobacco and cannabis use was assessed with the Cannabis Abuse Screening Test at age 14 (Legleye et al., 2013) and the Fagerstrom Test for Nicotine Dependence at age 14 (Heatherton et al., 1991).

Antisocial activities at age 8 was assessed via 11 questions regarding antisocial activities that were taken from the self-reported antisocial behavior for young children questionnaire (Loeber et al., 1989). Items regarded stealing (bicycles, from a shop, from a house/garden, from a car, entered a building to steal, pickpocketing), substance use (drank alcohol, smoked cigarettes without parental permission), set fire, carried a weapon and cruelty to animals. It was conducted as a structured interview and was provided in the format of a posting task. Each of the questions was written on a different envelope. The children were asked to place the envelope into one of the two boxes marked as "ever" or "never." Scores were summed into a total antisocial activity score.

DNA methylation levels were corrected for maternal smoking, sex, batch and cell-type proportions (CD8 T-lymphocytes, CD4 T-lymphocytes, natural killer cells, B-lymphocytes, monocytes) at birth, age 7 and age 15–17 (Houseman et al., 2012). Age 15–17 ($M = 16$ years, $SD = 0.97$)

Sex was dummy coded, 0 = boys; 1 = girls.

Statistical analyses

Our first research goal was to identify DNA methylation patterns related to sensation-seeking. To do so the following steps were undertaken. First, to identify children with a stable high sensation-seeking profile across ages 11 and 14 a Latent Transition Analysis (LTA) was performed. The objective of the LTA is to identify the smallest number of classes of children who may follow distinct profiles of sensation-seeking across ages 11 and 14 years (e.g., stable high versus lower levels of sensation-seeking across timepoints). Entropy and the percentage of youth in each profile (>5% children in each class) were used to come to the optimal number of classes. LTA was performed in Mplus (Muthén, 1998-2012). We then performed an epigenome-wide association study (EWAS) of DNA methylation levels (at age 15–17) between children with a stable high sensation-seeking profile across age 11 and age 14 years versus all other children using a general linear model. Statistical significance was determined using a Bonferroni correction, giving a threshold of $p < 1.3 \times 10^{-7}$. Tests with $p < 5 \times 10^{-5}$ were defined as reaching suggestive significance (Roberts et al., 2019). Methylation analyses were performed in R using the package Meffil (Min et al., 2018). All (suggestive) hits will be examined for possible genetic influences on the levels of methylation by searching the mQTLdb from the GoDMC study (http://mqtldb.godmc.org.uk/).

Our second research goal was to investigate whether there is an association between these DNA methylation patterns and delinquency in late adolescence. To minimize multiple testing burden, we grouped the top probes (significant or suggestive significant probes) found in the EWAS into a single cumulative DNAm risk score. Therefore, we multiplied the methylation values by their respective regression weights form the EWAS, and then summed these weighted methylation values into the sensation-seeking DNAm risk score (Shah et al., 2015). Also, we calculated DNAm risk scores at birth and age 7 years using the same probes and weights from the DNAm risk score at age 15–17 years. This was done to enable studying change in DNAm risk across childhood into adolescence. We disentangled within-person variation from between-person variation in DNAm over time by specifying a random intercept for DNAm over the three timepoints (Hamaker et al., 2015). This enables us to assess changes in DNAm over time while accounting for static DNAm levels that differed between individuals at birth, age 7 and age 15–17. To investigate the association between these DNA methylation patterns and delinquency in late adolescence, we fitted a path model in Mplus in which delinquency at age 17–19 was predicted by DNAm at age 15–17, while controlling (both DNAm and delinquency) for antisocial activities at age 8, substance use and sex.

Our third research question was whether experiences of childhood victimization are related to sensation-seeking DNAm correlates and whether these adverse experiences via DNAm associate with the development of delinquent behavior later in adolescence. Therefore, a model testing indirect effects as depicted in Figure 1 was fitted. We included childhood victimization in the model and allowed for paths of childhood victimization at age 8–9 to the (changes in) DNAm risk score at age 15–17 and subsequent delinquency at age 17–19. In this model, we controlled for antisocial activities at age 8, childhood victimization between birth - age 7, substance use and stable DNAm risk score differences over time between participants. Bootstrapped (10,000 times) estimates of the indirect effect of childhood victimization via DNAm change to delinquency were estimated with bias-corrected 95% confidence intervals (CIs).

All models were fitted in Mplus version 7.1. Model fit was determined through the CFI and TLI (acceptable fit = > 0.90; Bentler & Bonett, 1980) and RMSEA (acceptable fit = < 0.08; Marsh et al., 2004). Maximum likelihood estimation with robust standard errors was used to estimate the model parameters, and missing data were handled through full information maximum likelihood estimation.

Results

Preliminary analyses

To identify the children with stable high sensation-seeking profiles over time, an LTA was performed and yielded a three class-profile solution. Among those profiles, there was a discernable group of children with stable high sensation-seeking at both ages 11 and age 14 years. This high sensation-seeking class (15%) consisted of $n = 140$ children and was contrasted in the EWAS with the other children ($n = 765$). For a detailed description of the LTA see Table S2.

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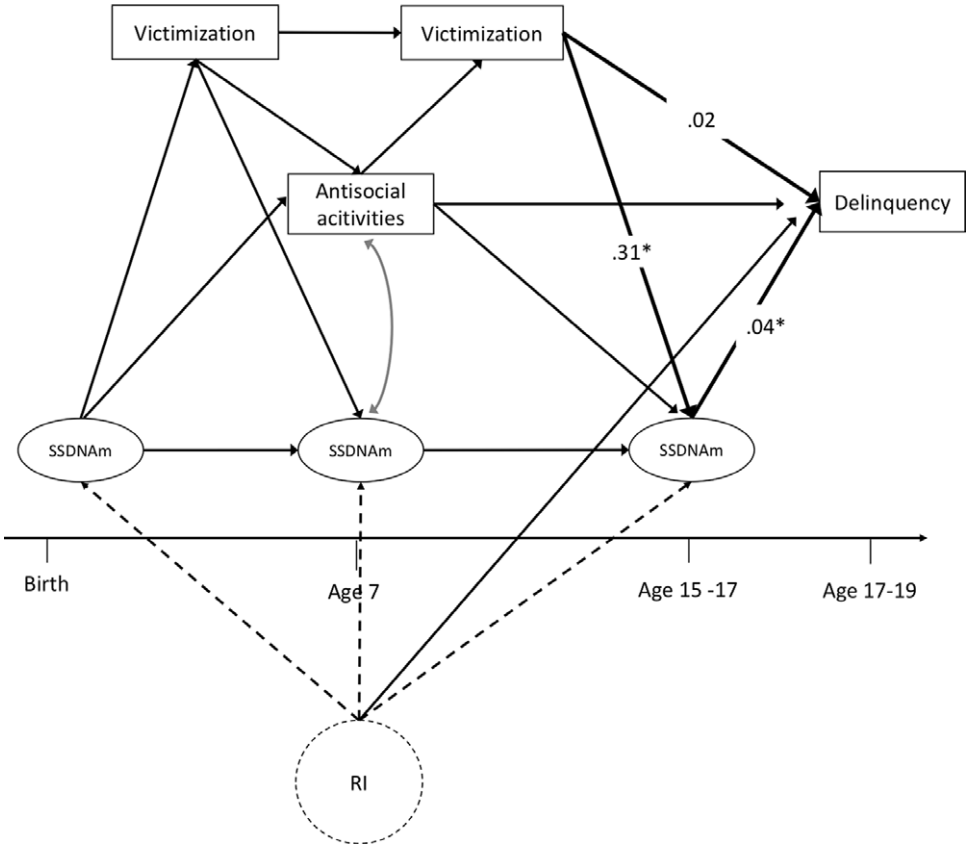

Figure 1. Graphical representation of the model including regression path estimates of the indirect effect of childhood victimization via DNAm changes to delinquency. *Note*. All other estimates can be found in Table 3. For sake of simplicity control paths for age, sex and substance use are not represented in this figure. * = $p < .05$.

Epigenome-wide association analysis of sensation-seeking

Results from the EWAS showed that that none of the probes reached the critical significance level of $p < 1.3 \times 10^{-7}$. However, 20 methylation probes were nominally significantly ($p < 5 \times 10^{-5}$, depicted in Table 1) differentially methylated in children with stable high sensation-seeking scores compared to the rest of the sample. See Table S3 for detailed information about the exact positions and the effects of the probes. These probes were annotated to 12 genes, see Table S3. The most strongly associated probe, cg16495212, is located in *CPEB1*, which is broadly expressed in brain tissue (see Table S4) and plays an important role in synaptic efficacy, plasticity and hippocampal-dependent learning (Ivshina et al., 2014). *CPEB1* is also broadly expressed in the uterus and testis, important tissues for the production of gonadal hormones, which have been implicated in reward sensitivity (Harden et al., 2018) and in the dopaminergic system (Kuhn et al., 2010). Other annotated genes include *TEKT1*(cg12685753) and *SNED1*(cg08233654), also both predominantly expressed in the testis and uterus; *WSCD1* (cg04869532), broadly expressed in the brain and *TNXB* (cg19609334) and *PRR14* (cg00879206) two genes that have been implicated in risk-taking behavior in a previous genome wide analysis study (Linnér et al., 2018). To investigate whether the DMPs were located on regulatory sites of the chromatin, DMPs were uploaded in Genome Browser for functional characterization, based on ENCODE data on regulatory elements (http://genome.ucsc.edu/ENCODE/). All DMPs overlapped with histone marks; 55% coincide with transcription factor binding sites; and 80% were located within DNAse I hypersensitive clusters. Overall, 40% of DMPs were mapped to all three regulatory elements, see Table S3, indicating that a great part of the DMPs have a functional relevance. After running the suggestive hits through the mQTL database of the GoDMC consortium study, 60% of the suggestive hits showed evidence to be associated with known mQTL.

Sensation-seeking DNAm patterns and the development of delinquency

Sensation-seeking-related cumulative DNAm risk scores were computed based on the 20 suggestive hits (i.e., the probed that came most close to the critical value of $p < 1.3 \times 10^{-7}$, which were all probes with $p < 5 \times 10^{-5}$). Correlations between the cumulative DNAm risk score and all other study variables are presented in Table 2. To test the association of sensation-seeking-related DNA methylation patterns and late adolescent delinquency, a path model was fitted. We included the DNAm risk scores at birth, age 7 and age 15–17 years in the model to be able to assess change in DNAm over time. Next, we included delinquency at age 17–19, our outcome measure, and antisocial activities at age 8 years, to be able to control for possible reverse effects. Pathways were controlled for sex and substance use. This model showed good fit to the data: $\chi^2(11) = 18.615$, $p = .07$; CFI = 0.978; TLI = 0.940; RMSEA = 0.028, 90% CI [0.000–0.049]. Results showed that DNAm risk scores at age 15–17 years were related to delinquency at age 17–19 years, with a small effect size ($\beta = 0.146$, $B = 0.042$, SE = 0.015, $p = .007$).

Sensation-seeking DNAm patterns linking childhood victimization to adolescent delinquency

Our third research question focused on the link between childhood victimization – and sensation-seeking DNAm correlates and the

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Table 1. EWAS top 20 probes: Methylation at age 15–17 and sensation-seeking profile (high vs. others)

Probe	*p*-value	*t*-statistic	Chromosome	Annotated gene
cg16495212	2.55E-06	−4.74	chr15	*CPEB1*
cg26014401	3.56E-06	−4.67	chr22	
cg04626491	5.36E-06	−4.58	chr6	
cg17122157	9.95E-06	4.44	chr21	
cg15763984	1.16E-05	4.41	chr4	*KIAA1530/UVSSA*
cg03806812	1.27E-05	−4.39	chr2	
cg23684139	1.73E-05	4.32	chr14	
cg12685753	1.91E-05	−4.30	chr17	*TEKT1*
cg09965297	2.06E-05	4.28	chr16	*FANCA*
cg27128883	2.68E-05	4.22	chr8	
cg20728696	2.70E-05	−4.22	chr11	*INS-IGF2;IGF2*
cg26329692	2.83E-05	4.21	chr17	*NT5C*
cg04869532	3.27E-05	−4.18	chr17	*WSCD1*
cg08233654	3.41E-05	4.17	chr2	*SNED1*
cg19609334	3.93E-05	4.13	chr6	*TNXB*
cg08348186	4.07E-05	4.12	chr17	*C17orf54/LINC00469*
cg00879206	4.35E-05	−4.11	chr16	*PRR14*
cg26153885	4.37E-05	4.11	chr21	*KCNE2*
cg06098368	4.84E-05	4.08	chr7	
cg00782200	4.94E-05	−4.74	chr2	

possible indirect association between childhood victimization, sensation-seeking DNAm correlates and delinquency. Childhood victimization between age 8–9 years was added to the model (see Figure 1). Results of all path estimates are presented in Table 3. This model showed adequate fit to the data: $\chi^2(21) = 41.317$, $p = .005$; CFI = 0.961; TLI = 0.909; RMSEA = 0.033, 90% CI [0.018–0.047]. Results show that the exposure to childhood victimization around age 8–9 years was associated with increases in DNAm risk score at age 15–17 years, with a small effect size ($\beta = 0.082$, $B = 0.31$, SE = 0.14, $p = .02$), which, in turn, was associated with increased delinquency at age 17–19 years ($B = 0.04$, SE = 0.02, $\beta = 0.141$, $p < .01$). The indirect effect of victimization to delinquency via change in sensation-seeking-related DNAm risk score was significant ($B = 0.012$; 95% CI [0.002–0.036]. For a graphical representation of the results, see Figure 1. For all path estimates in the model, see Table 3.

Discussion

This study was set out to identify DNAm patterns related to sensation-seeking, to investigate the association between these DNAm patterns with delinquency in late adolescence, and to investigate whether experiences of childhood victimization were related to sensation-seeking DNAm patterns and the development of delinquent behavior in adolescence. Key findings of the present study were threefold. First, the EWAS on sensation-seeking did not reveal significant probes but we followed up on 20 suggestive sites that showed up to be marginally significantly differential methylated in children who show stable high sensation-seeking at age 11 and age14. Second, these differential methylated loci, collectively, were related to the development of delinquent behavior in late adolescence. Third, early experiences of childhood victimization were associated with these sensation-seeking-related DNA methylation patterns and indirectly with the development of delinquency.

Epigenetic variation associated with sensation-seeking

To our knowledge, this is the first study to examine the epigenomic profile of children who show stable high sensation-seeking across time. The EWAS revealed no differential methylated loci reaching $p < 1.3 \times 10^{-7}$. However, 20 suggestive hits reaching $p < 5 \times 10^{-5}$ were identified in children who show stable high sensation-seeking behavior. These loci were annotated to 12 different genes and were related to a range of biological processes, including neural processes related to reward sensitivity. The locus with the highest difference in methylation levels between high versus non-high sensations seekers was *CPEB1*. *CPEB1* is highly expressed in brain tissue, including regions implicated in reward-seeking behavior (e.g., in the nucleus accumbens, substantia nigra and the hippocampus). This finding is in accordance with the found link between reward sensitivity and sensation-seeking behavior (Gjedde et al., 2010) and might indicate that differential methylation of this gene underlies differences in reward sensitivity. Other relevant differentially methylated loci were located at *TEKT1* (cg12685753) and *SNED1*(cg08233654) that are broadly expressed in the testis and uterus, which are important tissues for gonadal hormone production and transmission. Dysregulations of these gonadal hormones, such as testosterone, have been linked to sensation-seeking behavior before (Aluja & Torrubia, 2004; Campbell et al., 2010). However, those functional annotations have to be interpreted with caution. The specific functionality of those genes was not the focus of the current study and to understand the specific biological function of those genes as well as their interaction and the link with sensation-seeking behavior, more in depth research into the functionality of those genes is needed.

Sensation-seeking-related DNA methylation patterns, delinquency and childhood victimization

To investigate the potential role of these sensation-seeking-related DNA methylation patterns in a developmental perspective, we focused our research on two pathways of interest. First, we showed that changes in DNA methylation patterns between age 7 and age 15–17 related to sensation-seeking, are associated with the development of delinquency in late adolescence. Second, we showed that early experiences of childhood victimization are associated with changes in those sensation-seeking-related DNA methylation patterns. Moreover, we found that childhood victimization was indirectly related to delinquency via changes in those sensation-seeking-related DNAm patterns. The finding that a biological correlate of sensation-seeking is related to the development of delinquency is in line with previous research where the link between sensation-seeking and delinquency is shown (Harden et al., 2012; Mann et al., 2015). In addition, the finding that early adverse childhood experiences are related to a biological correlate of sensation-seeking is also in line with previous research where the association between childhood victimization and sensation-seeking have been documented (Bornovalova et al., 2008). In this study, we provide evidence for the proposed developmental pathway from childhood victimization via sensation-seeking to delinquency (Van Goozen et al., 2008).

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Table 2. Correlations between study variables

	Variables	1	2	3	4	5	6	7	8
1	Sensation-seeking age 11	–							
2	Sensation-seeking age 14	0.61**	–						
3	Antisocial activities age 8	0.17**	0.19**	–					
4	Delinquency age 18	0.22**	0.30**	0.18**	–				
5	DNAm birth	0.04	0.08*	−0.07	−0.02	–			
6	DNAm age 7	0.09**	0.18**	0.01	0.02	0.31**	–		
7	DNAm age 15–17	0.07*	0.18**	0.02	0.11**	0.30**	0.47**	–	
8	Victimization (birth – 7)	0.07*	0.07*	0.09**	0.10*	0.04	0.04	0.03	–
9	Victimization (8–10)	0.07*	0.02	0.17**	0.09*	−0.02	0.08*	0.08*	0.25**

Note. * $p < .05$; ** $p < .01$.

Table 3. Path estimates of the full indirect effect model including study and control variables

			β	B	95% CI
Sensation-seeking DNA methylation risk scores					
DNAm birth	→	DNAm 7	−0.09	−0.10	[−0.32, 0.10]
Victimization birth - 7	→	DNAm 7	0.03	0.10	[−0.17, 0.37]
DNAm7	→	DNAm 15–17	0.23	0.28**	[0.15, 0.39]
Antisocial activity 8	→	DNAm 15–17	0.04	0.09	[−0.07, 0.25]
Victimization 8–9	→	DNAm 15–17	0.08	0.31*	[0.04, 0.57]
Age	→	DNAm 15–17	−0.01	−0.04	[−0.29, 0.21]
Tobacco use 14	→	DNAm 15–17	−0.01	−0.02	[−0.41, 0.36]
Cannabis use 14	→	DNAm 15–17	−0.02	−0.12	[−0.78, 0.59]
Antisocial activities and Delinquency					
DNAm 7	→	Antisocial activity 8	0.03	0.01	[−0.03, 0.06]
Victimization birth - 7	→	Antisocial activity 8	0.07	0.12	[−0.03, 0.30]
Sex	→	Antisocial activity 8	−0.14	−0.40**	[−0.60, −0.20]
Antisocial activity 8	→	Delinquency 17–19	0.11	0.07†	[−0.00, 0.15]
DNAm 15–17	→	Delinquency 17–19	0.14	0.04*	[0.01, 0.07]
Random intercept DNAm	→	Delinquency 17–19	−0.01	0.00	[−0.05, 0.04]
Victimization 8–9	→	Delinquency 17–19	0.02	0.02	[−0.06, 0.10]
Sex	→	Delinquency 17–19	−0.18	−0.32**	[−0.46, −0.19]
Childhood victimization					
DNAm birth	→	Victimization birth - 7	0.02	0.00	[−0.03, 0.04]
Sex	→	Victimization birth - 7	−0.13	−0.22**	[−0.32, −0.11]
Victimization birth - 7	→	Victimization 8–9	0.23	0.24**	[0.16, 0.33]
DNAm 7	→	Victimization 8–9	0.07	0.02†	[0.00, 0.05]
Antisocial activities 8	→	Victimization 8–9	0.14	0.08**	[0.04, 0.12]
Sex	→	Victimization 8–9	−0.01	−0.02	[−0.13, 0.09]

Note. † $p < .10$, * $p < .05$, ** $p < .01$.

Moreover, we extended earlier findings by showing that these associations might also be present at the epigenetic level. Especially the finding that DNA methylation correlates of sensation-seeking are related to both a relevant environmental factor and a developmental maladaptive outcome shows that these DNA methylation patterns are a promising avenue for further research into the working mechanisms behind the possible cascadic events of childhood victimization, via sensation-seeking to the development of delinquency (Van Goozen et al., 2008). Further research into the specific biological mechanisms related to the identified probes here will generate important information on the working mechanisms behind

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the link between sensation-seeking, childhood victimization and delinquency.

Limitations and future directions

This study has several limitations that should be considered while interpreting the results. First, the results of our study are based on a modestly sized population-based sample of youth and to be able to test the robustness of our findings replication on other samples is needed. However, to date there is, to our knowledge no other sample that assess DNA methylation in relation to sensation-seeking in the same age period as we did. This led to another limitation, that we were not able to use external weights to calculate our sensation-seeking DNAm risk scores (Hüls & Czamara, 2020) which can increase the risk of the observed association reported being influenced by overfitting. As such, our findings should be considered as hypothesis-generating and replication studies are needed to draw more conclusive interpretations. Second, it should be kept in mind that our findings are based on DNAm from peripheral samples. For obvious reasons, we could not test whether the DNAm results found in blood samples mirrored those in brain tissues. However, Hannon et al. (2015) showed that a considerable proportion of DNAm sites show crosstissue concordance. Third, in this study we assessed a variety score of delinquent acts and we did not investigate frequency of delinquency. Although variety and frequency scores are thought to be highly concordant, specific (environmental) factors may have different influences on variety versus frequency scores (Monahan & Piquero, 2009) and future studies may want to investigate whether childhood victimization is also related to the frequency of delinquent acts via sensation-seeking and DNA methylation changes. In addition, here we show a specific link between a possible sensation-seeking-related biomarker and delinquency. However, the sensation-seeking DNAm risk score might also be related to the development of various other forms of impulse control behaviors such as for example oppositional behavior, or even general risk-taking behavior or mild rule-breaking behavior such as truancy. Future research is important to further unravel the possible role of the sensation-seeking biomarker in a range of impulse control behaviors and mild deviancy throughout adolescence. Fourth, 60% of the suggestive hits found in this study are associated with known mQTL and consequently likely to be under significant genetic control. The identified SNPs are important to further investigate in relation to sensation-seeking and delinquency, in order to disentangle potential genetic and environmental influences on the development of delinquency (via sensation-seeking). We note that we were unpowered to carry out such analyses. Fifth, despite the fact that we used longitudinal data and our DNAm is measured prospectively to delinquency measures and was controlled for potential reverse effects of prior antisocial behavior on DNAm changes, it is not possible to establish causality in the course of events. Finally, we focused exclusively on DNA methylation, while other epigenetics processes, such as histone modification are also likely to play a role.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579422000049.

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

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