Correspondence

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Sensitive Periods for the Effect of Childhood Adversity on DNA Methylation: Updated Results From a Prospective, Longitudinal Study

To the Editor:

Childhood adversity is a potent but preventable risk factor for many physical and mental illnesses (1–3). Although the mechanisms underlying these associations remain unknown, DNA methylation (DNAm) and other epigenetic modifications have emerged as potential pathways for the biological embedding of early-life environments (4).

In a recent publication (5), we showed that 7 types of childhood adversity had time-dependent effects on DNAm at age 7 years. Data came from the Avon Longitudinal Study of Parents and Children (ALSPAC) and were analyzed using the structured life course modeling approach (SLCMA) (6,7). We identified potential sensitive periods, largely occurring in the first 3 years of life, when childhood adversity exposure appeared to have greater effects on DNAm (5).

Since the publication of this research, several improvements were made to increase the accuracy and robustness of the results. First, the ALSPAC investigators revised the individual-level DNAm data available to researchers. DNAm data are now derived from processing pipelines that use functional normalization and preprocessing approaches to reduce technical variation and false positives, increase statistical power, and reduce heterogeneity in downstream meta-analyses (8). Second, we refined the statistical framework of the SLCMA (9), as it had not been applied to high-dimensional data prior to our work in the ALSPAC (5). Specifically, we improved the estimation methods that the SLCMA uses in high-dimensional settings to reduce the likelihood of false positives and obtain higher confidence associations. Elsewhere, we describe how these updates shifted the original results, with an emphasis on how even modest changes to epigenetic data and analytic approaches can shape the replicability of epigenome-wide associations (10). In brief, the updated results recapitulate the main finding by Dunn *et al.* (5) in showing that sensitive periods in development play an important role in the biological embedding of childhood adversity. There were other similarities: the magnitude and direction of adversity-to-DNAm associations were stable across analyses, as were the selected life course hypotheses for most CpGs. However, and as expected, different top loci were identified at conventional *p*-value thresholds. For these reasons, we urged investigators performing the SLCMA or a traditional epigenome-wide association study to extend their replication analyses beyond traditional metrics of significance alone (10).

In this report, we focus on the biological relevance of this updated set of top loci. Our updated analyses revealed 46 loci showing time-dependent associations between childhood adversity and DNAm levels at a 5% false discovery rate (FDR) (Figure 1; Table 1) (10). As previously shown (5), we continued to find evidence in support of sensitive periods among this new set of loci. However, exposure to adversity during early childhood, meaning between ages 3 and 5, was most frequently associated with DNAm differences (39 of 46 top loci), rather than exposure to adversity between ages 0 and 3, as

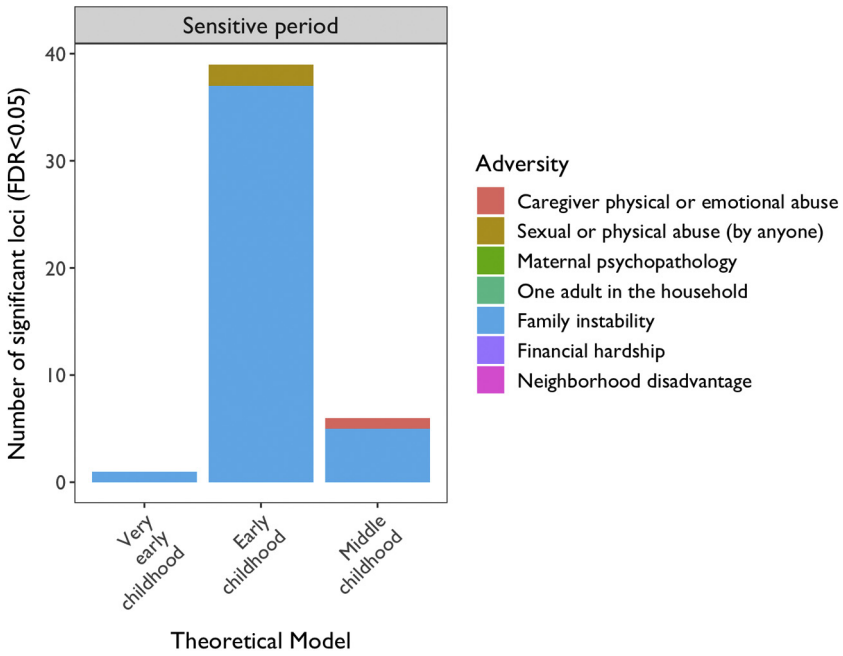

Figure 1. Frequency of life course model selection for each type of childhood adversity. The number of loci for which adversity predicted DNA methylation levels at 5% false discovery rate (FDR) is shown here. Sensitive period hypotheses, or theoretical models, included very early (0–3 years), early (3–5 years), or middle childhood (6–7 years). Additive hypotheses included recency and accumulation (not shown, as there were no associations at an FDR $<$ .05).

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Table 1. Time-Dependent Associations Between Childhood Adversity and DNAm at 7 Years of Age

Adversity	CpG	Hypothesis (Age in Years)	DNAm (Unexposed)[a]	DNAm (Exposed)[b]	DNAm Difference[c]	Effect Estimate[d]	SE	*p* Value	FDR	Nearest Gene	pLI[e]
Caregiver physical or emotional abuse (n = 698)	cg12023170[f]	Middle childhood (6)	0.091	0.125	0.034	0.034	0.005	1.25×10^{-9}	5.48×10^{-4}	*TCEA3*	9.66×10^{-4}
Physical or sexual abuse (n = 681)	cg20369299	Early childhood (4.75)	0.724	0.628	−0.096	−0.091	0.018	2.12×10^{-7}	4.67×10^{-2}	*MIR4776-1*	NA
	cg13817046[f]	Early childhood (4.75)	0.483	0.411	−0.072	−0.075	0.013	5.07×10^{-8}	2.23×10^{-2}	*PRR15*	4.47×10^{-1}
Family instability (n = 681)	cg04079399[f]	Very early childhood (2.5)	0.891	0.870	−0.021	−0.020	0.004	6.15×10^{-8}	8.79×10^{-3}	*LINC00398*	NA
	cg01407460[f]	Early childhood (4.75)	0.025	0.021	−0.004	−0.004	0.001	3.10×10^{-8}	6.82×10^{-3}	*CORO7-PAM16*	1.63×10^{-12}
	cg01587190	Early childhood (4.75)	0.067	0.078	0.010	0.011	0.002	1.11×10^{-6}	2.53×10^{-2}	*ERCC2*	3.14×10^{-13}
	cg22346081	Early childhood (4.75)	0.863	0.844	−0.019	−0.019	0.004	3.48×10^{-6}	3.92×10^{-2}	*SORT1*	1.00
	cg14948379	Early childhood (4.75)	0.855	0.822	−0.034	−0.035	0.006	4.10×10^{-7}	2.07×10^{-2}	*MRPS9*	3.36×10^{-6}
	cg17134302	Early childhood (4.75)	0.851	0.834	−0.017	−0.018	0.004	2.91×10^{-6}	3.92×10^{-2}	*FBXO36*	3.23×10^{-6}
	cg22060367	Early childhood (4.75)	0.887	0.867	−0.020	−0.020	0.004	1.84×10^{-7}	1.62×10^{-2}	*TANK*	9.44×10^{-1}
	cg01100868	Early childhood (4.75)	0.903	0.885	−0.018	−0.018	0.003	2.07×10^{-6}	3.37×10^{-2}	*SLIT3*	9.92×10^{-1}
	cg16338178	Early childhood (4.75)	0.830	0.800	−0.030	−0.030	0.006	3.22×10^{-6}	3.92×10^{-2}	*LINC01845*	NA
	cg27639644	Early childhood (4.75)	0.858	0.827	−0.031	−0.031	0.006	5.64×10^{-7}	2.07×10^{-2}	*RAB9BP1*	NA
	cg00943585	Early childhood (4.75)	0.834	0.785	−0.049	−0.048	0.010	3.48×10^{-6}	3.92×10^{-2}	*LOC154449*	NA
	cg27061903	Early childhood (4.75)	0.052	0.070	0.018	0.018	0.003	2.23×10^{-6}	3.51×10^{-2}	*COX7A2*	3.76×10^{-1}
	cg01023798	Early childhood (4.75)	0.865	0.839	−0.026	−0.026	0.005	1.54×10^{-6}	2.82×10^{-2}	*SDK1*	5.02×10^{-3}
	cg02886132	Early childhood (4.75)	0.885	0.868	−0.017	−0.017	0.004	1.18×10^{-6}	2.53×10^{-2}	*TYW1B*	8.12×10^{-9}
	cg10571837	Early childhood (4.75)	0.901	0.888	−0.014	−0.014	0.003	5.35×10^{-7}	2.07×10^{-2}	*ZNF713*	1.12×10^{-3}
	cg23184756	Early childhood (4.75)	0.847	0.822	−0.025	−0.025	0.005	4.89×10^{-7}	2.07×10^{-2}	*ZNF735*	NA
	cg01654242	Early childhood (4.75)	0.802	0.752	−0.050	−0.050	0.009	1.95×10^{-6}	3.31×10^{-2}	*FBXO43*	1.50×10^{-4}
	cg16231917	Early childhood (4.75)	0.211	0.268	0.057	0.057	0.012	4.09×10^{-6}	4.39×10^{-2}	*PVT1*	NA
	cg27457457[f]	Early childhood (4.75)	0.695	0.623	−0.073	−0.075	0.013	2.77×10^{-8}	6.82×10^{-3}	*RIPK2*	5.54×10^{-1}
	cg13876553	Early childhood (4.75)	0.812	0.775	−0.037	−0.039	0.008	3.88×10^{-6}	4.27×10^{-2}	*DOCK8*	1.35×10^{-4}
	cg21172807	Early childhood (4.75)	0.104	0.128	0.024	0.024	0.005	3.14×10^{-6}	3.92×10^{-2}	*BRINP1*	9.95×10^{-1}
	cg05886789	Early childhood (4.75)	0.845	0.817	−0.028	−0.029	0.005	2.57×10^{-7}	1.89×10^{-2}	*PLXDC2*	6.13×10^{-1}
	cg07206497	Early childhood (4.75)	0.876	0.854	−0.022	−0.023	0.004	1.16×10^{-6}	2.53×10^{-2}	*USP6NL*	1.02×10^{-1}
	cg08971940	Early childhood (4.75)	0.784	0.741	−0.043	−0.045	0.009	1.73×10^{-6}	3.05×10^{-2}	*FZD8*	NA
	cg01504589	Early childhood (4.75)	0.851	0.809	−0.043	−0.042	0.008	8.53×10^{-7}	2.53×10^{-2}	*ZC3H12C*	9.99×10^{-1}
	cg22011436	Early childhood (4.75)	0.855	0.826	−0.029	−0.030	0.005	1.21×10^{-6}	2.53×10^{-2}	*SYT13*	2.20×10^{-1}
	cg26997966	Early childhood (4.75)	0.853	0.829	−0.025	−0.025	0.005	3.14×10^{-7}	1.97×10^{-2}	*RNF214*	8.30×10^{-1}
	cg00967695	Early childhood (4.75)	0.885	0.847	−0.038	−0.039	0.007	1.30×10^{-6}	2.56×10^{-2}	*CHFR*	6.37×10^{-1}
	cg01267076	Early childhood (4.75)	0.865	0.841	−0.024	−0.024	0.004	1.34×10^{-6}	2.56×10^{-2}	–	–
	cg13706680[f]	Early childhood (4.75)	0.881	0.859	−0.021	−0.022	0.004	7.98×10^{-8}	8.79×10^{-3}	*KITLG*	5.09×10^{-1}
	cg14637285	Early childhood (4.75)	0.855	0.828	−0.027	−0.027	0.005	2.82×10^{-6}	3.92×10^{-2}	–	–
	cg12188526	Early childhood (4.75)	0.889	0.873	−0.016	−0.016	0.003	3.24×10^{-6}	3.92×10^{-2}	*SNORD56B*	NA
	cg01841772	Early childhood (4.75)	0.806	0.772	−0.035	−0.036	0.009	4.52×10^{-6}	4.63×10^{-2}	*NOB1*	8.61×10^{-8}
	cg09305491	Early childhood (4.75)	0.913	0.899	−0.015	−0.015	0.003	1.02×10^{-6}	2.53×10^{-2}	*PRKCB*	1.00
	cg27567416	Early childhood (4.75)	0.891	0.876	−0.015	−0.015	0.003	1.12×10^{-6}	2.53×10^{-2}	*ADCY9*	9.74×10^{-1}

Table 1. Continued

Adversity	CpG	Hypothesis (Age in Years)	DNAm (Unexposed)[a]	DNAm (Exposed)[b]	DNAm Difference[c]	Effect Estimate[d]	SE	*p* Value	FDR	Nearest Gene	pLI[e]
	cg05353659	Early childhood (4.75)	0.897	0.881	−0.016	−0.017	0.003	1.02×10^{-6}	2.53×10^{-2}	*G6PC*	1.81×10^{-3}
	cg11438065	Early childhood (4.75)	0.901	0.886	−0.015	−0.016	0.003	5.06×10^{-7}	2.07×10^{-2}	*ZNF780B*	3.90×10^{-13}
	cg14401897	Early childhood (4.75)	0.830	0.784	−0.046	−0.044	0.009	2.34×10^{-6}	3.56×10^{-2}	*SBNO2*	2.44×10^{-2}
	cg06770536	Middle childhood (5.75)	0.740	0.688	−0.052	−0.051	0.010	4.31×10^{-6}	4.51×10^{-2}	*C1orf127*	1.33×10^{-5}
	cg26848593	Middle childhood (5.75)	0.025	0.030	0.005	0.005	0.001	1.10×10^{-6}	2.53×10^{-2}	*UBOX5*	1.79×10^{-3}
	cg17719337	Middle childhood (5.75)	0.036	0.045	0.009	0.009	0.002	2.48×10^{-6}	3.65×10^{-2}	*CNPY1*	8.75×10^{-3}
	cg19569074	Middle childhood (6.75)	0.673	0.594	−0.079	−0.079	0.017	3.03×10^{-6}	3.92×10^{-2}	*SDK1*	5.02×10^{-3}
	cg10940545	Middle childhood (6.75)	0.819	0.750	−0.069	−0.073	0.015	3.47×10^{-6}	3.92×10^{-2}	*BRI3BP*	1.25×10^{-1}

DNAm, DNA methylation; FDR, false discovery rate; NA, nearest gene was not in the Exome Aggregation Consortium list.
[a]Mean DNAm levels in individuals unexposed to adversity.
[b]Mean DNAm levels in individuals exposed to adversity.
[c]Differences in DNAm levels between exposed and unexposed individuals.
[d]Effect estimates from linear regression of exposure to adversity and DNAm, adjusting for cell types, child sex, race/ethnicity, birth weight, maternal education, maternal age at birth, number of previous pregnancies, and maternal smoking during pregnancy.
[e]Probability of intolerance to loss of function from the Exome Aggregation Consortium for the gene nearest to the significant locus (12).
[f]Significant at a genome-wide Bonferroni-corrected threshold $p < 1.13 \times 10^{-7}$.

previously reported (5). Exposure to adversity during other sensitive periods before age 7 was associated with DNAm differences at 7 loci (1 for very early childhood and 6 for middle childhood). An accumulation model (i.e., the cumulative number of exposed time points) or a recency model (i.e., the cumulative number of exposed time points from ages 0 to 7 weighted by exposure timing) was not associated with any DNAm differences. Childhood adversity was mostly associated with decreased DNAm levels (89.1% negative effect estimates; $\chi^2_1 = 28.2$; $p = 1.1 \times 10^{-7}$). On average, children exposed to adversity showed a 3.1% absolute difference in DNAm levels (range, 0.4%–9.6%).

Most associations in the updated results came from family instability (43 loci), followed by sexual/physical abuse (2 loci) and caregiver physical/emotional abuse (1 locus). Exposures to maternal psychopathology, neighborhood disadvantage, or 1 adult in the household were not associated with any DNAm differences (FDR $<$ .05). We did not detect any of these adversity-DNAm associations in DNAm measured from cord blood at birth, suggesting that our observed differences in DNAm likely resulted from postnatal exposures. Similar to our earlier study, we observed more associations than a traditional epigenome-wide association study comparing ever with never-exposed individuals (10).

From a biological standpoint, FDR-significant loci were more often located in predicted enhancer regions ($\chi^2_1 = 10.6$; $p = 1.1 \times 10^{-3}$) and slightly less often located in gene promoters ($\chi^2_1 = 1.82$; $p = .18$). Top loci were also more likely to be away from, rather than inside or near, CpG islands compared with all loci tested ($\chi^2_5 = 22.1$; $p = 5.0 \times 10^{-4}$). These findings suggest that enhancers and regions of low CpG density may be more responsive to childhood adversity than CpG-dense regions.

To probe the biological relevance of FDR-significant loci, we examined the correlation between DNAm levels in blood and brain using publicly available data (11). Two-thirds of loci (30 of 46) showed small but positive correlations between blood and brain region DNAm (prefrontal cortex: $r_{avg\_positive} = 0.13$; entorhinal cortex: $r_{avg\_positive} = 0.13$; superior temporal gyrus: $r_{avg\_positive} = 0.15$; cerebellum: $r_{avg\_positive} = 0.1$), providing some evidence that adversity-induced changes in blood could reflect parallel changes in the brain.

We next assessed the biological functions of genes near FDR-significant loci ($n = 42$ genes) using the DAVID gene ontology tool, identifying 25 clusters of processes involved in metabolism, cell death, and epigenetic regulation (12,13). Only 1 cluster related to hemopoeisis and immune development was enriched in our top loci ($p = .024$), highlighting a potential relationship between childhood adversity and immune function, consistent with prior literature (14).

To further understand the broader epigenetic context of FDR-significant loci, we investigated their likely chromatin context (15). There was no overrepresentation of DNase I–hypersensitive regions or coincident histone H3 marks in top loci (FDR $<$ .05). However, top loci were slightly overrepresented within H3 marks in primary T cells from cord blood ($p = .007$), further linking childhood adversity to immune functioning.

Finally, 7 FDR-significant loci were located in genes with high probabilities of intolerance to loss-of-function variation (pLI $>$ 0.9) (16), suggesting that certain genes associated with

childhood adversity may be under higher evolutionary constraint for human survival and reproduction (Table 1).

Overall, our latest results parallel the primary finding from our original article (5) in showing that sensitive periods appear to play an important role in the DNAm differences associated with exposure to postnatal adversity. However, current findings—for the FDR-significant loci specifically—emphasize the salience of adversity exposure during early childhood (between ages 3 and 5), rather than exposure during very early childhood (before age 3) as previously identified. We think that this shift likely reflects a more robust and reproducible set of loci thanks to the implementation of methods explicitly designed to reduce false positives (8,9). However, it is also possible that both early and very early childhood are sensitive periods with partially overlapping effects that may be difficult to disentangle in a single analysis. The analysis of sensitive periods for the biological embedding of early-life environments is a relatively novel and emerging field. Thus, the evolution of methods and findings is not unsurprising. It is also reminiscent of the early days of genome-wide association studies, when analyses of psychiatric disorders yielded few associations, a problem eventually remedied by larger sample sizes and methodological advances (17,18).

Perhaps most importantly, the partial dependence of some findings on technical details is not at all new to epidemiology. Such findings emphasize the importance of cross-examining evidence (for all findings) relative to existing literature, complementary statistical methods, diverse populations, and alternative measurements of exposures and outcomes. Our findings also point to the urgent need for meta-analyses that combine data across multiple cohorts to increase statistical power to detect associations and replicate findings of sensitive periods. Further studies are also needed to assess the persistence of effects we have identified into adolescence and adulthood, as well as their role in psychiatric disease risk. Ultimately, continued efforts will help determine when and how early-life experiences influence epigenetic mechanisms and health across the life course.

Alexandre A. Lussier
Yiwen Zhu
Brooke J. Smith
Andrew J. Simpkin
Andrew D.A.C. Smith
Matthew J. Suderman
Esther Walton
Caroline L. Relton
Kerry J. Ressler
Erin C. Dunn

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Article Information

From the Psychiatric and Neurodevelopmental Genetics Unit (AAL, YZ, BJS, ECD), Center for Genomic Medicine, Massachusetts General Hospital; Department of Psychiatry (AAL, KJR, ECD), Harvard Medical School; and Department of Epidemiology (YZ), Harvard T.H. Chan School of Public Health, Boston; Stanley Center for Psychiatric Research (AAL, ECD), Broad Institute of MIT and Harvard; and Center on the Developing Child (ECD), Harvard University, Cambridge; and McLean Hospital (KJR), Belmont, Massachusetts; School of Mathematics, Statistics and Applied Mathematics (AJS), National University of Ireland, Galway, Ireland; Mathematics and Statistics Research Group (ADACS), University of the West of England; and MRC Integrative Epidemiology Unit (MJS, CLR), Population Health Sciences, Bristol Medical School, University of Bristol, Bristol; and the Department of Psychology (EW), University of Bath, Bath, United Kingdom.

Address correspondence to Alexandre A. Lussier, Ph.D., at alussier@mgh.harvard.edu, or Erin C. Dunn, Sc.D., at edunn2@mgh.harvard.edu.

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