Adolescent depression linked to socioeconomic status? Molecular approaches for revealing premorbid risk factors

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The means by which social environmental exposures influence risk of mental disorders is a persistent and still open question. A key candidate mechanism for the biologic mediation of environmental effects involves epigenetic factors, which regulate gene function without altering underlying DNA sequence. Recent work has shown that environmental exposures such as childhood abuse, family history of mental disorder, and low socioeconomic status (SES) associate with differential DNA methylation (5mC) – a relatively stable, but modifiable, epigenetic factor. However, the longitudinal relation among SES, 5mC, brain function, and risk of depression remains to be elucidated. Here, we briefly review literature relevant to these associations and discuss recent findings that, for the first time, prospectively demonstrate sequential links between low SES, changes in 5mC, changes in brain function, and risk of depression in a cohort of adolescents.

Keywords:
biomarker; epigenetics; longitudinal study

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Abbreviations:
5mC, 5-methylcytosine; **GWAS,** genome-wide association studies; **SES,** socioeconomic status.

Introduction

Major depressive disorder (MDD) is a debilitating psychiatric condition with a substantial public health impact. In the United States, current lifetime estimates of MDD stand at approximately 16.6% [1], and costs attributable to the disorder are estimated at ~98.9 Billion dollars per year [2]. The disorder frequently co-occurs with a range of physical conditions, including diabetes, asthma, heart disease, and arthritis, among others [3], further exacerbating its burden. Risk of depression begins to increase markedly during adolescence [4], particularly among girls [5]. Globally, depression is the second leading cause of disability [6], and is predicted to become the leading cause by the year 2030 [7]. These facts underscore the urgent need to identify salient precursors of depression, in order to target those most at risk of developing the disorder and to enhance opportunities for preventive interventions.

Some of the most well-established risk factors for depression include low socioeconomic status (SES) and a positive family history of the disorder; embedded in the latter is the contribution of genetics. Although genome-wide association studies (GWAS) have yet to identify specific loci that reliably increase risk of depression [8], twin and family studies have firmly established a role for genetic variation in depression risk [9]. As previously noted [10], a challenge in current GWAS investigations of depression is the general lack of consideration of environmental variables, such as stressful life events or early life adversity (ELA), which may plausibly interact with extant variation either to reduce or increase risk of mental illness [11, 12]. Indeed, twin studies suggest that interplay between genetic and environmental factors is especially apparent during adolescence [13], a key period of depression risk emergence [5].

A substantial body of evidence has also implicated low SES as a risk factor for depression. Meta-analysis confirms that low SES individuals have higher odds of depression compared to

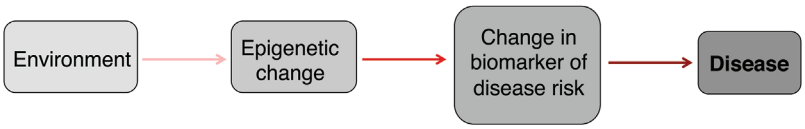

Figure 1. Schematic of a prospective study design that can increase the likelihood of establishing causality between epigenetically mediated environmental influences and disease outcome. Baseline measurements of environmental factors, coupled with subsequent longitudinal measurements of epigenetic and other biomarkers of disease, can do much to eliminate concerns of reverse causation that hamper causal inference in cross-sectional studies of disease risk.

high SES individuals [14]. Moreover, a dose-response relationship exists between SES and depression, such that with each additional year of education or percentage increase in relative income, the odds of being depressed decrease by up to three percent [14]. This general pattern holds for adolescents, where low SES is associated with increased risk of depression in large registry-based studies [15], and in systematic reviews of both western [16] and non-western [17] samples. Mechanistically, however, it remains unclear how low SES translates to increased risk of depression; that is how a social exposure, specifically low SES, gets "under the skin" and transduced into a mental disorder, specifically depression.

What is the biological impact of early life adversity?

Candidate mechanisms for effecting such biological mediation include modifiable genomic factors such as gene expression and epigenetics. Epigenetic mechanisms include DNA methylation, histone modifications, and non-coding RNAs, all of which serve to regulate gene function without changing underlying DNA sequences [18, 19]. DNA methylation (5mC) in particular has been well studied in relation to ELA (for recent reviews, see [20–22]), and has implicated many of the same pathways in relation to low SES as have studies of gene expression. For example, the lasting imprint of low SES has been demonstrated to affect blood gene expression patterns into adulthood, such that individuals with low early life SES show transcriptional profiles indicating increased pro-inflammatory and decreased glucocorticoid signaling, even after accounting for possibly higher SES circumstances during adulthood [23]. These profiles have previously been linked to adverse health outcomes, including chronic diseases such as cardiovascular disease, diabetes, and some cancers [24]. Similarly, exposure to low early life SES has been linked to 5mC differences when measured in adulthood [25, 26], in particular within inflammation- and stress-related genes [27, 28]. In some cases, these epigenetic differences have also been linked to gene expression differences, suggesting that the observed low SES differential 5mC has potential functional consequences [28]. Though compelling in terms of demonstrating links between SES exposures and persistent biological effects, what is generally missing from such investigations is a direct demonstration of the impact of such mechanisms on brain function, the target organ involved in depression.

A small but growing literature suggests that low early life SES is associated with differences in brain structure and brain activity. Recent work, for example, has demonstrated a link between SES and hippocampal volume, such that children from lower SES backgrounds show lower volume in the hippocampus [29–31], a brain region important for learning and memory. Moreover, a large ($n > 1{,}000$) sample including both children and adolescents identified multiple additional brain regions associated with SES gradients, including the insula, temporal pole, anterior and posterior cingulate, as well as the right dorsal frontal regions of the brain [32]. Importantly, exposure to childhood poverty has been associated with differential brain structure and activity patterns in adulthood, including altered default mode network activity [33] and lower orbitofrontal cortex volumes [34]; as with the genomic studies, these relationships – detected in adulthood – were independent of current SES, suggesting again a lasting biologic impact of early life adversity.

Taken together, these partially overlapping literatures indicate that both genetic and environmental factors, in particular low SES, shape risk of depression. In addition, evidence confirms that these factors are mediated by genomic molecular mechanisms such as gene expression and 5mC that can transduce externally experienced events into physiological consequences in part by activating (or deactivating) underlying gene sequences. Finally, results from these complementary studies demonstrate that the brain itself is impacted by adverse early life exposures in a manner salient to subsequent mental health (reviewed in [35, 36]). What remains unaddressed, however, are the sequential linkages between SES exposure, molecular mechanism, brain function, and mental health. Thus, the question remains: can we observe an effect of low SES on 5mC that can be demonstrated to show an effect on brain function and subsequent risk of depression? Moreover, can this effect be demonstrated in a manner in which these steps are shown in sequence and within a longitudinal framework; that is in a manner more likely to establish causality (Fig. 1)?

Can elevated premorbid risk of depression be indexed by epigenetic mechanisms?

These outstanding questions have recently been addressed through findings by Swartz et al. [37]. In this work, the authors sought to test whether differential gene 5mC, as a function of exposure to adversity, contributes to the subsequent emergence of individual risk of mental illness. More specifically, recognizing that low SES accounts for a high proportion of the population-level burden of mental health disorders, Swartz et al. honed in on the question of how low SES – a common, but non-specific risk factor – mechanistically confers risk of such disorders. For depression in particular, we know that the population-attributable fraction, that is, the proportion of cases that would not exist with the elimination of a particular

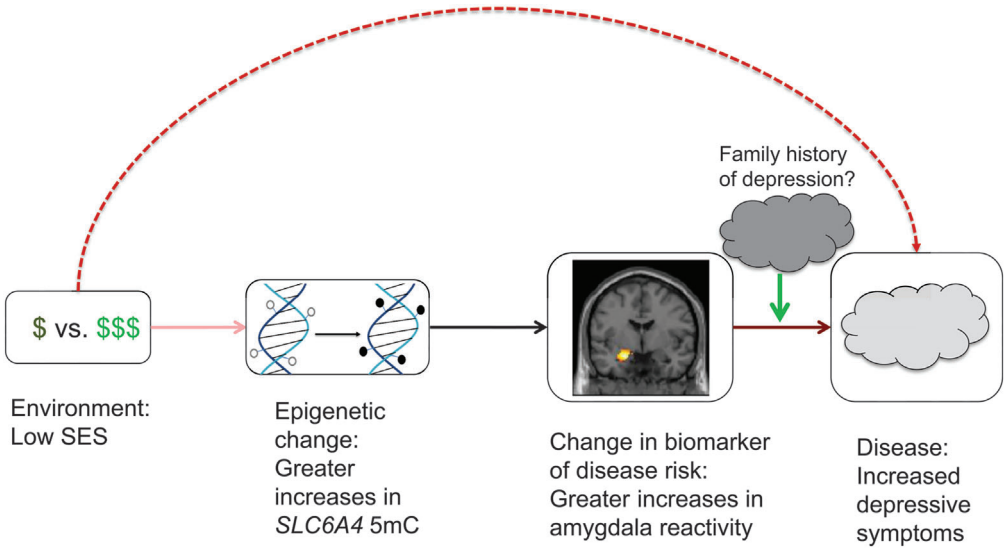

Figure 2. Prospective study design employed by Swartz et al. [37] to assess the epigenetically mediated impact of social environmental factors on risk of depression via changes in neural activity. Red arrows indicate prediction based on measurements taken from a baseline timepoint to a subsequent timepoint. Black arrow indicates prediction based on measurements taken from concurrent timepoints. Green arrow indicates a positive family history of depression. Adapted by permission from MacMillan Publishers Ltd: Swartz et al. [37].

exposure, is substantial for the effect of low SES on depression in adolescents (26–40%) [38], thus this question is particularly salient: while removing exposure to low SES would be ideal, another possible strategy to mitigate depression risk is to identify the biological processes mediating such risk, which will make it possible to target those processes for intervention.

Swartz et al. take on this task by leveraging longitudinal epigenetic, neuroimaging, and structured clinical interview data from a cohort of adolescents recruited into the Teen Alcohol Outcomes Study [39]. Honing in on a particular gene that has previously been associated with differential stress reactivity [40] and early life adversity [41] – the serotonin transporter promoter (*SLC6A4*) – they tested whether exposure to a number of environmental risk factors was associated with differential *changes* in 5mC in the promoter region, a gene region that serves to modulate gene function, including within this locus [42, 43]. Environmental risk factors of interest included emotional neglect during childhood, stressful life events (SLEs) during the prior year, and low SES, all of which had shown associations with differential *SLC6A4* 5mC in previous cross-sectional studies [44–46]. They further tested whether the extent of 5mC change was associated with a brain-level indicator of differential risk of depression, specifically changes in threat-related amygdala reactivity, which had been previously associated with depression risk in cross-sectional studies [47–49] and with age-related changes in reactivity in the absence of depression in the authors' prior work [50]. The final step of their model tested whether increased changes in threat-related amygdala reactivity predicted individual risk of depression, and whether the risk was specific to youth at high risk of this disorder (i.e. youths with a positive family history of depression). This research design, summarized in Fig. 2, enabled the investigators to test their hypothesis that prospective changes in DNA methylation that are associated with adverse environmental exposure are associated with changes in brain activity that then predict changes in depressive symptoms. By addressing these questions within the context of an adolescent cohort, Swartz et al. performed a focused testing of their hypotheses during a developmental period that coincides with the emergence of heightened risk of depression [4].

Low SES uniquely predicts greater *SLC6A4* methylation change and is linked to amygdala reactivity and future depressive symptoms in at-risk youth

Swartz et al. found that of all the environmental variables tested, only lower SES at the first wave of the study predicted greater increases in *SLC6A4* DNA methylation at wave 2. Other recent work has identified childhood maltreatment [51] and SLEs [46] to be associated with differential 5mC in this gene; however, it should be noted that these earlier studies focused largely on physical and sexual abuse, rather than emotional neglect, as tested in this study, and that objective ratings of SLEs were used as the predictor of interest, rather than subjective ratings as is frequently used in related work. Swartz et al.'s findings are in line with emerging work that has begun to demonstrate associations between low SES and higher 5mC in the *SLC6A4* promoter region [45, 52], although these previous findings have often been specific to subgroups within larger samples. Because genetic variation at this locus has been associated with susceptibility to depression and stressful life events across multiple studies (reviewed in [40]), the authors also controlled for the well-known tri-allelic variation in the *SLC6A4* promoter region in their models in a subset of their participants who had available genotype data, and retained this covariate in models that continued to show good fit to the data with its inclusion.

Second, greater increases in *SLC6A4* promoter region 5mC between waves 1 and 2 of the study predicted greater increases in threat-related amygdala activity over the same period of time. A relationship between increased promoter region 5mC at this locus and greater threat-related amygdala reactivity had been detected in a previous cross-sectional study by members of the same researcher team [53]. Similarly, this team's recent work

Recently in press

Table 1. Summary of studies that have analyzed saliva-derived DNA in relation to brain activity or structure

Year	First author	Molecular technique	Imaging technique	Locus of interest	Sample	Main methylation-imaging findings
2014	Nikolova [53]	Pyrosequencing	fMRI	*SLC6A4*	Discovery sample: 80 young adults; Replication cohort: TAOS study	Increased *SLC6A4* promoter region DNA methylation was associated with greater amygdala rectivity to threatening faces, independent of genotype.
2014	Vukojevic [69]	Pyrosequencing	fMRI	*NR3C1*	fMRI sample: 72 healthy subjects	Male participants with higher DNA methylation showed reduced picture recognition. A positive correlation between DNA methylation and recognition memory-related brain activity was also observed in males.
2015	Moser [70]	Pyrosequencing	fMRI	*BDNF*	46 mothers: 18 with Intimate Partner Violence (IPV)-related PTSD, 8 subthreshold PTSD, 20 controls	Maternal vmPFC activity was positively associated with *BDNF* DNA methylation when mothers watched children during scenes of separation versus play. Mean overall *BDNF* methylation correlated negatively with maternal neural activity in five clusters, including the hippocampus.
2015	Schechter [71]	Pyrosequencing	fMRI	*NR3C1*	45 mothers: 28 with IPV-related PTSD, 17 controls	Lower neural activity in the PFC and greater parenting stress were each associated with lower mean percentage of *NR3C1* DNA methylation.
2016	Schechter [72]	Pyrosequencing	fMRI	*HTR3A*	35 mothers: 18 mothers with IPV-PTSD, 17 controls	*HTR3A* DNA methylation was negatively correlated with dmPFC and dlPFC activity in response to film-stimuli of adult male–female interactions evocative of violence as compared to prosocial and neutral interactions.
2016	Sparrow [73]	Microarray, pyrosequencing	dMRI	Genome-scale	72 infants: 36 preterm, 36 term	Right corticospinal tract was associated with the 6th principal component derived from genome-scale DNA methylation data.
2016	Swartz [37]	Pyrosequencing	fMRI	*SLC6A4*	132 adolescents from the TAOS study	Lower SES was associated with greater changes in DNA methylation, which predicted greater change in amygdala reactivity and greater prospective risk for depression among high-risk adolescents.
2016	Haas [74]	Mass spectrometry	fMRI, structural MRI	*OXT*	129 healthy adults	Higher DNA methylation was associated with less secure attachments, reduced neural activity in brain regions important for social functioning, and reduced gray matter volume in the right fusiform gyrus.

demonstrated the longitudinal emergence of amygdala reactivity within this cohort in relation to SLE exposure and family history of depression [50]. Results in this most recent work, however, represent the first demonstration of *prospective* changes in differential 5mC being associated with *prospective* changes in amygdala reactivity (albeit over the same time period), thus addressing a critical a gap in the literature.

Third, greater increases in threat-related amygdala reactivity between waves 1 and 2 of the study predicted subsequent increases in depressive symptoms between waves 2 and 3 of the study 1 year later. Of note, unlike the prior two findings, this third path showed evidence of moderation by family history of depression; that is, greater increases in amygdala reactivity from waves 1 to 2 predicted greater increases in depression symptoms from waves 2 to 3, but only among those with a positive family history of depression (this can also be described as effect modification by family history).

Finally, to estimate the effect of lower baseline SES on changes in depressive symptoms via changes in *SLC6A4* 5mC and threat-related reactivity, the authors tested an indirect effects model, allowing the final path in the model to vary according to family history. Consistent with the individual paths tested in their prior models, the results from this indirect effects model showed that lower SES predicted greater than expected increases in *SLC6A4* 5mC and amygdala reactivity, which in turn predicted greater than expected increases in subsequent depressive symptoms – but only in those positive for a family history of depression. Taken together, these results provide the first prospective evidence that low SES becomes embedded via dynamic biologic processes in a manner that is associated with brain function, and, in turn, heightens future liability for depression among high-risk adolescents.

Strengths and limitations of the current study

The multiple strengths of the Swartz et al. study have been alluded to above: prospective study design, examination of multiple stress-related exposures, and accounting for the known contribution of family history of depression, a potent risk factor for this disorder. In addition, the authors conducted several supplementary analyses to evaluate the robustness of their results, including testing for the effects of outliers, removing any participants with an anxiety or depression diagnosis before the second wave of their study, and testing for the potentially moderating effect of gender, an especially salient predictor of depression in adolescence [5]. All of their main results remained the same in these and other supplementary analyses.

As with most studies, that of Swartz et al. also has some limitations. First, 5mC is known to be tissue-specific [54], thus it is unclear how changes in DNA 5mC, measured in saliva, could be a mediating factor of activities going on in the brain, as suggested by the authors. Rather, these changes are more likely to be a proxy for other, as yet unobserved processes. Recent advances have made it possible to image histone deacetylases (HDACs)-based epigenetic mechanisms directly within the human brain [55]; at the moment, however, it is important to keep in mind the constraints inherent in measuring 5mC in living humans, where such advances have yet to be reported.

Second, saliva is a heterogeneous tissue, comprising varying proportions of epithelial and leukocyte cells [56]; without adjusting for this heterogeneity, it is difficult accurately to estimate 5mC changes and their relation to other variables (i.e. SES). Bioinformatic methods are now readily available to do just that [57, 58]. However, they typically require estimates of 5mC across multiple CpG sites in hundreds of genes that are derived from genome-scale technologies, which can be cost prohibitive. Future work would benefit from accounting for potential cellular heterogeneity in estimates of 5mC and/or 5mC change.

Third, although SES carried forward as the predictor of interest in all three of the tested paths, as well as the indirect effects model, the final path linking changes in amygdala reactivity to changes in depressive symptoms also showed an effect of wave 1 emotional neglect. This effect, shown in both the high and low risk groups, confirms its well-established role in the etiology of depression [59, 60] and reminds us that it, too, is a relevant target for intervention on this disorder, even if no association with 5mC was observed in this study.

Finally, as with any candidate gene approach, the results reported by Swartz et al. may well be missing the influence of other genes not considered in their study. Although genome-scale methylation analyses would be underpowered within the context of relatively small sample sizes such as that tested in this work ($n = 132$), future work might permit the development of epigenetic risk scores [61], similar to polygenic risk scores based on GWAS data [62], which would enable testing of risk based on aggregate epigenetic load, even within smaller sample sizes. Similarly, the strengths of *region of interest* (ROI) analyses for neuroimaging, and the specific role of the amygdala in threat processing and risk of depression, are well-known. Yet, an ROI approach does not provide a whole-brain mechanistic understanding of the key brain regions involved in the processes under study. Future research might therefore use whole-brain approaches, as well as functional connectivity measures, to better identify neural pathways that link SES, 5mC, and risk of depression.

Conclusions and outlook

Despite these limitations, this work does much to push the field of neuroimaging genomics forward, and it is exciting to contemplate next steps in the field. If replicated, this work may lead to the prospective examination of other mental disorders by similarly merging data from social-environmental variables, molecular variables, neuroimaging data, and symptom-related measures. More broadly, this work has exciting implications for examining the effects of interventions across multiple levels, both in terms of depression and other mental disorders. For example, saliva-derived DNA is an easily accessible peripheral tissue that has already shown promise for studying the epigenetic basis of psychiatric traits [56]. In addition, 5mC analyses of saliva-derived DNA have been linked to brain function and activity in a small but growing number of candidate gene studies (Table 1), and

therapeutic interventions designed to reduce symptoms of mental distress haven been associated with changes in brain activity [63, 64]. If 5mC measurements from saliva can be used as a robust and reliable biomarker of brain-related activity, even if only in specific genomic regions, then one could foresee a day when this biomarker alone may be targeted for intervention, and/or to stratify individuals for specific treatments according to baseline 5mC measurements, as seen in emerging work using DNA derived from blood [65–67]. This would help both to assess whether a chosen intervention may be having the desired effect on brain function, and to optimize treatment outcomes by allocating individuals to specific treatments only if they have a baseline epigenetic profile consistent with a favorable outcome for that treatment. Furthermore, as costs for genomic testing continue to decline, this scenario may be especially helpful in resource-poor settings where access to a magnetic resonance imaging scanner may not be possible.

In summary, the study by Swartz et al. does much to advance the field of neurogenomics. A small but growing literature has documented the relation between peripheral epigenetic measures and brain function (reviewed in [68]); however, this work to date has done so in a cross-sectional context. The focus by Swartz et al. on longitudinal measures of 5mC change and amygdala reactivity changes, paired to changes in depressive symptoms, enables testing of these relations within a causal framework. Although, as mentioned above, it remains unclear mechanistically how changes in saliva mediate changes in the brain, these results do present a sequential set of findings in which these changes are firmly established as premorbid biomarkers of risk—something sorely missing in prior work in the field. More broadly, these findings begin to unpack the processes by which external exposures, here SES, impact biology in a developmentally sensitive context and, subsequently, relates the impact of this biology on a specific health outcome: depressive symptoms. With depression predicted to be leading cause of burden worldwide by year 2030, this work represents a key insight into the chain of causality relating external exposures to health outcomes with a large public health impact.

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